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INGENEIOUS

NEWS FROM COMBIGENE AB

NUMBER 1 • 2020

EDITORIAL:

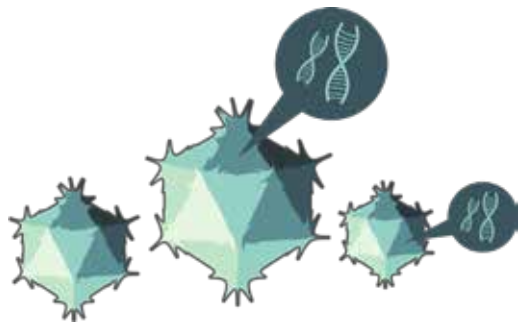
CombiGene

The gene therapy explorer

This newsletter has been produced by CombiGene AB

2020-03

INTERVIEW WITH CEO JAN NILSSON



2019 was an eventful year for CombiGene, what do you feel are the most significant changes in CombiGene this year, as compared to a year ago?

We've brought the company forward considerably over the past year and, in my eyes, CombiGene is a completely different company than it was one year ago. Perhaps the most notable difference is that we are now focussing not solely on epilepsy. Our project portfolio has been broadened with a promising gene therapy project in the area of metabolic disorders, where today's treatments are insufficient and extremely costly. Another important difference, which may not have received as much attention, is that we are now on our way to conclude the extensive development work surrounding our manufacturing method for CG01, and we have reached agreements with manufacturers. Everyone who works with gene therapy is well aware of the challenge manufacturing poses, and the fact that we have reached this stage adds considerable value in our discussions with potential collaborative partners.

You mention in the year-end statement that CombiGene has taken important steps forward where partnering is concerned. Can you elaborate on that?

It is always difficult to provide information about our partnering efforts, since we only want to give the market significant information without the risk of misinterpretation or pure speculation. Over the past year we have had several successful meetings with pharmaceutical companies, in both the largest category (Big Pharma) and with niched companies (Speciality Pharma), based mainly on interest in our candidate drug, CG01. These types of discussions always take place over a longer period. As a rule, initial contacts are characterized by tentative information exchange, and updates are often given in conjunction with larger partnering conferences (e.g., BioEurope). During subsequent stages information is exchanged in accordance with confidentiality agreements. Here, results from study reports are discussed and meetings with the scientific teams are held. The subsequent process varies depending on who the counterpart is, but typically involves access to a data room, question-and-answer rounds (scientific, commercial and regulatory due diligence) and dialogues concerning the terms of possible commercial collaboration. In some cases, the counterpart wants to see certain data before making a decision. Several of these types of dialogues have taken place during 2019 and are ongoing, but to avoid misunderstanding, we have chosen not to share any specific information about our current status in this regard.

Partnering dialogues usually take place over a period of several years and have a lot to do with building trust and credibility from both parties, not only in terms of data but also in terms of the people who work within the company, which is an important consideration for a partner.

CombiGene announced on February 18th that the company intends to carry out a rights issue. Had you foreseen that the market would react negatively?

CombiGene is a development company with no revenue, so I don't think it came as a surprise for our owners that the company needs additional funding in order to carry our projects forward. We have carried out new issues before and are aware that this usually results in a decline in the share price. This time, other factors are coming into play, primarily, the coronavirus outbreak, which is having a negative impact on many markets. It is always difficult to predict how the market will react. We are therefore trying to focus on long-term value creation by delivering on our development plan.

What is CombiGene's strategy for establishing the terms for an issue?

