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to CombiGene from Horizon 2020

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INGENEIOUS

NEWS FROM COMBIGENE AB

NUMBER 4 • 2019

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CombiGene

The gene therapy explorer

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2019-12

WORD FROM OUR CEO

A look back at a successful year

As 2019 draws to a close, this is a good opportunity to briefly sum up the past year.

2019 has been a very good year for CombiGene. Our CG01 epilepsy project has reached several significant milestones. The acquisition of Panion gives us full control over all intangible assets related to the CG01 project, which will be very valuable when we begin negotiations with potential partners. The agreement with CRO Northern Biomedical Research has paved the way for the toxicity and safety studies that are necessary before human studies can be initiated. Last but not least, we have signed an agreement with CDMO (Contract Development and Manufacturing Organization) Cobra Biologics for GMP manufacturing of CG01 for clinical studies and future commercial production. Production capacity is starting to become a bottleneck in the gene therapy sector and we are very pleased to have been able to secure the supplier we need in order to begin clinical studies.

During 2019 we have also broadened our business with an additional gene therapy project – the lipodystrophy project, which was inlicensed from Lipigon. This means that CombiGene is now active within two very interesting areas of gene therapy: diseases related to the central nervous system and the metabolic system.

In other words, 2019 has been a year during which the CG01 project has advanced in a very satisfactory manner. We have all the pieces in place to be able to take the final decisive step towards the first studies in humans. In addition, we have broadened our business with another project, something we have been working intensively towards for quite some time.

I extend my warmest thanks to all of my colleagues at CombiGene and all of our partners throughout the world. To all of our shareholders, I wish to express my sincere gratitude. Without you, these successes would never have been possible.

Jan Nilsson
CEO

GENE THERAPY – THE FUTURE OF HEALTH CARE

CombiGene is an integrated part of a dynamic gene-therapeutic landscape

■ *Gene therapy is now one of the hottest areas in the pharma industry. Naturally, this is due mainly to the great expectations that medicine is placing on gene therapy. Suddenly, there is hope that patients who suffer from serious illnesses may receive effective treatments that will decisively improve their quality of life and the possibilities for living without limitations.*

370 candidate drugs in the clinical phase

Today, 370 clinical studies in gene therapy are currently running (ARM Q3, 2019), of which 32 are in clinical phase III. Many of the candidate drugs under development are targeted at serious and rare diseases for which effective forms of treatment are currently lacking. For many people, the quality of life could thereby be considerably improved. For certain diseases, gene therapy can potentially mean the difference between life and death.

On August 31st 2017, the US Food and Drug Administration (FDA) approved the first gene-therapeutic drug, for clinical treatment of acute lymphoblastic leukaemia. Since then, additional gene therapies have achieved market approval and the number of approved gene-therapy treatments is expected to increase dramatically in the coming years. In other words, there is good reason to assume that gene therapy will play a major role in future health care.

Significant commercial potential

The advances in medicine also imply potentially great commercial successes for the companies that succeed in developing effective gene therapies. Belief in the commercial viability of gene therapy is reflected in, among other things, the considerable investments that are being made in this area, which during the first nine months of 2019 amounted to some USD 5.6 billion (ARM Q3, 2019).

As the leading Nordic gene-therapy company, CombiGene is an integrated part of a dynamic gene-therapeutic landscape. The company has two exciting projects: CG01, which is being developed for treatment of drug-resistant focal epilepsy and the project for treating the rare disorder lipodystrophy that was recently inlicensed from Lipigon.

CG01 is being developed to treat a large group of patients

The CG01 project differs from many other gene therapy projects in that the number of potential patients is very large. In the USA alone some 14,000 patients are diagnosed with drug-resistant focal epilepsy each year, patients who could be candidates for surgery. CombiGene estimates

