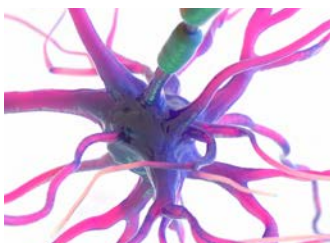
Significant progress in the CGT2 project

Highly qualified scientists recruited to the project

More on pages 2–3



Bright market prospects for CG01 and CGT2

Monocl analyses the market potential

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INGENEIOUS

NEWS FROM COMBIGENE AB

NUMBER 2 • 2020

EDITORIAL:

CombiGene

The gene therapy explorer

This newsletter has been produced by CombiGene AB

LEADER

Growing enthusiasm
New evaluation of our projects

■ Despite the covid-19-pandemic, 2020 has brought much good news for CombiGene. Via a preference issue and a directed issue, we have strengthened our capital by nearly SEK 30 million before issuing expenses. This will enable continued work with our two promising projects, the epilepsy project CG01 and the lipodystrophy project, CGT2.

Since the most recent edition of Ingeneious was published, we have done, together with an external consultant, a careful evaluation of the potential value of our projects. The evaluations are described in greater detail in a separate article in this edition but I am pleased to already here report that the potential annual sales value of our CG01 epilepsy project is estimated between USD 750 and 1,500 million. The total estimated sales value of the CGT2 lipodystrophy project is a maximum of USD 1,450 million.

The CG01 project continues to move forward according to plan. This year, we have published positive results from a preclinical pharmacokinetic study and a learning and memory study, as well as received the first plasmid from Cobra Biologics. For each step we take, our enthusiasm and our confidence in the project grow. The epilepsy project is more exciting than ever, and I look forward to one of the most central milestones in drug development: the first study in humans. In my experience, that is when you can really see a marked increase in value in the project.

The covid-19 pandemic is affecting all facets of society and will continue to do so for some time to come. No one can predict the exact magnitude of the outcomes and effects of this unique situation. Our lipodystrophy project, which is currently in progress at laboratories in Umeå and Stockholm, has not thus far been appreciably affected by the ongoing pandemic. Meetings, project follow-ups and daily contacts are managed digitally. As for our CG01 epilepsy project, we are now working with two partners in the UK: CGT Catapult and Cobra Biologics. CGT Catapult, who is helping us to develop a manufacturing method for CG01, is based in central London. Laboratory operations in this unit are presently still partly closed. If this slowdown persists, it could potentially entail delays for CG01, even if Catapult really excels in making the best of the situation. Our other supplier, Cobra Biologics, who will produce CG01, is working according to plan and has so far experienced no delays.

We are following the progression of the covid-19 pandemic and any consequences it may have for the company. However, for the time being, we foresee no serious delays for either of our projects.

Jan Nilsson
CEO

CGT2 – UPDATE

The lipodystrophy project reaches a significant milestone

■ *Covid-19 is sweeping the world. A very considerable share of healthcare resources is now being devoted to those who have fallen ill with covid-19 and enormous research efforts are being made to develop a vaccine for the disease and to find drugs that can ease symptoms and shorten the stay in hospital. At the same time the research community continues its long-term work within a range of other areas that do not receive as much media attention, but will nonetheless have great significance for the care sector and patients in the future. An example of this is CombiGene's CGT2 project, of which the aim is to develop a gene therapeutic treatment for the rare disorder partial lipodystrophy.*

CombiGene inlicensed CGT2 from the Umeå-based company Lipigon Pharmaceuticals in autumn 2019. Since the project was inlicensed the pace of development has accelerated and we are now seeing the first results in the form of a completed design of the so-called expression plasmids, which are the starting material for the gene therapy vectors that will treat the disorder. This is a significant milestone for the project.

Ingeneious contacted Annika Ericsson, Senior Project Manager at CombiGene, to discuss the CGT2 project.

Can you describe the disease partial lipodystrophy and the CGT2 project in layman's terms?

"I'll do my best," replies Annika. "Lipodystrophy is a medical condition that is characterized by abnormal distribution of fat in the body. This can lead to a range of medical complications such as hepatic steatosis (fatty liver disease), diabetes and various cardiovascular diseases. With the CGT2 project we are attempting to develop a gene therapy for treating accumulation of fat in the liver. If we succeed, the treatment will probably also have a positive effect on the other conditions, i.e., diabetes and cardiovascular diseases."

Can you give us an idea of how far you have come?

"CGT2 is in an early preclinical phase. We have conducted a number of experiments and we have designed the expression plasmids which are the starting material for the gene therapy vectors with which we intend to treat the disease. This is a major advance, although it is the first step of a long journey."

Has the covid-19 pandemic impacted the way you work, or slowed the pace of the project?

