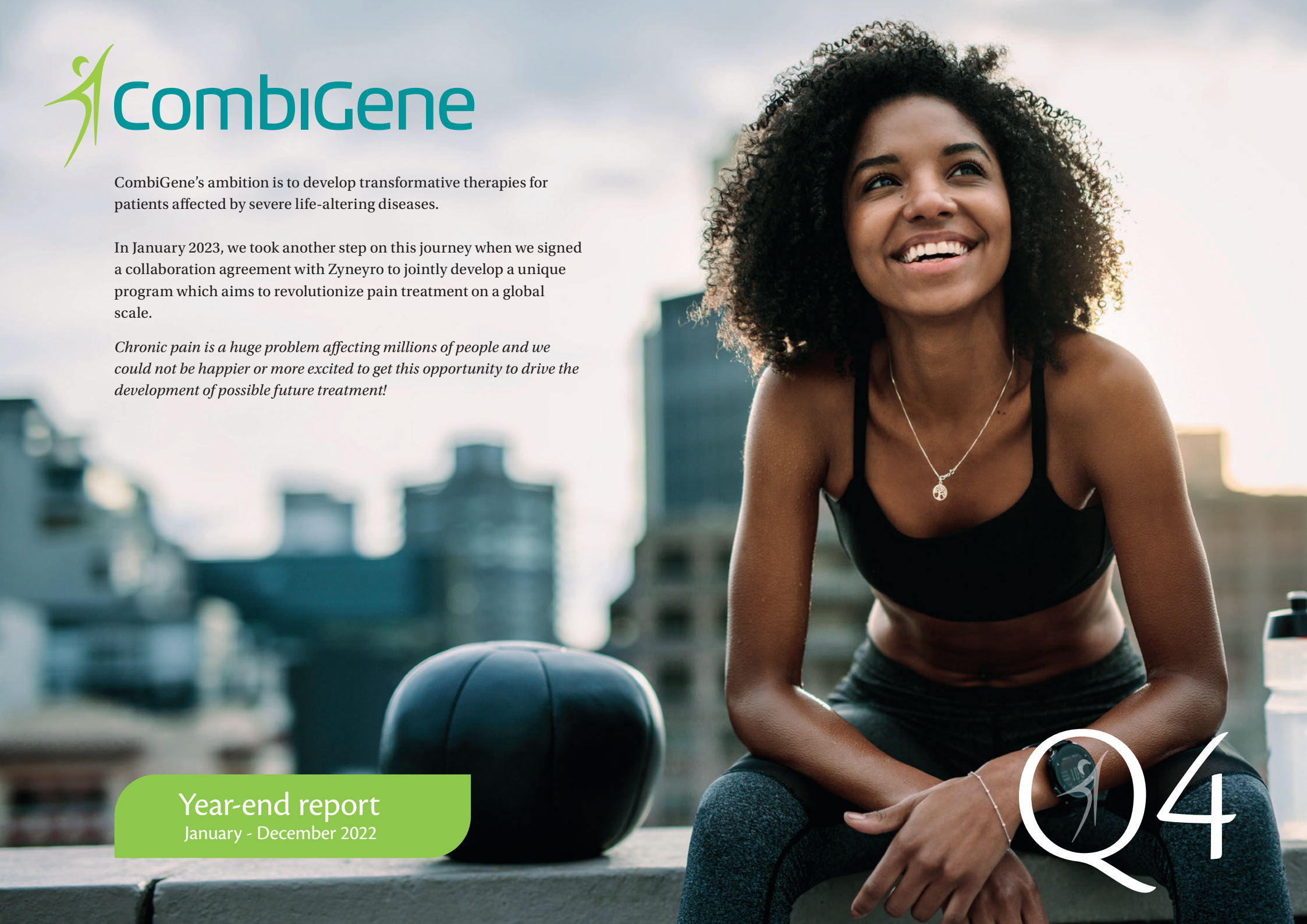
CombiGene

CombiGene's ambition is to develop transformative therapies for patients affected by severe life-altering diseases.

In January 2023, we took another step on this journey when we signed a collaboration agreement with Zyneyro to jointly develop a unique program which aims to revolutionize pain treatment on a global scale.

Chronic pain is a huge problem affecting millions of people and we could not be happier or more excited to get this opportunity to drive the development of possible future treatment!



Year-end report

January - December 2022

Q4

Summary of the report

Events during the period

- No reportable events took place during the period.

Events after the end of the period

- CombiGene enters into a collaboration agreement with Zyneyro for the development of a unique concept for effective relief of chronic pain. The agreement with Zyneyro is a cooperation agreement that means that Zyneyro and CombiGene share the project's costs and revenues equally. According to the agreement CombiGene will pay Zyneyro an upfront of DKK 5 million in connection with the signing of the agreement. CombiGene has furthermore committed to pay an additional maximum of DKK 11.4 million in continued development support towards a clinical study in Phase 1.

Financial information

October – December 2022

- Net sales: TSEK 5,346 (84,042).
- Other operating revenues: TSEK 674 (1,098).
- Profit from financial items: TSEK -11,942 (57,448).
- Earnings per share: SEK -0.60 (2.90).

January – December 2022

- Net sales: TSEK 26,699 (84,042).
- Other operating revenues: TSEK 15,044 (7,478).
- Profit from financial items: TSEK -6,157 (20,965).
- Earnings per share: SEK -0.31 (1.21).
- Cash and cash equivalents as per the end of the reporting period: TSEK 131,777 (136,744).
- Equity ratio as per the end of the reporting period: 96 (95) %.

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Note to the reader

Amounts in brackets refer to the corresponding period of the previous year.

CombiGene at a glance

The company

CombiGene is the only listed gene therapy company in the Nordic Region. The company was listed on May 25, 2015 on SPOTLIGHT Stock Market (then AktieTorget). In December 2018, CombiGene was approved for listing on Nasdaq First North Stockholm.