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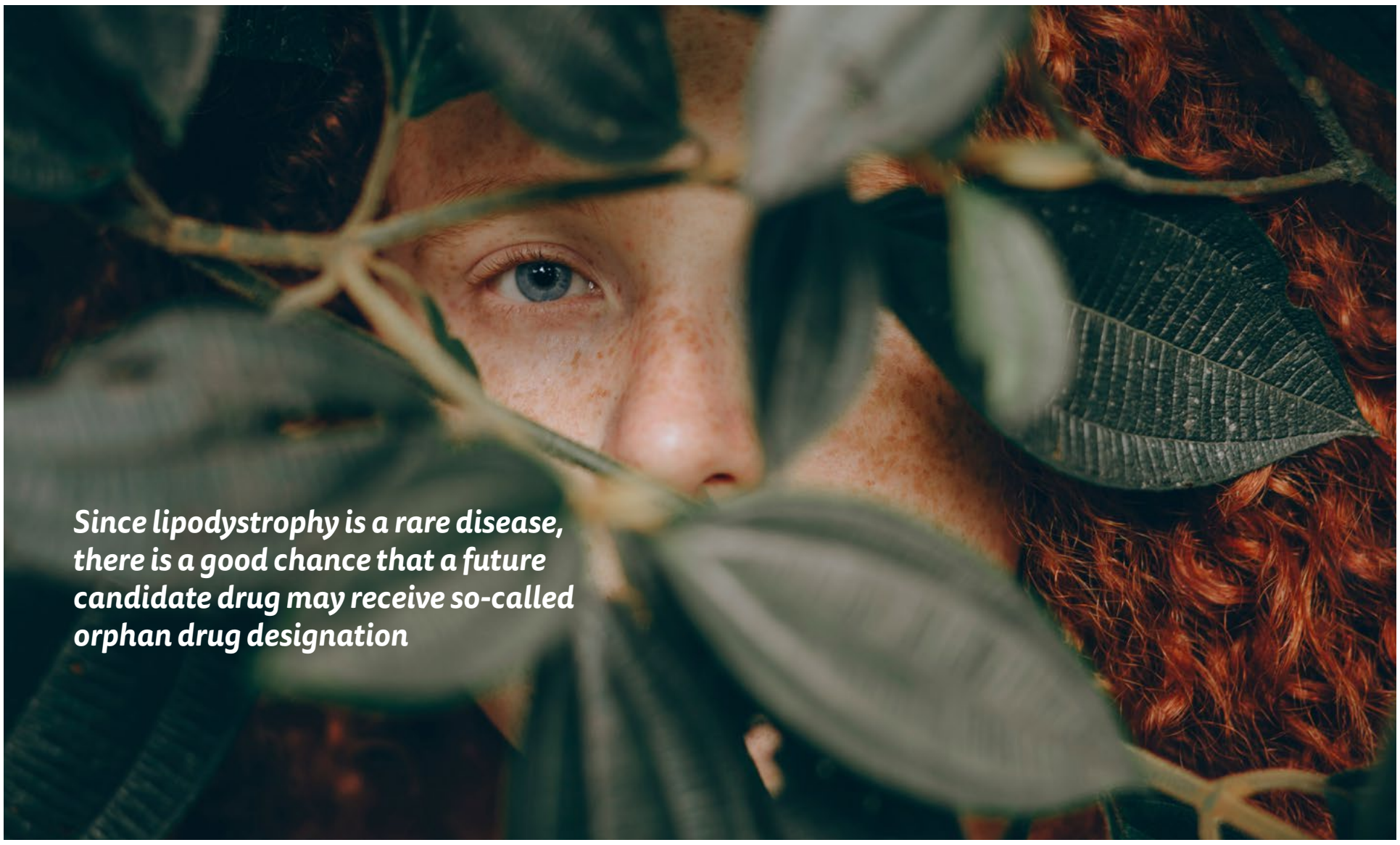


that, realistically, 10–20 percent of these patients could be treated with the company's candidate drug, CG01. Living with untreated epilepsy entails great limitations in day-to-day life and constant worry about having to face sudden, unpredictable epileptic seizures. The large number of potential patients also means that the commercial potential of the project is very large. CombiGene has begun to carry out the concluding stages of the preclinical programme, after which the first studies in humans will commence.

With the lipodystrophy project, CombiGene is expanding into another area of therapy

The lipodystrophy project is in an early preclinical phase. As opposed to CG01, which targets a large patient population, this project refers to a small group of patients who have the rare disorder partial lipodystrophy, for which there are currently no effective treatments. Since lipodystrophy is a rare disease, there is a good chance that a future candidate drug may receive so-called orphan drug designation. Orphan drugs offer a means by which regulatory authorities, including the American FDA and the European EMA, can encourage the pharmaceutical industry to develop drugs for rare diseases. Obtaining orphan drug designation brings many great advantages. Essentially, this means that development can proceed faster and at a lower cost. An orphan drug designation also means that the chances of reaching the market are greater and the price of the approved drug is usually higher as compared to drugs for commonly occurring diseases.