Since it is important that we identify collaborative partners who believe in CombiGene and on whom we can rely, we normally procure an advisor prior to each new capital acquisition. In each financing round, the aim is always to raise the capital we need at the best possible terms for our shareholders. Finding 'the best possible terms' is more difficult than one might think and we must get used to the fact that, unfortunately, it is impossible to

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Production:
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Text: Columbi Communications AB

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Medicon Village, SE-223 81 Lund
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CombiGene is listed on Nasdaq First North Growth Market.
www.combigene.com

satisfy all shareholders. People in the management and the board are also shareholders, which makes it natural to try to find a good balance. Usually, the first decision to make is what discount to offer on the share price to create an incentive for subscribing without diminishing the value for our existing shareholders. This can be difficult since, as a company, it is hard to influence your market capitalization at the point in time when a capital requirement arises. To minimize dilution, it is therefore logical to design a funding strategy whereby warrants can be converted at future points in time when the company has reached development milestones and increased in value. Similarly, investors in development companies normally opt to inject capital at intervals, instead of making a single large investment. Finally, we have seen that guaranteed issues have a greater probability of attracting interest, so this is usually a safe way of ensuring that the target for the issue is reached.

What would you like to say to shareholders who are concerned about CombiGene's current market cap?

Of course, I think that the situation is regrettable. It is completely reasonable to worry when the share price is lower than the acquisition value. The share price is beyond my control and I hope that our shareholders feel confident when they consider how CombiGene has developed during my years as CEO. As I mentioned earlier, our CG01 development programme has made very considerable progress and our portfolio has been broadened in the past year to include another project. These activities create value for the company and should eventually result in increased shareholder value.

How would you describe the motives for the issue?

The purpose of the issue is to secure resources to drive our epilepsy project, CG01, forward with full force. Results from animal studies and studies by our scientific founders on NPY in donated human brain tissue show very promising potential. Most of the funds raised from the issue will be used to produce CG01 material, which will enable us to conduct the safety and biodistribution studies before we can start the first clinical study.

What is the time horizon for these activities?

During 2020 we will also use the material to conduct studies to determine how best to administer CG01 to the human brain.

"Even a conservative estimate places the market potential for CG01 at 4-10 billion kronor per year"

During 2021 we plan to carry out the safety studies (biodistribution and toxicology) that are necessary to obtain authorization from regulatory authorities to conduct studies in humans. The safety studies will take about six months, after which it will take about a further six months to analyse the results. Concurrently, we are also making preparations for the start of the clinical study. For example, we will design the study, meet with the regulatory authorities and discuss our project with the clinics that have expressed interest in conducting the clinical study.

When do you think the first study in humans will begin?

There is always a degree of uncertainty when a new therapy is developed, but as soon as we have the final report from the safety studies, our plan and ambition is to submit an application to the regulatory authorities for authorization to start the first human study.

That sounds very exciting.

It certainly is. To have the opportunity to work with a project that can ultimately help people is very gratifying. However, as with all drug development, it is very time consuming and resource intensive. There are many significant milestones along the way, but one of the most important is the start of the first clinical study. In my experience, it is also one of the milestones when you can really see a marked increase in value in the project.

Many gene-therapy projects, both those which have reached the market and those which are still under development, are aimed at very rare diseases. This is not the case with CG01.

Precisely. CG01 will address a very big target group. In the USA alone some 14,000 patients are diagnosed with drug-resistant focal epilepsy each year. Realistically, 10-20 percent of these patients could be treated with CG01 and even a conservative estimate places the market potential for CG01 at 4-10 billion kronor per year.
Our lipodystrophy project is different in the sense that it is aimed at a rare patient group for which the majority of patients now lack a satisfactory treatment. The current treatment for lipodystrophy, Myalept, can unfortunetly not help the sub-population we aim to help. Myalept is without exception the most expensive drug in the USA, which shows that there is a very high degree of willingness to pay for treatment of lipodystrophy.

How long will funds from the issue last?

The further you proceed with a drug development project, the more it costs. Funding from the ongoing issue will mean that we can drive CG01 with full force through 2020. That horizon is appropriate, since it will allow us to reach a number of important milestones, which we feel makes the offer attractive for our existing shareholders and new investors in this issue. Thereafter, we will need additional capital.