"No, I wouldn't say that. Our project organization was ready for a pandemic before covid-19. Four people are the core of the organization. Björn Eriksson and Ingela Bergqvist work at Lipigon's lab in Umeå and the Brazilian researcher Ruda Feitoza is working at Stockholm University. I am the fourth member of the group and I have overall responsibility for the project. Since the project team is spread throughout the country, the obvious choice was to rely on digital communication right from the outset. So far, this has worked very well and I am satisfied that the project is off to a good start," concludes Annika.

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Lipodystrophy leads to a number of medical complications such as fatty liver, diabetes and cardiovascular diseases. CombiGene's ambition is to develop an effective gene therapy that enhances quality of life for those affected.

Lipigon strengthens the CGT2 project organization

■ The news from Umeå is very positive. Ingeneious had a chance to speak with Lipigon's CEO Stefan K Nilsson, as well as Ingela Bergqvist and Björn Eriksson, who were recently hired by Lipigon to work with the CGT2 project.

"The agreement with CombiGene allows Lipigon to grow," says CEO Stefan K Nilsson. "We're very excited. We have recruited Björn Eriksson and Ingela Bergqvist, two very experienced researchers who will work with the CGT2 project on behalf of CombiGene. It's going to be very exciting to follow the progress of the project."

"I'm really pleased to be working with CombiGene's gene therapy project," says Ingela Bergqvist. "The early phase of drug development is extremely laboratory-intensive and exciting, and it is very stimulating to be part of the project."

"Working in the gene therapy field is very developing and exciting. Both Ingela and I have a background in diabetes research and that's a perfect fit for the CGT2 project," concludes Björn Eriksson.

"This is a major advance, although it is the first step of a long journey."

Annika Ericsson, Senior Project Manager, CombiGene

Brazilian researcher joins the project

■ In spring 2020 Brazilian researcher Ruda Feitoza joined the CGT2 project. His doctoral studies focussed on how mitochondrial function can be affected by drugs and nutrient uptake. Mitochondria are usually described as the powerhouses of the cell and transform nutrients into energy. Ruda is now working at the Wenner-Grens Institute at Stockholm University. His current work concerns detailed understanding of the mitochondrial functions and conditions in the liver, the organ which is the focus of the CGT2 project.

What are your impressions of Sweden?

"I am impressed by the nature and the way Stockholm has developed in relation to its surroundings. I think the first challenge for me will be the weather. But, since I arrived in the spring, adapting to the climate has so far been very easy."

What has it been like for you to leave Brazil for Sweden during the ongoing pandemic?

"Of course, I have been worried and I often think of my family in Brazil. The virus is widely spread in both Sweden and Brazil. But I keep in close touch with my family and I am convinced that we are all taking the right precautions. As for my day-to-day life, I follow the authorities' recommendations and have so far had no real difficulties. The project is in an early stage of development and we have not yet experienced any significant covid-19-related problems, as we have been able to hold our meetings digitally."

Ingenious contacted CombiGene's CEO, Jan Nilsson, to hear his thoughts on the development of the CGT2 project.

"I am very pleased with the way the project has developed since we inlicensed it from Lipigon," says Jan.

"We are still in an early phase, but the fact that we now have access to the starting material for production of the future gene therapy vectors is quite an important milestone. Collaboration with Lipigon is excellent and Ruda Feitoza's work at the Wenner-Grens Institute will give us a detailed understanding of how we can control the liver's mitochondrial functions. The CGT2 project, of which the ambition is to treat partial lipodystrophy, is very interesting. I am also convinced that the project will generate a lot of knowledge that will aid in the treatment of other metabolic disorders, which may eventually lead to other interesting projects."

"The project is in an early stage of development and we have not yet experienced any significant covid-19-related problems."

Ruda Feitoza, researcher, Wenner-Grens institutet

THE MARKET FOR GENE THERAPY

Significant commercial opportunities

The markets for CombiGene's projects, CG01 and CGT2, are both very interesting, even if they differ considerably with respect to the prospective patients. To gain an up-to-date and representative overview of the commercial opportunities, CombiGene, together with the international consultancy firm Monocl, has analyzed the market potential of each project.

The global annual market for the candidate drug, CG01, is estimated at USD 750 – 1,500 million

Epilepsy is a global problem. The disease affects an estimated 0.6 to 0.8 percent of the world's population. In 2016 there were 5.7 million diagnosed epilepsy patients in the US, the EU5 and Japan. About one-third of these patients do not respond to conventional medical treatment. Of these, some 60 percent suffer from focal epilepsy, i.e., a form of epilepsy in which seizures arise in a well-defined area of the brain. Many of these patients suffer from such a difficult-to-treat form of epilepsy that they are examined to determine if they can be considered for surgical treatment. It is mainly this patient group CombiGene intends to help with its candidate drug, CG01.