"During the past year CombiGene has taken significant steps forward," says CombiGene's CEO, Jan Nilsson. "CG01 is a project that is targeted at a very large group of patients, which is relatively unusual for a gene therapy project. It is important to note that in the CG01 project we are not only developing a GMP-classed production method, which is a challenge for all gene therapy projects, we have also signed a Master Service Agreement with Cobra Biologics for production of CG01 for both clinical studies and commercial production of a future, approved CG01 drug. Furthermore, our lipodystrophy project has the potential to be an orphan drug, which makes our situation even more favourable.

Both of our projects are also within very interesting areas. With the CG01 project we acquire great knowledge of the central nervous system and, with the lipodystrophy project, we will build up considerable knowledge surrounding gene therapy and the metabolic system. All in all, this confirms my confidence in a very positive future for CombiGene as the leading Nordic gene-therapy company."

CombiGene receives the second instalment of EUR 1.21 million from Horizon 2020

In May 2018 Horizon 2020, the EU framework programme for research and development, decided to invest EUR 3.36 million in the ongoing development and commercialization of the CGO1 gene therapy project. The initial payment from Horizon 2020, made in autumn 2018, amounted to EUR 1.51 million. The second payment amounted to EUR 1.21 million and was made in November this year after a thorough review of the project by the EU and external reviewers.

"The payment from Horizon 2020 is an acknowledgement of the progress that has been made in the CG01 project and, not least, of the work we are doing with CGT Catapult to develop a GMP-adapted production method," says Karin Agerman, Chief Research and Development Officer at CombiGene. "In addition to having our project report approved and funding paid out, we have also received positive feedback and valuable recommendations from Horizon 2020's external reviewers. That our epilepsy project is one of the projects which Horizon 2020 has chosen to invest in means a lot to CombiGene. Besides the capital injection in the project, this is also a valuable stamp of quality assurance for our development work and our commercial potential."

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

INTERVIEW WITH ANNIKA ERICSSON, SENIOR PROJECT MANAGER

Genergy at CombiGene

■ *There is no energy shortage at CombiGene. That conclusion can be easily drawn after speaking with Annika Ericsson, Senior Project Manager at CombiGene. Annika not only holds a PhD in gene therapy from Karolinska Institutet, she is also one of the world's top-ranked swimrun competitors, having won the prestigious ÖtillÖ (Island to Island) race outside Stockholm four years running.*

When *Ingeneious* meets Annika she has just returned from a World Cup competition in swimrun in Malta, where she placed third in the mixed category together with her temporary team mate, Stefano Prestinoni.

Let's start with your academic merits. Can you tell us about them?

"Absolutely. I did my PhD studies at Karolinska Institutet (KI) in a project on acute intermittent porphyria (AIP). Porphyrias are a group of rare heme synthesis disorders. Heme is a component of haemoglobin. In Sweden, about one person in 10,000 suffers from the disorder. The symptoms vary, but include, among other things, abdominal pain, various symptoms of the nervous system and psychiatric symptoms. The research at KI gave me indepth knowledge of gene therapy, even though it didn't lead to an effective treatment for the disease. After completing my PhD studies I did a postdoc at Mount Sinai School of Medicine, in New York. Subsequently, for the past fourteen years I have been working in the biotech sector."

What is a typical day for you?

"I guess you could say I live a rather disciplined life. My day begins and ends with training. Each morning I swim, and then I cycle to work. My days at CombiGene are devoted to the exciting lipodystrophy project that we inlicensed earlier this autumn, as well as a lot of work with CG01. When I arrive home after work, my family is my priority. My husband works at Ericsson and we have two daughters, both of whom are football enthusiasts. The youngest still swims competitively. I usually round off the day with a run."

That sounds like a very hectic schedule.

"Well, in a way it is. But, at the same time, it gives me energy. Mostly from my family, of course, but my work and training also fill my energy reserves. I don't see it as making sacrifices. On the contrary; I derive a lot of joy from everything I do."

Interest in sports is big in Sweden. Can you describe your career as a swimrunner?

"Gladly. Swimrun is a competitive sport that originated in Stockholm and is now spreading quickly throughout the world. The original competition, ÖtillÖ in Stockholm, involves 65 kilometres of running and ten kilometres of swimming. Last year, when I won the competition for the fourth consecutive time, my partner Kristin Larsson and I were the first women's team to complete the race in less than nine hours. We still hold that record. That may not mean much to the uninitiated, but it can probably be compared to the dream mile, i.e., running a mile in under four minutes, something that eluded the world's elite runners until Englishman Roger Bannister did it in 1954."