Our projects

CombiGene currently has three projects:

- The pain program COZY which consists of one peptide treatment and one gene therapy
- The lipodystrophy project CGT2
- The epilepsy project CG01, which was outlicensed to Spark Therapeutics 2021

Our team

CombiGene has 11 employess. Our team is made up of very knowledgeable and experienced professionals with longstanding experience from the international pharma industry and the biotech arena and has a thorough knowledge of different aspects of gene therapy.

Cash position

At the end of the fourth quarter 2022, CombiGene had cash and cash equivalents amounting to TSEK 131,777 (136,744).

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

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

Our new pain program COZY has the potential to improve life for millions of people

On January 9, 2023, we signed a collaboration agreement with the Danish company Zyneyro regarding the continued development of treatments for chronic pain conditions – a peptide with great potential for short-term treatment and a gene therapy with potentially lifelong effects. The agreement is a result of our focused business development effort. The treatments for pain that are available today have several shortcomings, and together with Zyneyro we see a huge opportunity to develop effective pain relief without the side effects that today's treatments often give rise to.

The agreement with Zyneyro is a cooperation agreement that means that Zyneyro and CombiGene share the project's costs and revenues equally. According to the agreement CombiGene will pay Zyneyro an upfront of DKK 5 million in connection with the signing of the agreement. CombiGene has furthermore committed to pay an additional maximum of DKK 11.4 million in continued development support towards a clinical study in Phase 1.

The pain program consists of two projects: a peptide treatment and a gene therapy. The peptide-based treatment is expected to be ready for the first human dosing within a few years, while the AAV-based treatment will need additional development time to reach the same point.

Pain is a major global problem

About 20 percent of the world's adult population suffers from some form of chronic pain. Conventional treatment of severe pain consists primarily of anti-inflammatory drugs, antidepressants, antispasmodic drugs, and opioids (a group of substances with a morphine-like mechanism of action).

The problem with these treatments is that they are not specifically developed to treat chronic pain. The pain relief that is achieved often has a number of disabling side effects such as addiction problems, depression, anxiety, fatigue, impaired physical and mental ability, and harmful impact on the gastrointestinal and cardiovascular systems. In the United States, an estimated 700,000 people have died due to opioid abuse in the past 20 years.

Devastating impact on the individual

Living with constant pain is incredibly tiring. Long-term/chronic pain risks to completely dominate life with restrictions in mobility and daily activities and inability to work, which often results in a low quality of life and a negative social situation. It is not uncommon for pain to lead to stress, sleep problems, depression, and anxiety, which in turn can enhance the pain experience. And, as we have seen with the opioid crisis in the US, the risk of developing dependance is very significant.

COZY – a unique concept

The program consists of two projects: a peptide for short-term treatment (COZY01) and a gene therapy treatment (COZY02) with potentially lifelong effect. The patient's

clinical picture and potentially other factors will guide the choice of therapy.

In severe temporary pain conditions, the intention is to administer the peptide directly to the patient on one or more occasions to achieve effective pain relief.

In severe chronic pain conditions, pain relief can be achieved by treating the patient with an AAV vector that "instructs" the body to establish the pain-relieving mechanism on its own. In this way, one can achieve long-term pain relief without daily medication.

Further studies required in our lipodystrophy project CGT2

Our ambition for 2022 was to bring the CGT2 project to the stage where a proof-of-concept study can be initiated. However, some of the studies that were carried out last year gave inconclusive results and need to be repeated. We therefore concluded that further studies are needed before we proceed to the preclinical proof-of-concept study.

Collaboration with Spark Therapeutics

We have now been working together with Spark since mid-October 2021, and we have developed a very good collaboration. As I have mentioned before, I am particularly pleased with the decision to prioritize the expansion of CG01's clinical development program to include the U.S. as this will allow the project to find a natural foothold in the world's largest pharmaceutical market, and at the same time Spark can utilize their impressive resources, know-how and networks in an optimal way.

Our business development continues with undiminished force

Our new collaboration with Zyneyro on the pain program has strengthened CombiGene's position quite decisively. We now have two projects that target large patient populations, the epilepsy project CG01 and the pain program COZY – quite a unique situation for a gene therapy company. Alongside these projects we also have the lipodystrophy project CGT2, which targets a rather small number of patients.

Going forward, it is our ambition to evaluate interesting opportunities to find additional projects to complement our current portfolio. Our focused efforts within this area continues with the same force as in 2022.

Outlook

We are now looking forward to another intense year where we will continue to develop all our projects as successfully as possible and continue our search for new and promising assets for inlicensing – all with the ambition to build an ever-stronger company.

Jan Nilsson
CEO

The pain program COZY – a unique opportunity to revolutionize pain treatment on a global scale

The pain program COZY is being developed jointly with the Danish company Zyneyro. The goal is to develop an effective treatment for severe chronic pain, a relatively common and often difficult-to-treat condition. The program consists of two projects – a peptide treatment and a gene therapy treatment (AAV), each of which builds upon a new principle for pain treatment, but which are both based on the same pain-relieving mechanism. In the peptide project, we are developing a synthetic molecule for short-term treatment and in the AAV project, we are developing a gene therapy for severely debilitating pain conditions with potentially lifelong effect.

CombiGene's and Zyneyro's pain program is being developed to offer effective pain relief without the side effects that today's treatments often give rise to. This is possible thanks to Zyneyro's researchers having identified a new biological mechanism of action, which forms the basis for the drug candidates.

The agreement with Zyneyro

The agreement with Zyneyro is a cooperation agreement that means that Zyneyro and CombiGene share the project's costs and revenues equally. According to the agreement CombiGene will pay Zyneyro an upfront of DKK 5 million in connection with the signing of the agreement. CombiGene has furthermore committed to pay an additional maximum of DKK 11.4 million in continued development support towards clinical Phase 1.

One program - two projects

The program consists of two projects: a peptide for short-term treatment (COZY01) and a gene therapy treatment (COZY02) with potentially lifelong effect. The patient's disease picture and possibly other factors will potentially guide the choice of therapy.

In severe temporary pain conditions, the intention is to administer the peptide directly to the patient on one or more occasions to achieve effective pain relief.