Enormous potential for CombiGene

It is estimated that some 47,000 patients with drug-resistant focal epilepsy are considered for surgical treatment each year in the US, EU5, Japan and China. CombiGene estimates that, realistically, 10 –20 percent of these patients could be treated with the company's candidate drug, CG01. Assuming that the treatment cost per patient amounts to somewhere between USD 134,000 and USD 200,000 (which is low in comparison with approved gene therapy drugs), annual sales could be as much as between USD 750 and USD 1,500 million.

The global market for the candidate drug, CGT2, is estimated at USD 700 – 1,450 million

With the lipodystrophy project, which was in-licensed from Lipigon Pharmaceuticals in autumn 2019, CombiGene has expanded its operations to include metabolic disorders. The initial aim of the project is to develop a gene therapeutic treatment for partial lipodystrophy, a very rare condition for which there is currently no adequate treatment. The project is in an early stage of development.

Partial lipodystrophy is a very rare disorder for which there are no effective treatment alternatives. It is estimated that there are about 500 patients in the US and 300 patients in the EU, and that the patient population is expected to grow by four percent per year. Assuming that CGT2 will be used to treat between 25 and 50 percent of the patients and that the treatment per patient costs USD 1.5 million in the US and USD 1.3 million in Europa, the total sales potential is USD 700 – 1,450 million.

Another group of patients with lipodystrophy lack a hormone called leptin. This group of patients cannot be treated with CGT2, but there is a medical treatment which costs USD 850,000 per patient and year in the US, indicating that there is a high willingness to pay for treating this type of disease.

CG01 – UPDATE

Continued advances in the CG01 epilepsy project

The CG01 project has advanced in terms of knowledge acquisition via two concluded preclinical studies. The most significant advances are summarized below.

Significant events during the first quarter of 2020

- During the quarter we reported the outcome of the preclinical pharmacokinetic study that was conducted to determine the expected duration of the effect of a CG01 treatment. The results of the study are very promising, confirming that CG01 creates long-term expression of the active substances NPY and Y2. The study shows that expression (occurrence) of neuropeptide Y (NPY) and its receptor, Y2, increase markedly during the first three weeks, thereafter reaching a plateau that persists for the entire duration of the study, i.e., six months. A rule of thumb is that six months in the experimental model we have used for our pharmacokinetic study corresponds to 15 years in humans.
- We also reported the results from CG01's learning and memory study. The outcome of the study is very gratifying and shows that NPY and Y2 have no significant negative effect on cognitive functions.
- Discussions concerning the design of the first clinical study have also been held with additional physicians who are interested in participating in the study.

Significant events during the beginning of the second quarter of the year

- Early in the second quarter our production partner, Cobra Biologics, reached an important milestone in the CG01 project with the delivery of the first DNA plasmid.

Co-financed by the Connecting Europe Facility of the European Union

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

CGT2 – UPDATE

The pace of the CGT2 lipodystrophy project accelerates

CGT2, CombiGene's project to develop a gene therapeutic treatment for partial lipodystrophy, is now in an early preclinical development phase. Since we inlicensed the project from Lipigon in 2019 the pace of the project has accelerated and we are now seeing the first results of this work.

Significant events during the first quarter of 2020

- During the first quarter we have designed and ordered expression plasmids, which are the starting material for the gene therapeutic vectors CombiGene intends to develop.
- Resources for the project have also been augmented with the appointment of a postdoctoral research position at Stockholm University.

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Gene therapies carry high price tags

■ One of the maintopics for discussion in gene therapy is how treatments should be priced. One challenge is to compare the cost of life-long treatment with conventional drugs and the cost of a single gene therapeutic treatment that can cure or have a long-term effect in alleviating a medical disorder. Another issue is how to place a monetary value on a treatment that can potentially cure a disease for which there is currently no adequate treatment. The landscape for various replacement models is developing rapidly and it is apparent that many gene therapies are valued very high by healthcare authorities and providers.

One example is Novartis's gene therapeutic drug Zolgensma. Japanese public health authorities have set the price of this treatment at yen 167 million, or USD 1.55 million.

Zolgensma is thereby the most expensive medication funded by the country's national insurance system. Zolgensma has been developed to be administered in a single treatment to patients under two years of age to treat the rare disorder spinal muscular atrophy (SMA), which is characterized by the progressive degeneration of spinal and brainstem motor neurons.

The Japanese authorities estimate that about 25 patients will be treated each year.

In the EU, where Zolgensma was recently granted conditional approval, between 500 and 600 children are born with SMA each year. The cost of care for each individual is estimated at between euros 2.5 and 4.0 million for the first ten years.

Sources: The Alliance for Regenerative Medicine (ARM), Swedish National Board of Health and Welfare (Socialstyrelsen), Novartis.