Will this mean another rights issue during 2021?

It's too soon to say. A rights issues is one of several alternatives. We also have the option of applying for other types of grants, just as we did, successfully, with Horizon 2020.
A directed share issue is also plausible, or we may by then have found a strong investment partner. For the time being, I am not discounting any alternatives.
I wish to add that we are working continuously on several fronts to secure long-term funding for our projects. This effort includes all of the alternatives I mentioned above.

Am I right in understanding that the funds from the ongoing issue will primarily be used in the CG01 project and not the lipodystrophy project?

That is correct. The reason is that CG01 has come a lot farther development-wise and therefore costs more, precisely as I explained earlier. However, our level of ambition for the lipodystrophy project remains high. The project is off to a very good start and we are managing it exactly as planned, but since the project is still in an early stage of development, it is not as costly as CG01.

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

CG01 – UPDATE

Further steps towards studies in humans

CombiGene has recently concluded two planed preclinical studies in the CG01 project: a pharmacokinetic study and a memory study. The outcomes from both studies are positive and mean that CombiGene now has answers to several key questions from both physicians and regulatory authorities.

Successful pharmacokinetic study confirms that CG01 has a very lasting effect

CombiGene's candidate drug, CG01, is being developed for treatment of patients with focal epilepsy. The aim is to enable a very long-term therapeutic effect through a one-time administration. To determine how the body takes up a drug and how lasting the effect is, so-called pharmacokinetic studies are conducted. CombiGene recently concluded a study of this kind, the results of which are extremely encouraging.

The concluded study clearly shows that the expression (occurrence) of neuropeptide Y (NPY) and its receptor, Y2, increases markedly after only one week following administration of CG01, and then continues to increase during the following two weeks, reaching a plateau after three weeks. It is particularly pleasing to note that the level achieved after three weeks remained stable throughout the duration of the study, i.e., six months.

"One question that often arises in our discussions with physicians is how long we can expect to see an effect in humans after an injection and whether several injections will be necessary to maintain the effect. This study shows that the expression or occurrence of NPY/Y2 persists over a long period. This provides further evidence that a single injection should have an effect that lasts for many years. 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. The results from the pharmacokinetic study are extremely encouraging," says a very satisfied Annika Ericsson, Senior Project Manager, CombiGene.

Findings from the pharmacokinetic study are gratifying in other respects as well. Understanding how CG01 acts in the brain is also an important piece of knowledge that will aid the planning of the coming safety studies (toxicology and biodistribution). Knowledge gained from the pharmacokinetic study will also constitute a central component in the design of the first study in humans.

No negative effect on cognitive function

NPY, the active substances in CG01, is associated with several physiological processes in the body, among others, memory and learning. CombiGene has therefore received an inquiry from the FDA and the Swedish Medical Products Agency as to whether CG01 has any impact on cognitive functions. The concluded memory study answers that important question: increased expression of NPY and Y2 has no significant negative effect on memory or learning functions in the experimental model used in the study.

David Woldbye, one of CombiGene's scientific founders, commented on the results of the study. "The results of earlier academic studies on the effect of NPY on memory and learning have been contradictory. It is therefore especially pleasing to note that we can now demonstrate that we do not affect memory and learning when we inject CG01 into one of the brain's two hippocampi, precisely as we intend to do in humans."

Karin Agerman, CombiGene's Chief Research and Development Officer, is also very satisfied with the outcome of the two studies. "With the completion of the pharmacokinetic study and the memory study it is very reassuring to have successfully answered several questions from the FDA and the Swedish Medical Products Agency. This brings us one step closer to starting the first study in humans. More and more pieces of the CG01 project are now falling into place."

