Final preclinical studies in 2021 pave the way for the first study in humans in 2022

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The epilepsy project CG01 is estimated to have an annual sales potential of USD 750–1500 million

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NEWS FROM COMBIGENE AB

ISSUE 4 • 2020

The epilepsy project CG01 moves towards clinical studies in 2022

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CombiGene

The gene therapy explorer

EDITORIAL

Final preclinical studies in 2021 pave the way for the first study in humans in 2022

■ At CombiGene, we have just put a very intense period behind us as we established an effective and future-proof production platform for our drug candidate CG01, which is developed for focal, drug-resistant epilepsy.

During the autumn we will now test our new production platform to quality assure the entire process and produce material for the final preclinical studies. This work is expected to be completed sometime around the end of 2020 or beginning 2021, which means that we will be able to start the final preclinical studies early in 2021.

Next year will thus be a year in which we focus on completing the preclinical program with the important biodistribution and safety studies.

When the preclinical program is completed, we will apply for permission to start the first study in humans, so-called clinical studies. If everything goes according to plan – and at CombiGene we have put an honor in keeping our plans – we will be able to begin the clinical program sometime in 2022.

Since so much has happened in the CG01 project recently and since the path to the first human study is now clear, we want to make this special edition of Genevägen where we present this very exciting project in a cohesive way.

Jan Nilsson,
CEO

■ *All pharmaceutical productions are performed under a strict regulatory framework called Good Manufacturing Practice or GMP. The purpose of this regulation is to ensure that all pharmaceutical products are of the same quality every time they are produced and thereby safe to use in healthcare and have the intended effect. This also applies, of course, to gene therapeutic treatments such as CombiGene's drug candidate CG01, which is being developed as a therapy for drug-resistant focal epilepsy. In 2020, CombiGene has put a lot of effort into building a coherent and quality-assured production platform that is easy to scale up for future commercial volumes.*

The challenges of establishing a production that can deliver material for the final preclinical studies, future studies in humans and future commercial clinical use have been significant and involved several different suppliers. In this article, Ingeneious reviews all the steps taken by the CombiGene team in 2020 to build a scalable and future-proof production platform.

Starting material for production

Before the actual production of CG01 can begin, the plasmids that are the starting material for production must be produced.

"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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“The fact that we now have a complete and future safe production platform is a very significant milestone in the CG01 project.

Three different plasmids (circular DNA molecules) are required for production. One of these plasmids is a carrier of DNA that encodes for CG01's active substances neuropeptide Y and receptor Y2. To ensure that the quality of the plasmids is exactly the same at each individual production batch, CombiGene has together with Cobra Biologics developed so-called master cell banks that ensure that the quality of the plasmids is exactly the same at each future production time. In other words, master cell banks are a cornerstone of CG01 quality assurance.

Analysis methods for quality assurance

The next step to quality assure the production of CG01 was to develop both general and specific analytical methods and integrate them into the production process. The general analyses are common to similar AAV gene therapies, while the specific analyses are specially developed for CG01.

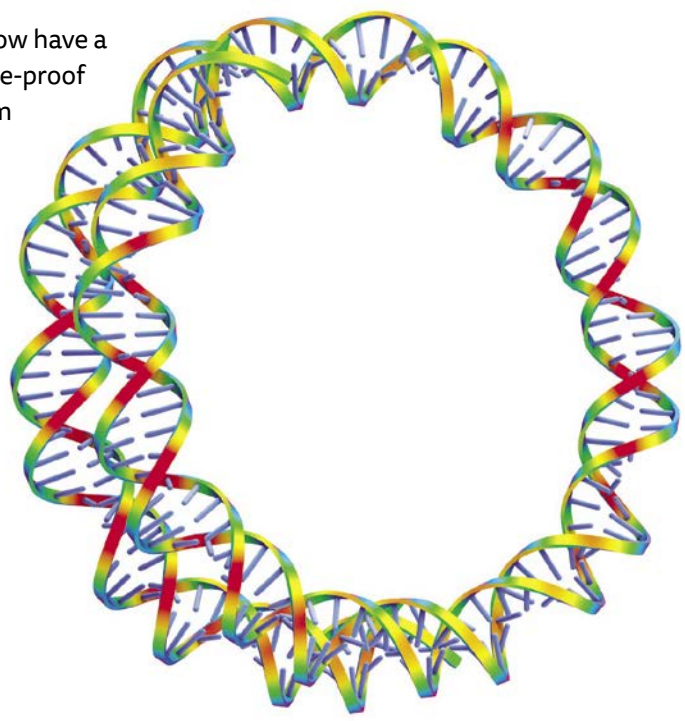
In 2020, CombiGene, together with the British organization CGT Catapult, has developed seven different analyses for the production of CG01.

Selection of production method

There are mainly two different types of production methods for virus-based gene therapies, adherent production and suspension-based production. The adherent method is well suited for the production of limited volumes. CombiGene has so far used the adherent production method in the CG01 project to produce materials for the many preclinical studies conducted. As CG01 is developed for the treatment of epilepsy, the potential number of patients is considerably greater than that of the gene therapies developed for the treatment of rare diseases.