Events

PREVIOUS EVENTS

March 18 2020
Analysguiden – on CombiGenes progress with CG01
https://combigene.com/nyheter/analysguiden-jan-nilsson-vd-pa-combigene-berattar-om-framstegen-med-cg01/

March 16 2020
Aktiedagen in Stockholm – Company Presentation
https://combigene.com/videopresentationer/bolagspresentation-pa-aktiedagen-i-stockholm-den-16-mars/

February 6 2020
Swiss Nordic Bio – partnering- and investor conference
https://combigene.com/kalendarium_tidigare/6-februari-swiss-nordic-bio-2020-zurich-switzerland/

Read all of our news in one place

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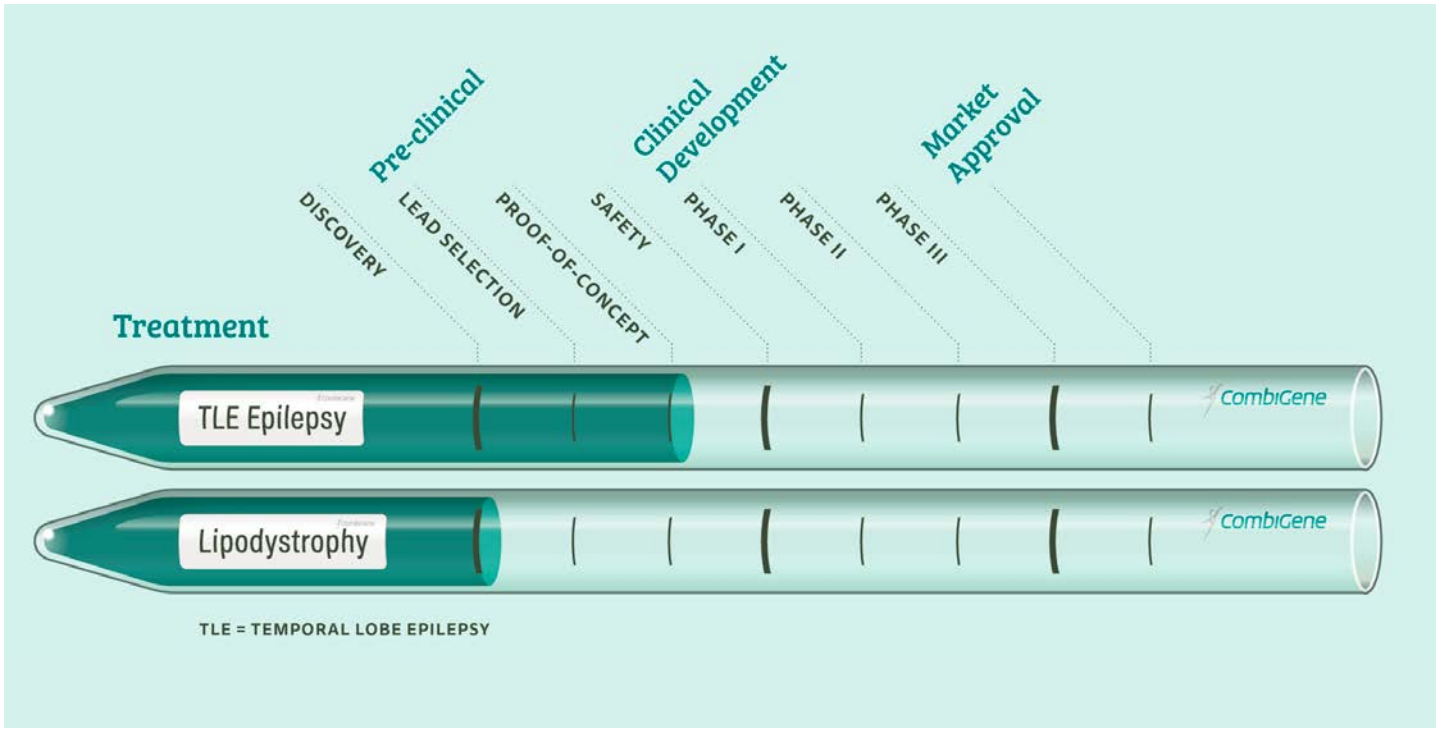

PROJECT OVERVIEW

CombiGene moves from one development stage to the next

In the CG01 project, together with British CGT Catapult, we're developing a manufacturing method for our candidate drug and we have selected both CDMO and CRO partners. This means that we have taken several very significant steps forward in the CG01 project.

Co-financed by the Connecting Europe Facility of the European Union

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

CombiGene – The gene therapy explorer

With one project nearing the clinical-study phase and one project in an early 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 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. We are now continuing our voyage of discovery with another exciting project – the CGT2 lipodystrophy project. Even here, we we expect to create new and valuable knowledge as we carry this project forward.

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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