In severe chronic pain conditions such as neuropathic pain, phantom pain and pain associated with various types of nerve injuries, which in conventional treatment require daily medication, our intention is to achieve pain relief by treating the patient with an AAV vector that "instructs" the body to establish the pain-relieving mechanism itself. In this way, one can achieve long-term pain relief without daily medication. Since the AAV vector encodes the peptide, the intention is that both the mechanism of action and the effect are the same as in direct administration of the peptide.

The concept could potentially also offer an opportunity to check that a patient responds well to treatment with the peptide before proceeding with the more costly gene therapy. By using the peptide treatment on potential gene therapy patients before a costly AAV treatment is initiated, it would possibly be feasible to increase the accuracy of the gene therapy treatment.

In the United States, between four and eight percent of the population is estimated to be affected by high impact chronic pain.

Pain is a major global problem

About 20 percent of the world's adult population suffers from some form of chronic pain. In the United States, between four and eight percent of the population is estimated to be affected by high impact chronic pain. Conventional treatment of severe pain consists primarily of anti-inflammatory drugs, antidepressants, antispasmodic drugs, and opioids (a group of substances with a morphine-like mechanism of action). [1]

The problem with these treatments is that they are not specifically developed to treat chronic pain. The pain relief that is achieved therefore often has a number of disabling side effects such as addiction problems, depression, anxiety, fatigue, impaired physical and mental ability. In the United States, an estimated 700,000 people have died due to opioid abuse in the past 20 years.

[1] Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016; CDC; Morbidity and Mortality Weekly Report Weekly / Vol. 67 / No. 36 September 14, 2018

The scientific basis of the COZY program

The program is based on discoveries regarding the role of an intracellular protein called PICK1 (protein interacting with C-kinase 1) in modulating neuronal signal transmission via AMPA receptors in pain. Simply put, it can be described as PICK1 binds to and controls the localization and activation of receptors that participate in the transmission of pain signals between nerves in chronic pain. By blocking the interaction between PICK1 and receptor, you prevent a certain type of receptors from reaching the cell membrane and becoming activated, thereby inhibiting the pain signal.

(Sørensen AT, Rombach J, Gether U, Madsen KL. The Scaffold Protein PICK1 as a target in chronic pain. Cells. 2022;11(8):1255.)

Zyneyro's CEO Peter Horn Møller talks about the unique features of the pain program COZY

"There are several things that make this program unique. First, our scientific team is the group in the world that knows most about the biological target that is at the heart of our concept, PICK1. We have been working on PICK1 and PICK1's role in pain for the past 20 years at the University of Copenhagen.

"Among other things, we have found that PICK1 regulates a special receptor that is of central importance for the development of chronic pain. Unfortunately, you cannot block this receptor directly due to side effects. However, PICK1 is required to move this receptor to the surface of patients' nerve cells and our approach is to block PICK1, thereby ensuring that the receptor does not come to the surface of the cell at all. This is a unique principle and has been shown to be exceptionally effective in relieving chronic pain in our experimental models.

"Our data from the models tested show that we can eliminate the pain and restore normal sensitivity without the usual side effects and without creating addiction. This is actually groundbreaking in itself. At the same time, we have developed a therapeutic variant, which can be given as gene therapy, where the body itself produces the drug. This means that you ultimately only need one treatment to potentially achieve lifelong pain relief.

"All in all, if successful, this will be life-changing for the many millions of pain patients for whom there is no effective treatment available today."

COZY01 – peptide treatment of severe temporary pain conditions

The peptide treatment is based on the molecule mPD5, which has shown good effects in various preclinical models of chronic pain. Further development will focus on carrying out as quickly and efficiently as possible the necessary preclinical studies to evaluate safety and toxicology, as well as producing clinical trial material with the aim of obtaining the approval of a regulatory authority to conduct the first human clinical trials with mPD5.

An independent evaluation of the potential of mPD5 as a future pain treatment is underway at the National Institute of Health (NIH) research institute in the US, in a government-funded program (Preclinical Screening Platform for Pain, PSPP). The peptide, mPD5, has undergone the first test level out of three and has been selected to move on to the next level where the substance will be tested in different pain models.

COZY02 – gene therapy treatment for severe chronic pain conditions

A prototype of the AAV vector that acts as a carrier of the genetic material in gene therapy has been developed by Zyneyro and tested in a preclinical pain model with very good and long-lasting effect. The upcoming work is focused on optimizing the genetic material to be included in the vector. AAV is the vector type that CombiGene has extensive experience of from our other projects. When the vector is optimized, preclinical studies follow to investigate and characterize distribution, protein expression, efficacy, and toxicology.

In parallel with the preclinical development, we will develop a process for the manufacturing of the selected vector for preclinical studies and for future clinical trials. Data from this work will form the basis for seeking permission to conduct a clinical trial in patients with severe chronic pain.

CGT2 – further studies needed before a new schedule for the proof-of-concept study can be made

CGT2, CombiGene's project to develop a gene therapy treatment for partial lipodystrophy, is in early preclinical development. The first step in designing gene therapy vectors and testing them in vitro (tests on different liver cells) has been carried out with good results. Since then, several in vivo studies have been performed to evaluate efficacy and gradually narrow down the number of potential gene therapy candidates.

Further studies needed

The ambition for 2022 was to bring the CGT2 project to the stage where a proof-of-concept study could be initiated. However, some of the studies that were carried out in 2022 gave ambiguous results and need to be repeated. For example, we need to establish whether the lack of clear treatment effect in some models is due to insufficient expression of our gene therapy vector or whether the underlying hypothesis for the mechanism of action of CGT2 is incorrect. CombiGene has therefore decided to undertake further studies before it is possible to proceed to the preclinical proof-of-concept study.

Grants from the EU's Eurostars international funding program

In February 2021, the Lipodystrophy project was awarded EUR 882,500 in project grants by the EU's Eurostars international funding program. Through this grant, CombiGene collaborates with the University Medical Center Hamburg-Eppendorf and its experts in lipid research. The Eurostars grant also covers our collaboration with Accelero, a German CRO company that works on developing analytical methods needed for the future development of CGT2.