CombiGene expects to be able to treat up to 10,000 patients a year with CG01. Using an adherent production method at that stage is not practical or economical. CombiGene has therefore decided to establish a suspension-based production method that will be able to produce materials not only for the final preclinical and human studies, but also have the capacity to meet future commercial volume requirements. At the beginning of September, CombiGene therefore signed an agreement for the production of CG01 with the Spanish producer Viralgen. Less than a month later, production of the first batch of CG01 began. The material from this first production will be analysed during the final quarter of the year to ensure that it meets all the high quality requirements. When the extensive quality work is completed, the produced material will be used in the future safety studies.

“The fact that we now have a complete and future-proof production platform is a very significant milestone in the CG01 project,” says CombiGene CEO Jan Nilsson. “We now have the capacity to produce the volumes we need to meet future commercial demand. It is also very valuable from a regulatory point of view that we can conduct the final preclinical studies and the upcoming clinical studies in humans with the same production platform that we will use for commercial production.”



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EPILEPSY PROJECT CG01

PLAN FOR 2021

Concluding preclinical studies

Since 2014, CombiGene has conducted a number of preclinical studies that have moved the epilepsy project CG01 forward. All studies have been completed according to plan and delivered positive results.

Among the most important studies are the screening studies to select the final drug candidate, the dose escalation study to determine which levels of the active substances neuropeptide Y and receptor Y2 are required to achieve a medical effect and the concept verification study. The results in these studies have consistently been positive and demonstrated clear antiepileptic effects, just as intended. Studies in human brain tissue also show that neuropeptide Y and the receptor Y2 are expressed from CG01 as intended.

CombiGene has also conducted a pharmacokinetics study confirming that CG01 creates a long-term expression of the active substances neuropeptide Y and receptor Y2 as well as a learning and memory study showing that CG01 has no significant negative impact on cognitive functions.

The preclinical program will be completed in 2021

The preclinical program of CG01 is concluded with two large studies – a biodistribution study and a safety study – that will be conducted together with CombiGene's CRO partner Northern Biomedical Research (NBR).

The biodistribution study is conducted to see where in the body CG01 appears. CG01 is injected directly into the area of the brain where the epileptic seizures occur. Most of the drug will remain in the injected part of the brain, but a smaller portion is expected to get into the blood stream and spread in the body. Through the biodistribution study CombiGene will get answers as to where in which organs this smaller part of CG01 appears. This knowledge will be central in the preparation of the treatment protocol for CG01.

The safety study is carried out to detect possible adverse effects of a treatment with CG01. Two of the aspects that will be studied are the physical procedure, i.e. that CG01 is injected into the brain, and possible immune reactions. The study will follow both what happens instantaneously in connection with the infusion itself and what possible effects can be seen over time with the expression of the two proteins, NPY and Y2. The study is conducted to ensure that CG01 can be given to patients safely.

Both the biodistribution study and the safety study will be conducted with the material that Viralgen produced in the autumn of 2020. This production is expected to be released in early 2021 after completion of quality assurance. The studies themselves take approximately six months. Thereafter extensive analyses will take place before the results can be presented.

"With the biodistribution and safety studies, the preclinical program of CG01 is concluded.