You began work at CombiGene approximately a year ago, December 12th 2018, to be exact. Now that you've had time to settle in, how would you describe the company?

"CombiGene is a tremendously exciting company in a very exciting sector. If you're interested in biotech, gene therapy is among the most fascinating fields, not least because what we do has the potential to improve life for so many people. The lipodystrophy project, which is what I am now focussing on, may provide an effective treatment for patients for whom there is currently no treatment at all. I know that is what drives everyone who works at CombiGene. We really want to be a part of healthcare development and make a contribution, so that patients all over the world can live life to the full."

Annika Ericsson has together with her swimrun partner Kristin Larsson won ÖtillÖ (Island to Island) three years in a row, and Annika and Kristin were the first and, so far, only women's team to break the nine-hour barrier. In total, Annika has won ÖtillÖ five times.

Facts about porphyria

Porphyria is a collective name for eight hereditary diseases which are caused by a deficiency of enzymes that contribute to the formation of the red-coloured compound called heme, a component of hemoglobin. The name derives from the Greek word porphyros, meaning purple. Acute intermittent porphyria (AIP) is the most common form of porphyria in Sweden and is characterized by abdominal pain, neurological symptoms and, sometimes, psychiatric symptoms. Over the long term it can also cause damage to the liver and kidneys.

Treatment of acute intermittent porphyria consists of preventative treatment and management of acute attacks. By regularly testing blood pressure and liver and kidney function, it is possible to prevent complications over the long term. Acute intermittent porphyria has been described in medical literature since the late 1800s, but in Sweden the disease was first noted in the early 1900s by Dr. Einar Wallquist in Arjeplog. Other names for the disease have been given, but the Swedish internist Jan Waldenström's studies of patients with acute intermittent porphyria gained such international recognition that the disease came to be called Swedish porphyria. Jan Waldenström coined the term acute intermittent porphyria, since the attacks occur intermittently.
Source: www.socialstyrelsen.se

PROJECTS AND ACTIVITIES

Business development is always a priority for CombiGene

■ *CombiGene's activities revolve around the company's two projects: CG01, which is being developed for treatment of drug-resistant focal epilepsy and the lipodystrophy project, which was inlicensed earlier this autumn. In addition to these projects, CombiGene also works continuously with business development to build and maintain relations with major pharma companies which may in future be suitable partners for taking CombiGene's projects forward through late clinical studies and commercialization.*

Ingenious met with CEO Jan Nilsson for a brief chat about business development.

Can you briefly describe how CombiGene pursues its business development?

"I can at least give it a try," replies Jan. "Developing a drug takes a long time and always involves some form of financial risk. As far as the situation for us at CombiGene goes, the longer we spend working on our projects, the higher their potential value. When it comes to our CG01 epilepsy project, we have identified several possible big pharma partners with whom we have an ongoing dialogue. Quite simply, we take every opportunity we can to keep them updated on the progress of the project. Several companies have expressed a definite interest, but common to all is that they would prefer to see the results from studies in humans before entering into partnership. Not surprisingly, this is completely in line with the scenario we've always followed." Jan pauses briefly. "Then, of course, there is another angle to our strategy, that is to say, we wish to inlicense research assets, which we will take to the preclinical phase and subsequently to studies in humans. The lipodystrophy project, which we inlicensed from Lipigon earlier this autumn, is one example."

Can you give us a rundown on the activities CombiGene has participated in during the year?

"Gladly. 2019 has been an intensive year of business development. In April Annika Ericsson (Senior Project Manager) and I attended the Cell & Gene Meeting on the Med in Barcelona, Spain, where we met several contract research organizations, some representatives from large pharmaceutical companies, and several life science investors. In April Karin Agerman (Chief Research and Development Officer) was invited to speak at the Swedish 4th Annual ATMP Conference in Gothenburg, where she gave a much appreciated presentation entitled Turning research into clinical use – gene therapy for treatment-resistant epilepsy. In May I was invited to speak at AstraZeneca's conference AZ Exchange, and in June CombiGene's chairman Arne Ferstad and I attended BIO 2019 in Philadelphia, USA, where we met with potential partners, investors and an American patient organization. I rounded off the autumn with a visit to NLS Days on 10-12 September in Malmö, where I had several interesting meetings with investors and big pharma companies. In November I also attended BioEurope in Hamburg, with further meetings with investors and major pharma companies."