PCT application

In August 2021, CombiGene submitted a PCT application to protect the vectors developed within the CGT2 project. The application builds on the UK patent application filed in 2020 and is a natural next step in ensuring adequate patent protection for the lipodystrophy project CGT2.

Important agreement with Professor Ormond MacDougald

In addition to the collaboration agreements with Stockholm University, University Medical Center Hamburg-Eppendorf and Accelero, CombiGene also has an agreement with Professor Ormond MacDougald at the University of Michigan Medical School in the US. The agreement comprises one pilot study and one main study in which CombiGene's most promising gene therapy candidate within the lipodystrophy project CGT2 will be tried and evaluated.

Milestones

2019
- The project is in-licensing from Lipigon.

2020
- Design of expression plasmids, which are the starting material for gene-therapeutic vectors CombiGene intends to develop for treatment of partial lipodystrophy.
- In vitro studies (tests on liver cells) show intended protein expression.
- Priority-based patent application is filed with the UK Patent Office.
- In vivo studies for evaluation of the different gene therapy vectors are initiated.

2021
- The lipodystrophy project receives EUR 882,500 in development grants from the EU Eurostars program.
- PCT application submitted.

2022
- CombiGene signs agreement with University of Michigan to evaluate the leading gene therapy candidate within the lipodystrophy project CGT2.

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

CG01 – outlicensed to Spark Therapeutics since October 2021

The epilepsy project CG01 was outlicensed to Spark Therapeutics in October 2021, and the remainder of the preclinical phase is now jointly run by the two companies. Once the project enters clinical phase, Spark will assume full responsibility for design and execution. Since October 2021, Spark also covers all costs associated with the preclinical development of CG01.

The scope of the agreement

The collaboration and licensing agreement between CombiGene and Spark is an exclusive worldwide licensing agreement, which gives Spark the right to develop the CG01 project throughout the preclinical and clinical phases of the program, to manufacture CG01, and to commercialize CG01 to the global market.

The financial terms of the agreement

The total potential value of the agreement amounts to USD 328.5 million, excluding royalties. The upfront payment amounted to USD 8.5 million. Milestone payments through the preclinical and clinical phases amount, in total, to USD 50 million. Royalties on future sales of CG01 range from the mid-single digits up to low double-digits based on net sales. All milestone payments will be communicated through CombiGene press releases as they occur.

The preclinical development program

The remainder of the preclinical program is performed by Spark in collaboration with CombiGene. Since the agreement was signed, the preclinical program has been expanded into a cohesive plan to meet the needs of an extended clinical trial submission which focuses on the US.

The clinical development program

Once the preclinical program is completed, Spark will assume responsibility for the design and execution of the clinical development. All results and knowhow from the preparatory work CombiGene made prior to the collaboration and licensing agreement has been transferred to Spark. As part of our current agreement, Spark will cover all costs on the clinical development work.

Communication regarding program updates and timeline

Future updates regarding the CG01 program will be provided by Spark in line with their standard practice.

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

CombiGene's ambitious business development continues to focus on finding new projects and developing partner relationships

Through dedicated efforts and, not least, the exclusive agreement with Spark Therapeutics in 2021, CombiGene is regarded as an innovative player in the international pharmaceutical market. The company has an extensive network of partners with specific competences within gene therapy. CombiGene has also ongoing dialogues with a number of Big Pharma companies to lay the ground for potential future collaborations.

CombiGene's business development spans three areas
Since the company was first established, CombiGene has had the ambition become a significant force in gene therapy. Recently, we have strengthened our organization and are now focusing on three distinct areas:

- In-licensing of new projects with high potential for value creation for CombiGene. The recent collaboration agreement with Zyneyro is a prime example of this.
- Alliances with partners and service companies that allow CombiGene to further develop licensed projects.
- Out-licensing of projects that target significant patient populations in late preclinical/early clinical phase. When it comes to drug candidates targeting limited patient populations, CombiGene may drive development and commercialization under its own management or seek strategic partnerships.

Successes so far
So far, CombiGene's business development has resulted in outlicensing of the CG01 epilepsy project to Spark Therapeutics in an agreement with a potential value of USD 328.5 million excluding royalties, the in-licensing of the CGT2 lipodystrophy project from Lipigon and most recently the collaboration agreement with Zyneyro for the pain program COZY.

Furthermore, CombiGene has established collaborations with a number of CRO and CDMO companies within the CG01 and CGT2 projects.

The importance of a portfolio of projects
Through the agreement with Spark, CombiGene became well placed to take the next step in the company's development by in-licensing additional gene therapy projects. The first tangible result of this is of course the collaboration agreement with Zyneyro.

We are now continuing our search for new projects to in-license with the ambition to build a broad portfolio that includes projects in several phases of drug development, ranging from projects in really early phase to projects in clinical development. One reason to have a broad portfolio is that far from all drug candidates make it all the way to market approval. By building a broad portfolio, chances of success increase.

The CombiGene share

CombiGene is a public company and is listed on Nasdaq First North Growth market. The share capital of the Company shall amount to no less than SEK 990,000 and no more than SEK 3,960,000 divided into no less than 19,800,000 shares and no more than 79,200 000 shares. CombiGene has one class of share. Each share carries equal rights to CombiGene's assets and profits and is entitled to one vote at the Annual General Meeting (AGM). The quota value is SEK 0.05. The CombiGene share register is maintained electronically by Euroclear. The share trades under the name CombiGene, the ticker is COMBI, and the ISIN-Code is SE0016101935.

The share

The average number of shares for the period is 19,801,197. All shares are of the same type and have the same voting rights. At the AGM of CombiGene on 25 May 2021 a reverse share split was resolved upon, whereby twenty (20) existing shares were consolidated into one (1) new share. Through the reverse share split, the number of shares in CombiGene decreased from 396,023,950 to 19,801,197. For comparability, a retroactive adjustment has been made to the number of shares.