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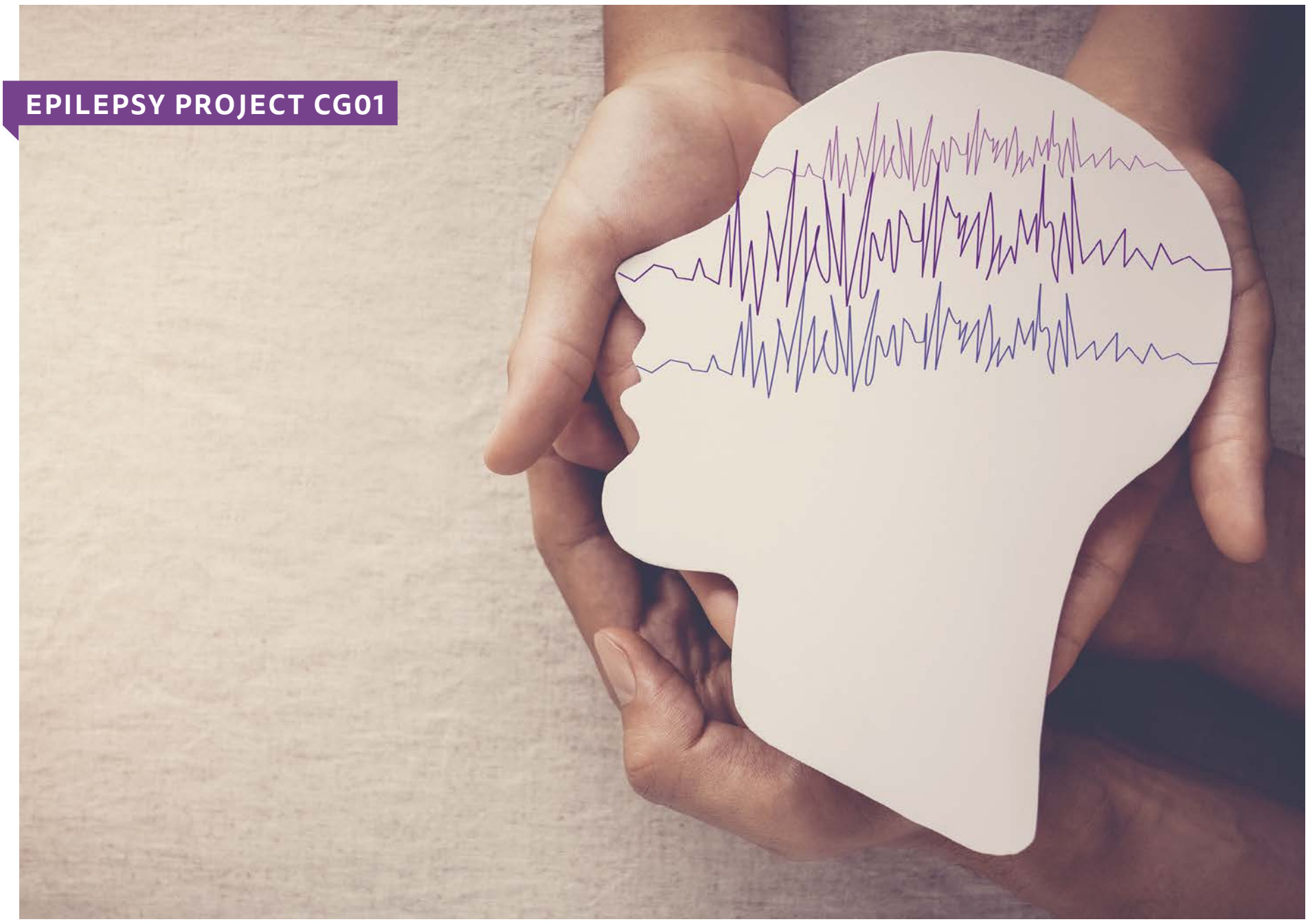

EPILEPSY PROJECT CG01

PLAN FOR 2022

First study in humans

When CG01's preclinical program is completed with an approved safety profile, it is time for one of the project's most important milestones: the first study in humans, a so-called clinical study, which can begin when CombiGene has received approval of their application for clinical trial by the authorities. As a rule, a clinical development program contains three different types of studies (phase I – III) before a drug can be launched on the market. After market introduction, further studies (Phase IV) are usually carried out.

The first study, the Phase I study, is conducted to ensure the safety profile of the drug. With traditional drugs, Phase I studies are usually conducted with healthy volunteers, but CombiGene will conduct all clinical studies with patients, which will mean that the company receives indications of the efficacy of CG01 in humans at an early stage. The Phase II study is conducted in a larger number of patients to show that the drug has the intended effect. During the Phase II study, work continues to find the optimal dose and safety and tolerability continues to be documented. In Phase III studies, a larger number of patients are involved and the effects of the drug are compared with current treatments or placebos.

Although CG01's clinical program will not begin until 2022, the company has already started extensive preparations.

The first study in humans is one of the most important milestones in all drug development and often involves a marked improvement in the evaluation of the project.

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THE MARKET FOR THE EPILEPSY PROJECT CG01

= Huge potential for CombiGene

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

Epilepsy is a major global problem. Studies show that 0.6 to 0.8% of the world's population suffers from the disease. In 2016, there were 5.7 million diagnosed epilepsy patients in the US, EU4 + UK and Japan. Approximately one third of these patients do not respond to traditional medical treatment. Of this third, about 60 percent have focal epilepsy, i.e. an epilepsy in which the seizure occurs in a well-defined area of the brain. It is this group of epileptics that CombiGene intends to help with its drug candidate CG01.

47,000 new patients each year

Every year, approximately 47,000 drug-resistant patients with focal epilepsy are estimated to be added in the US, EU4 + UK, Japan and China. CombiGene believes that it is realistic that 10-20 percent of these patients will be treated with the company's CG01. Assuming, for example, that the therapy cost per patient is somewhere between $134,000 and $200,000 (which compared to approved gene therapy drugs is low), it provides sales between $750-$1,500 million annually.

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Talk to us at CombiGene!

In recent months CombiGene has made great strides in our epilepsy project CG01. After a very intense period, we now have a complete production platform in place. This means that we now plan to conduct the final preclinical studies in 2021 and begin the first studies in humans in 2022.

Our development would not have been possible without the trust that our shareholders have shown us. We want you to know that we appreciate your support immensely. For two days we therefore invite you to ask us questions at CombiGene. We promise to answer the first 30 questions as best as we can.

Here's how it's done:

*Read more on **fraga.combigene.com**, ask your question and read our answers when published.*

Keep in mind:

- *Keep the question as brief and concrete as possible.*
- *Only ONE question per post*
- *We cannot/may not answer share price affecting or regulatory questions.*

Jan Nilsson *CEO*
Karin Agerman *Chief Research and Development Officer*
Annika Ericsson *Senior Project Manager*

Read all of our news in one place

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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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