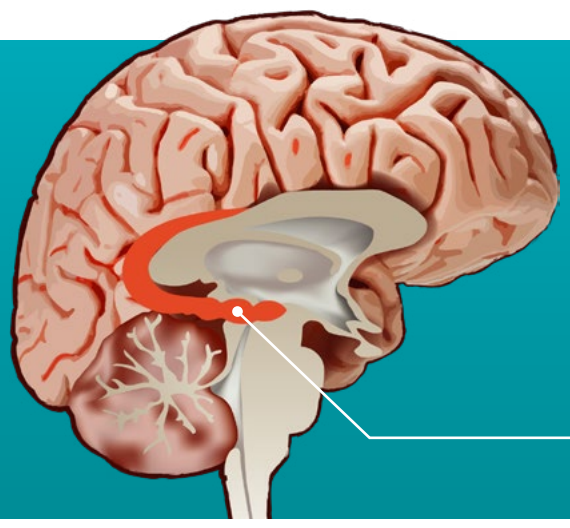
"At CombiGene we take every opportunity to meet companies that interest us and could one day be partners"

Just as Jan is concluding, Karin Agerman and Annika Ericsson look into the room.

"Don't forget that I gave a presentation on CombiGene at Biotech-Hanse Forum 2019 on June13th in Stockholm," says Annika. "And Annika and I were at the annual European Society of Gene and Cell Therapy conference (ESGCT) in Barcelona in October," adds Karin.

That sounds like an intensive year.

"In many ways it has been, but that's how it is. At CombiGene we take every opportunity to meet companies that interest us and could one day be partners. Putting an outlicensing deal together takes a long time and demands continuous communication. At the same time, it's tremendously stimulating and even more fun the farther we get with our projects."



Our CRO partner must be able to administer the candidate drug, CG01, to the hippocampus, i.e., the part of the brain that is to be treated with CG01.

INSIGHT

Academic successes for CombiGene's scientific founders

■ *Professor Merab Kokaia's and associate professor David Woldbyes proof-of-concept study has been published in Molecular Therapy: Methods & Clinical Development*

On February 19th 2018, Professor Merab Kokaia and associate professor David Woldbye, CombiGene's scientific founders, presented final data from the preclinical proof-of-concept study for CG01 that was conducted in 2017. The study confirmed that CG01 has clinically relevant anti-seizure effects in the form of fewer and shorter seizures. Following peer review, the study has now been published in Molecular Therapy: Methods & Clinical Development.

The study was designed to reflect a probable clinical scenario for treatment of epilepsy in humans. With the aid of magnetic resonance imaging, the hippocampus, i.e., the part of the brain in which the epileptic seizure arose and to which treatment was targeted, was localized. Subsequently, a unilateral focal treatment with CG01 was administered to the epileptic focus. Results of the treatment have been analysed with video EEG (electroencephalography) to observe and measure electrical activity in the brain during a seizure.

A histological analysis (tissue analysis) was also used to find detailed answers with respect to deviations in brain tissue and to determine how CG01 is expressed in the brain.

The results of the study show that CG01 has clinically relevant anti-seizure effects. Epileptic seizures were both fewer and shorter in duration and some of the animals were completely free of seizures after being treated.

For further readings:

The article on the proof-of-concept study is available here:
https://www.cell.com/molecular-therapy-family/methods/fulltext/S2329-0501(19)30102-0

CombiGene's CDMO partner Cobra is on the advance

These are busy times for CombiGene's CDMO partner, Cobra Biologics. To meet increasing demand for GMP manufacturing, Cobra is building Sweden's first facility for production of plasmid DNA for gene therapy. In November, it was announced that Cognate BioServices is acquiring Cobra to augment its own manufacturing of cell and cell-mediated gene-therapy products.

This will have no implications for the CG01 project. Agreed schedules and production volumes are fixed and Cognate BioServices's acquisition of Cobra clearly shows that CombiGene has chosen one of the world's leading manufacturers of gene-therapy products, and that CombiGene now has access to world-leading infrastructure.

cobra:bio

Cobra Biologics

Cobra Biologics is a leading international contract development and manufacturing organisation (CDMO) providing biologics and pharmaceuticals for preclinical, clinical and commercial supply. Cobra has broad expertise in areas including production of DNA, viral vectors, microbiota and proteins. The company is based at Keele Science Park, UK, and in Matfors, Sweden.