Authorization to issue new shares, warrants or convertibles

The AGM 2022 resolved, in accordance with the board of directors' proposal, to authorize the board of directors to, at one or several occasions and for the period up until the next annual general meeting, resolve to increase the company's share capital by issuing new shares, warrants or convertibles. Such issue resolution may be carried out with or without deviation from the shareholders' preferential rights and with or without provisions for contribution in kind, set-off or other conditions. The total number of shares that may be issued, or as regards issue of convertibles or warrants, issued by conversion or exercise, under the authorization shall not be limited in any other way than by the limits for the share capital and number of shares, as set forth from time to time in the registered articles of association.

LTI 2022

The AGM 2022 resolved, in accordance with the board of directors' proposal, on the implementation of a performance-based incentive program, named LTI 2022, directed issue of 900,000 warrants, transfer of the warrants to participants in LTI 2022 and transfer of warrants to cover costs for LTI 2022 and authorization to enter into swap agreement. A more detailed description of LTI 2022 can be found in the notice convening the Annual General Meeting 2022.

Ten largest shareholders as of December 31, 2022	Total holdings	Holding %
Myrlid AS	1,400,000	7.07%
Nordqvist, Jan Ivar	1,293,368	6.53%
Avanza Pension	1,153,219	5.82%
Nordnet Pensionsförsäkring AB	528,752	2.67%
Thoren Tillväxt AB	494,894	2.50%
Försäkringsaktiebolaget Skandia	279,646	1.41%
Olsson, Per Magnus	240,764	1.22%
Ferstad, Arne	214,072	1.08%
Darlista, Flamur	166,566	0.84%
Thomassen Skaar, Christian	153,314	0.77%

Financial information

Income and earnings
Net sales consist of milestone payments and compensation from license and cooperation agreements. In 2022, the net sales consists of compensation from Spark regarding costs during the preclinical development of CG01. Due to the nature of the business, there may be large fluctuations between revenues for different periods when revenue from milestone payments is recognized at the time when the performance obligations are met. The Group has a total net sale of TSEK 26,699 (84,042) during the period January-December. Other operating revenues amounts to TSEK 15,044 (7,478) and consist of TSEK 0 (5,671) which refers to the revenue-earned portion of the grant received from Horizon 2020 and TSEK 1,969 (1,406) which refers to the revenue-earned portion of the grant received from Eurostars, and primarily realized and unrealized foreign exchange gains. Operating profit for the period amounted to TSEK -6,947 (20,965). The main costs during the period have been related to research & development, fees for consultants and personnel costs.

Cash flow and financial position
Cash flow for the period January-December amounts to TSEK -16,666. Cash and cash equivalents at the end of the period amounts to TSEK 131,777. The equity ratio is 96.15%.

Liquidity and financing
The EU's Eurostars program, which is aimed at small and medium-sized enterprises wishing to collaborate on research and development projects, has allocated development grants to the CGT2 project. The total grant for CombiGene amounts to SEK 5 million, of which SEK 3.4 million has so far been paid out. The board and company management continuously evaluate alternatives to ensure the company's financing in the short and medium term.

Incentive programs and warrants
The 2022 Annual General Meeting resolved on a performance-based incentive program (LTI 2022). The duration of the program is approximately three years and will be offered to certain employees and consultants, or newly hired persons, in the company. A maximum of 617,220 Performance Share Rights may be allocated to the participants, corresponding to approximately 3 percent of the out-standing shares and votes in the Company, as well as 282,780 warrants issued to hedge the Company's cost under the Program, which corresponds to approximately 1.4 percent of the outstanding shares and votes in the Company. In accordance with the Board's proposal, the AGM resolved on a directed issue of 900,000 warrants with the right to subscribe for new shares in the company for the implementation of LTI 2022.

Employees
The number of employees in the Group at the end of the period was 11 (8), of whom 6 (5) are women.

Risks and uncertainties
A drug development company of CombiGene's type is characterized by a high operational and financial risk. The Company is dependent on current and future licensing, collaboration, and other agreements with experienced partners for the development and successful commercialization of existing and future drug candidates. The most significant example of this is CombiGene's exclusive global collaboration and licensing agreement with Spark Therapeutics, which has a potential total value of USD 328.5 million excluding royalties. The agreement with Spark is thus of great importance for CombiGene's future operations, earnings, and financial position. Other factors that may negatively affect the likelihood of commercial success include, among other things, the risk that CombiGene's gene therapies are not deemed safe or not effective, and the risk that the business may not receive the necessary funding.

Principles for preparation of the interim report
CombiGene prepares its financial reports in accordance with the Swedish Annual Accounts Act and BFNAR 2012:1 (K3) Annual Accounts and Consolidated Accounts. The same accounting principles have been applied in this interim report as were applied in the most recent annual report.

Proposed distribution of profits
The board proposes that no dividend will be paid for the 2022 financial year.

AGM and Annual Report
The Annual General Meeting for 2023 will be held on 25 May. More information regarding this will be published later. The Annual Report will be available to the public at the Company's office in Lidingö and will be published on the Company's website no later than three weeks before the AGM.

Review by auditors
This report has not been subject to review by the Company's auditors.

Future reporting dates
- Interim report January – March 2023, 12 May 2023.
- Interim report January – June 2023, 25 August 2023.
- Interim report January – September 2023, 10 November 2023.
- Year-end report 2023, 16 February 2024.