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"It is especially pleasing to note that we can now demonstrate that we do not effect memory and learning"

DAVID WOLDBYE *ONE OF COMBIGENES SCIENTIFIC FOUNDERS*

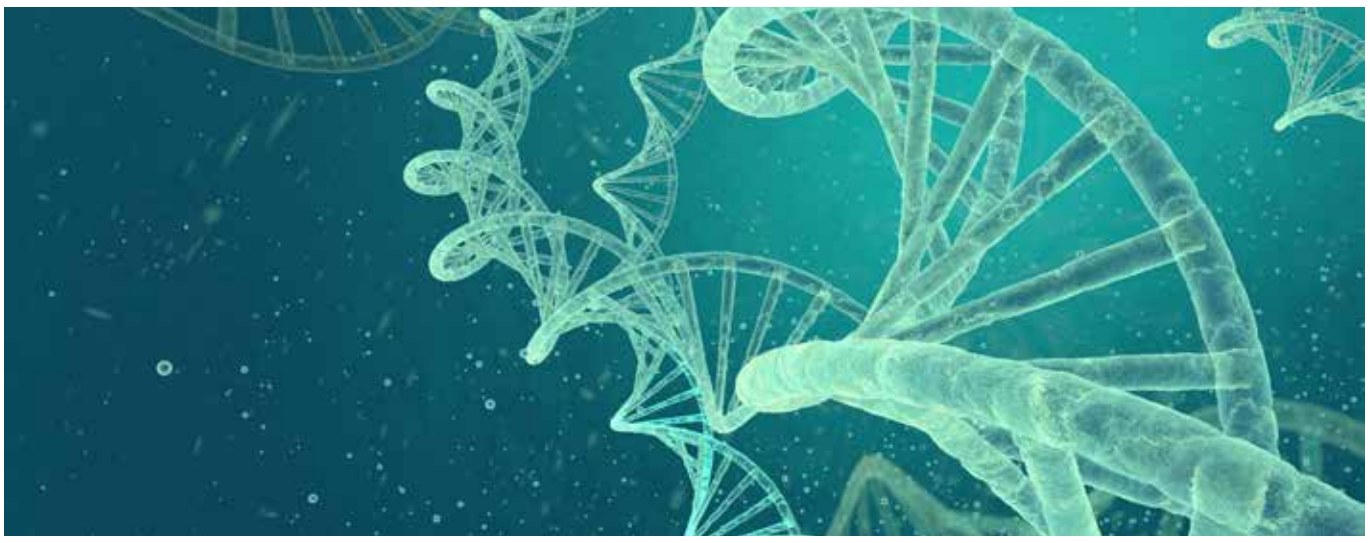
"With the completion of the pharmacokinetic study and the memory study it is very reassuring to have successfully answered several questions from the FDA and the Swedish Medical Products Agency."

KARIN AGERMAN *CHIEF RESEARCH AND DEVELOPMENT OFFICER*

THE MARKET FOR GENE THERAPY

Continued strong support for gene therapy from FDA

The US Food and Drug Administration (FDA) continues to show strong support for the development of new gene therapies.



The FDA has thus far approved four gene therapy products and the administration anticipates many more approvals over the coming year, owing not least to the fact that there are some 900 ongoing clinical studies in this area. The FDA believes this will provide patients and providers with increased therapeutic choices.

In January the FDA issued six guidelines covering, for example, manufacturing and clinical development of gene therapy products.

"The growth of innovative research and product development in the field of gene therapy is exciting to us as physicians, scientists and regulators," said FDA Commissioner Stephen M. Hahn, M.D.

"We understand and appreciate the tremendous impact that gene therapies can have on patients by potentially reversing the debilitating trajectory of diseases. These therapies, once only conceptual, are rapidly becoming a therapeutic reality for an increasing number of patients with a wide range of diseases, including rare genetic disorders and autoimmune diseases."