Events

PREVIOUS EVENTS

10-12 December 2019
Gene Therapy for Neurological Disorder, Boston
https://gtxn-summit.com

11-13 November 2019
BIO-Europe, Hamburg
https://ebdgroup.knect365.com/bioeurope/

4 November 2019
Stora Aktiedagen, Gothenburg
https://www.aktiespararna.se/aktiviteter/stora-atiedagen-goteborg-0

22-25 October 2019
European Society of Gene and Cell Therapy 27th annual congress, Barcelona
https://www.esgct.eu/congress/barcelona-2019.aspx

Read all of our news in one place

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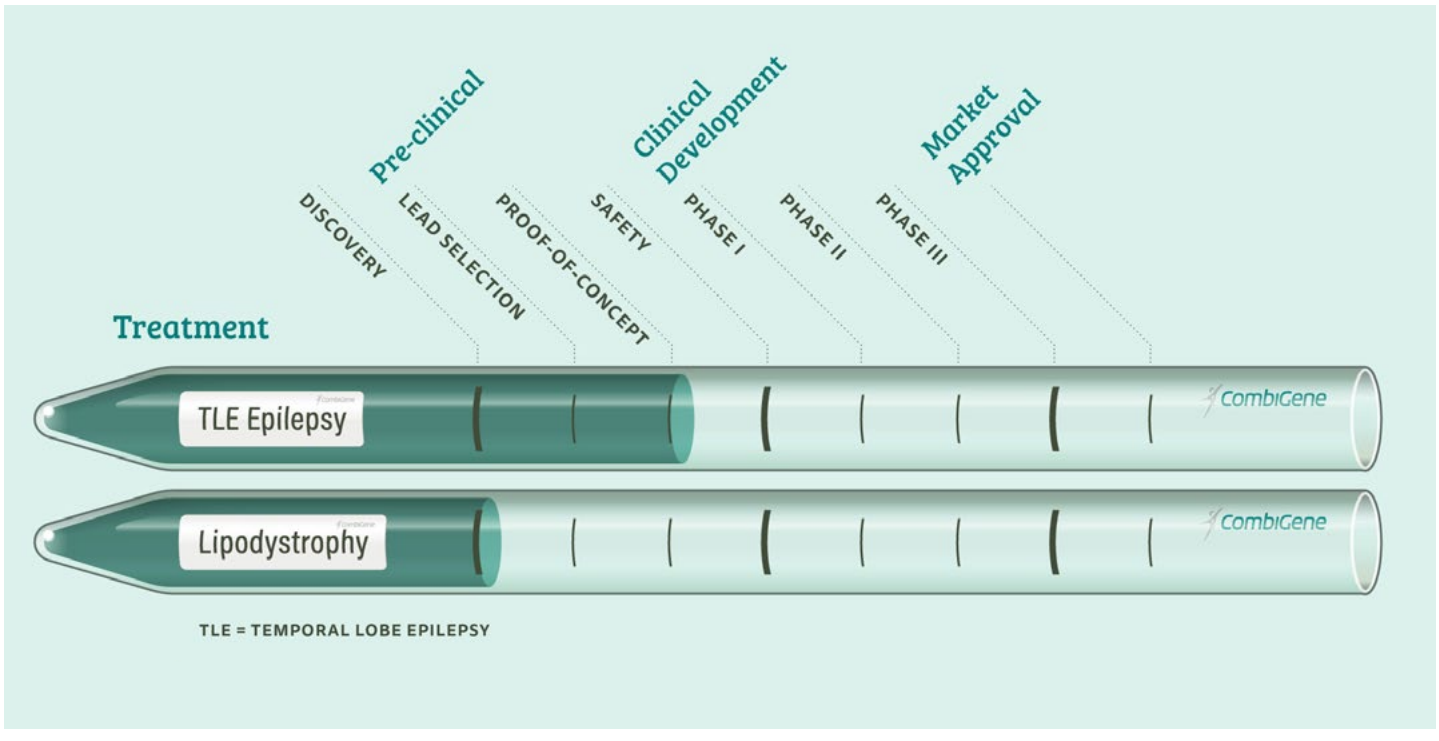

PROJECT OVERVIEW

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.

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 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. 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 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.

www.combigene.com