For further information, please contact:
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Group income statement in summary

Figures in TSEK	2022 Oct-Dec	2021 Oct-Dec	2022 Jan-Dec	2021 Jan-Dec
Operating income				
Net sales	5,346	84,042	26,699	84,042
Other operating revenues	674	1,098	15,044	7,478
Operating expenses				
Other external expenses	-6,869	-21,538	-32,567	-54,591
Personnel expenses	-4,221	-4,778	-13,032	-11,692
Other operating expenses	-7,013	-727	-496	-1,677
Profit/loss before depreciation	**-12,084**	**58,097**	**-4,352**	**23,560**
Depreciation	-649	-649	-2,595	-2,595
Profit/loss after depreciation	**-12,732**	**57,448**	**-6,947**	**20,965**
Net financial income/expense	790	0	790	0
Income after net financial items	**-11,942**	**57,448**	**-6,157**	**20,965**
Tax	0	0	0	0
Net profit/loss for the period	**-11,942**	**57,448**	**-6,157**	**20,965**
Attributable to				
Parent company shareholders	-11,942	57,448	-6,157	20,965
Earnings per share before dilution	-0.60	2.90	-0.31	1.21
Earnings per share after dilution	-0.60	2.90	-0.31	1.21
Average number of shares before dilution	19,801,197	19,801,197	19,801,197	17,311,414
Average number of shares after dilution	19,801,197	19,801,197	19,801,197	17,311,414
Total outstanding shares	*19,801,197*	*19,801,197*	*19,801,197*	*19,801,197*

Group balance sheet in summary

Figures in TSEK	2022 31 Dec	2021 31 Dec
ASSETS		
Intangible assets	19,004	21,599
Total fixed assets	**19,004**	**21,599**
Current assets		
Accounts receivable	4,216	0
Other receivables	3,223	7,472
Cash and bank balances	131,777	136,744
Total current assets	**139,217**	**144,216**
TOTAL ASSETS	**158,221**	**165,815**
SHAREHOLDERS' EQUITY AND LIABILITIES		
Share capital	990	990
Other capital contribution	224,124	224,124
Other shareholders' equity	-66,835	-87,800
Profit/loss for the period	-6,157	20,965
Equity attributable to parent company shareholders	**152,122**	**158,279**
Total equity	**152,122**	**158,279**
LIABILITIES		
Current liabilities	6,099	7,536
Total liabilities	**6,099**	**7,536**
TOTAL SHAREHOLDERS' EQUITY AND LIABILITIES	**158,221**	**165,815**

Summary report of changes in the Group's shareholders' equity

Figures in TSEK	Share capital	Other capital contribution	Other shareholders' equity	Accumulated profit/loss	Total shareholders' equity
Balance brought forward	**990**	**224,124**	**-87,800**	**20,965**	**158,279**
Allocation of profit/loss			20,965	-20,965	0
Net profit/loss for the period				-6,157	-6,157
Amount as per the end of the reporting period	**990**	**224,124**	**-66,835**	**-6,157**	**152,122**

Group cash flow statement in summary

Figures in TSEK	2022 Oct-Dec	2021 Oct-Dec	2022 Jan-Dec	2021 Jan-Dec
Cash flow from operating activities	-6,253	70,657	-16,666	22,115
Cash flow from investing activites	0	0	0	-148
Cash flow from financing activities	0	0	0	65,881
Cash flow for the period	**-6,253**	**70,657**	**-16,666**	**87,849**
Liquid assets at the beginning of the reporting period	144,940	66,087	136,744	48,895
Exchange rate difference cash and cash equivalents	-6,909	0	11,699	0
Liquid assets at the end of the reporting period	**131,777**	**136,744**	**131,777**	**136,744**

Group financial key ratios

	2022 Oct-Dec	2021 Oct-Dec	2022 Jan-Dec	2021 Jan-Dec
Earnings per share before dilution, SEK	-0.60	2.90	-0.31	1.21
Earnings per share after dilution, SEK	-0.60	2.90	-0.31	1.21
Shareholders' equity per share, SEK	7.68	7.99	7.68	7.99
Equity ratio, %	96.15	95.46	96.15	95.46
Average number of shares before dilution	19,801,197	19,801,197	19,801,197	17,311,414
Average number of shares after dilution	19,801,197	19,801,197	19,801,197	17,311,414
Total outstanding shares	19,801,197	19,801,197	19,801,197	19,801,197

Parent Company income statement in summary

Figures in TSEK	2022 Oct-Dec	2021 Oct-Dec	2022 Jan-Dec	2021 Jan-Dec
Operating income				
Net sales	5,346	84,042	26,699	84,042
Other operating revenues	674	1,098	15,044	7,478
Operating expenses				
Other external expenses	-6,854	-21,528	-32,494	-54,517
Personnel expenses	-4,221	-4,778	-13,032	-11,692
Other operating expenses	-7,011	-727	-492	-1,677
Profit/loss before depreciation	**-12,067**	**58,107**	**-4,275**	**23,634**
Depreciation	-75	-75	-300	-300
Profit/loss after depreciation	**-12,142**	**58,032**	**-4,575**	**23,334**
Net financial income/expense	217	-574	-1,505	-2,295
Income after net financial items	**-11,925**	**57,458**	**-6,080**	**21,039**
Tax	0	0	0	0
Net profit/loss for the period	**-11,925**	**57,458**	**-6,080**	**21,039**

Parent Company balance sheet in summary

Figures in TSEK	2022 31 Dec	2021 31 Dec
ASSETS		
Intangible assets	4,087	4,387
Financial assets	18,585	20,880
Total fixed assets	**22,673**	**25,267**
Current assets		
Accounts receivable	4,216	0
Other receivables	3,980	8,157
Cash and bank balances	131,583	136,545
Total current assets	**139,779**	**144,702**
TOTAL ASSETS	**162,452**	**169,970**
SHAREHOLDERS' EQUITY AND LIABILITIES		
Restricted equity		
Share capital	990	990
Statutory reserve	4	4
Reserve for development expenses	760	760
Non-restricted equity		
Share premium reserve	165,826	165,826
Accumulated loss including profit/loss for the period	-11,181	-5,101
Total shareholders' equity	**156,398**	**162,478**
LIABILITIES		
Current liabilities	6,054	7,491
Total liabilities	**6,054**	**7,491**
TOTAL SHAREHOLDERS' EQUITY AND LIABILITIES	**162,452**	**169,970**