Read the FDA press release here:

https://bit.ly/2Jey88A

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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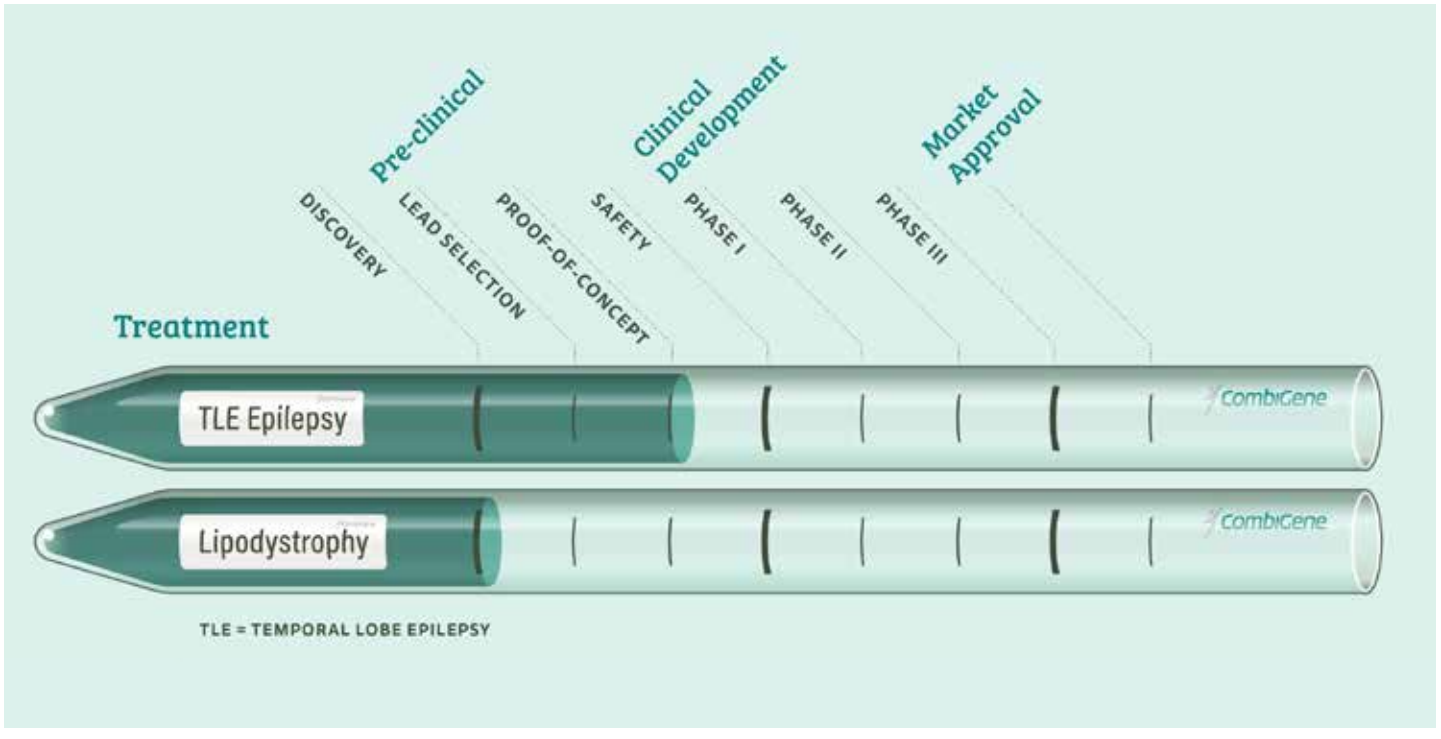

PROJECT OVERVIEW

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 recently selected both CDMO and CRO partners. This means that we have taken several very significant steps forward in the CG01 project. We have also inlicensed a new gene therapy project, of which the aim is to develop a treatment for the rare disorder lipodystrophy.

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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 as exciting and promising as gene therapy and, in many respects, CombiGene is at the very forefront of drug development. On a nearly daily basis, during our work with the CG01 epilepsy project, 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 lipodystrophy project. Even here, we expect to create new and valuable knowledge as we drive 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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