Summary report of changes in the Parent Company's shareholders' equity

Figures in TSEK	Share capital	Statutory reserve	Reserve for development expenses	Share premium reserve	Accumulated profit/loss	Profit/loss for the year	Total shareholders' equity
Balance brought forward	**990**	**4**	**760**	**165,826**	**-26,139**	**21,039**	**162,478**
Allocation of profit/loss					21,039	-21,039	0
Net profit/loss for the period						-6,080	-6,080
Amount as per the end of the reporting period	**990**	**4**	**760**	**165,826**	**-5,101**	**-6,080**	**156,398**

Parent Company cash flow statement in summary

Figures in TSEK	2022 Oct-Dec	2021 Oct-Dec	2022 Jan-Dec	2021 Jan-Dec
Cash flow from operating activities	-6,254	70,648	-16,661	22,109
Cash flow from investing activites	0	0	0	-148
Cash flow from financing activities	0	0	0	65,881
Cash flow for the period	**-6,254**	**70,648**	**-16,661**	**87,843**
Liquid assets at the beginning of the reporting period	144,747	65,897	136,545	48,703
Exchange rate difference cash and cash equivalents	-6,909	0	11,699	0
Liquid assets at the end of the reporting period	**131,583**	**136,545**	**131,583**	**136,545**

Share capital development

Year	Event	Total share capital (SEK)	Change (SEK)	Total shares	Change shares	Quotient (SEK)
1990	Company registration	50,000	50,000	500	500	100.00
1997	Bonus issue	100,000	50,000	1,000	500	100.00
2010	New share issue	102,600	2,600	1,026	26	100.00
2013	New share issue	143,600	41,000	1,436	410	100.00
2014	Bonus issue	574,400	430,800	5,744	4,308	100.00
2014	New share issue	604,400	30,000	6,044	300	100.00
2014	Split 1 000:1	604,400	0	6,044,000	6,037,956	0.10
2014	New share issue	884,400	280,000	8,844,000	2,800,000	0.10
2015	New share issue	1,134,400	250,000	11,344,000	2,500,000	0.10
2015	New share issue	1,138,197	3,797	11,381,970	37,970	0.10
2016	New share issue	1,180,159	41,962	11,801,590	419,620	0.10
2017	New share issue	1,652,223	472,064	16,522,230	4,720,637	0.10
2018	New share issue	1,719,783	67,560	17,197,836	675,596	0.10
2018	New share issue	5,159,348	3,439,565	51,593,476	34,395,650	0.10
2019	New share issue	6,372,384	1,213,036	63,723,836	12,130,360	0.10
2019	New share issue	6,373,090	706	63,730,896	7,060	0.10
2019	New share issue	6,505,365	132,275	65,053,647	1,322,751	0.10
2020	New share issue	11,762,201	5,256,836	117,622,007	52,568,360	0.10
2020	New share issue	12,562,201	800,000	125,622,007	8,000,000	0.10
2020	New share issue	14,721,013	2,158,813	147,210,132	21,588,125	0.10
2020	New share issue	17,666,081	2,945,068	176,660,811	29,450,679	0.10
2020	New share issue	17,822,218	156,137	178,222,176	1,561,365	0.10
2020	New share issue	20,768,890	2,946,672	207,688,899	29,466,723	0.10
2020	New share issue	22,927,702	2,158,813	229,277,024	21,588,125	0.10
2021	New share issue	39,602,395	16,674,693	396,023,950	166,746,926	0.10
2021	Reverse share split (1:20)	39,602,395	0	19,801,197	-376,222,753	2.00
2021	Reduction of share capital	990,060	-38,612,335	19,801,197	0	0.05
At the end of the period		**990,060**		**19,801,197**		**0.05**

Declaration by the Board of Directors and the CEO

The Board of Directors and the Chief Executive Officer certify that the year-end report provides a true and fair view of the company's business, financial position, performance and describes material risks and uncertainties, to which the company is exposed.

The year-end report has not been reviewed by the company's auditors.

Stockholm, February 17, 2023

Bert Junno
Chairman

Gunilla Lundmark
Board member

Peter Nilsson
Board member

Jonas Ekblom
Board member

Per Lundin
Board member

Jan Nilsson
CEO

The CombiGene family – the GeneTeam

CombiGene is an innovation company which conducts research and development by utilizing Contract Research Organizations (CRO´s) or by engaging in academic collaborations. All managed by CombiGene´s skilled and qualified staff.

The advantages with this type of collaboration are apparent. CombiGene is able to gain access to leading research from academia as well as industry without having to incur costs for resource-intensive research. In turn, the external researchers gain access to CombiGene's considerable expertise in pharmaceuticals development and project management, and financial resources to enable preclinical and clinical development.

CombiGene has a team of very knowledgeable and experienced professionals, as well as solid, longstanding experience from the international pharma industry and the biotech arena, together with a thorough knowledge of different aspects of gene therapy. This combination of experience and expertise allows CombiGene, together with its network of selected external partners who complement CombiGene's internal expertise, to conduct ground-breaking gene-therapeutic development very effectively.

Here are the people who do it!


Jan Nilsson
Chief Executive Officer


Karin Agerman
Chief Scientific Officer


Peter Ekolind
Chief Operating Officer


Louise Aspenberg
Chief Financial Officer


Annika Ericsson
Director Preclinical Development


Pernilla Fagergren
Director Clinical Development


Alvar Grönberg
Senior Program Director


Martin Linhult
Director CMC


Birgitta Ståhl
Senior Director In-licensing


Esbjörn Melin
Industrial post doc


Daniela Morath
Corporate Administration

The GeneTeam – Extended

Since CombiGene first was established, the company has built up a network of partners within all central aspects of pharmaceutical development and business management. Here's an overview of the different phases of CombiGene's asset development and key partners.

Inlicensing

Our business model is based on inlicensing projects which we develop to preclinical proof-of-concept or to the first clinical study before we out-license them to a strategic partner.

To identify interesting projects, we regularly participate in important congresses and conferences to actively find new projects and we have continuous dialogues with interesting players in both academia and industry. We have also used consulting firms to scout interesting gene therapy assets globally. In other words, we work broadly with many different activities.

When evaluating projects, it is important to thoroughly examine it from different angles, including mechanism of action, intended indication area, patent situation, competition, and market. We do this by, among other things, having leading medical experts in the indication area, experts in the current mechanism of action, patent lawyers and regulatory advisors involved in the evaluation process together with our own internal resources.

PARTNERS
Medical expertise
Mechanism of action experts
Patent lawyers
Regulatory advisors

Preclinic

Vector design. The AAV vector, which we mainly work with, has properties that are beneficial in clinical applications. A successful vector design requires early optimization of each unique vector to address the specific disease we intend to treat by modifying the vector's DNA.

Preclinical. During the preclinical work, the vectors are evaluated in a laboratory environment and on patient material in collaboration with CROs that have established analytical methods and experimental models within the specific disease we intend to treat.

The work will provide knowledge about how gene therapy affects its target structure, underlying molecular mechanisms and the link between dose and effect. A milestone is to be able to show proof of concept, that is, proof that the concept works in a disease model. When this step is achieved, we work out a translational plan for efficacy and safety.

PARTNERS
Experienced CROs
Partners within academia: Lund University, Stockholm University, Hamburg University, Copenhagen University, University of Michigan

Production method

For the preclinical trials, the active substance is produced in an R&D environment. The manufacturing process is then scaled up for clinical trials and commercial use. CombiGene does not have its own production but outsources the production to different CDMOs after a careful selection process. Some of the CDMOs that we work with are Viralgen and Charles River.

To ensure that the product is safe, it is produced according to Good Manufacturing Practice (GMP) which is a standard in the pharmaceutical industry.

CombiGene follows the development in the field closely. We are also a part of Genenova – a collaboration with KTH Royal Institute of Technology, Uppsala University, Karolinska Institutet, Biotage, AstraZeneca, Alfa-Laval, Vironova and Ziccum. The purpose of Genenova is to promote an innovative environment for a more effective and accessible AAV gene therapy. Genenova is led by Professor Johan Rockström, KTH, and has received funding from Vinnova.

PARTNERS
Selected CDMOs
Genenova collaboration

Preparation clinic

Already in the preclinical phase, you need to prepare the clinical development plan in terms of expected patient population, potential biomarkers and how the gene therapy will be administered, etc. Therefore, we have early contacts with leading medical experts in each indication area.

When it comes to gene therapy, both safety and treatment efficacy in patients will be evaluated already in the first clinical study (combined Phase I / II), unlike traditional drug development where the first clinical study is often a safety study (Phase I) conducted on healthy volunteers. For the performance of clinical studies, we will work with reputable CROs with experience in gene therapy studies.

We also consult regulatory expertise to ensure successful interactions with European and US regulatory authorities.

PARTNERS
Medical expertise
Experienced CROs
Regulatory expertise

Outlicensing

CombiGene have since many years back a continuous dialog with several big pharma/biotech companies. Out-licensing efforts begin by approaching Big Pharma players with a presence in the disease area in which we are developing our asset and present our projects to key people in the company. This first step in the process of building a strong relationship is often made at so-called partnering meetings. The relationship is then maintained through regular interactions of various kinds. A Confidential Disclosure Agreement (CDA) is signed when a potential partner wants to examine our company, team and scientific data in detail – a so called due diligence. If the result of this review is positive, discussions will follow on how a business transaction might look.

During the final parts of an out-licensing process, CombiGene relies on the support of key opinion leaders to verify the medical need of our therapy, our own researchers to explain the science and a legal team which is responsible for formalizing the deal into a legal agreement.

PARTNERS
Big pharma/biotech companies
Key opinion leaders
Legal experts

Glossary

AAV Adeno-associated virus.

AMPA receptor A transmembrane receptor subtype for glutamate that acts as an ion channel and mediates fast synaptic signal transmission in the central nervous system (CNS).

C-kinase A family of protein kinase enzymes that are involved in controlling the function of other proteins through the phosphorylation of hydroxyl groups of serine and threonine amino acid residues on these proteins, or a member of this family.

CDMO Contract development and manufacturing organization is a company that serves other companies in the pharmaceutical industry on a contract basis to provide comprehensive services from drug development through drug manufacturing.

Chronic pain Pain that has lasted longer than three months.

Clinical development Comprises three phases, see clinical phase I, II, III below.

Clinical phase I Phase I refers to the first instance of testing of a candidate drug on humans. Phase I trials are often conducted with a small group of healthy volunteer trial subjects to determine the safety and dosage of an as yet non-approved treatment method.

Clinical phase II Phase II trials refer to a pharmaceutical product under development that is administered to a small group of patients to study the safety, dosage and efficacy.

Clinical phase III Phase III studies include a sufficient number of patients to meet regulatory prerequisites for approval. The aim is to determine the statistical significance with respect to the effect of a new candidate drug, without major side effects and under carefully controlled real-world conditions. The new drug is sometimes compared with an established treatment, such as an approved drug.

Clinical study Research studies that explore whether a new, as yet non-approved, drug, medical strategy, treatment, or device is safe and effective for humans.

CRO Contract research organization is a company that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis.

Eurostars A funding instrument that supports innovative SMEs (Small and Medium-sized Enterprises), and project partners (large companies, universities, research organizations and other types of organizations) by funding international collaborative R&D and innovation projects.

Gene therapy A medical field which focuses on the genetic modification of cells to produce a therapeutic effect or the treatment of disease by repairing or reconstructing defective genetic material.

GMP Good Manufacturing Practice is a system for ensuring that pharmaceutical products are consistently produced and controlled according to quality standards. Permits for GMP are granted by the Food and Drug Administration in the country in question and the process is characterized by extremely rigid and high demands on quality in all respects.

In vitro A term used in biomedical science to describe a biological process made to occur in a laboratory vessel or other controlled experimental environment, for example cultivated cells, rather than within a living organism.

In vivo A term used in biomedical science to describe an experimental biological process, and observations thereof, made to occur within a living organism.

Lipodystrophy A rare disease characterized by altered fat distribution on the body. In the absence of normal body fat, various organs, primarily the liver, 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).

Neuropathic pain Nerve pain can occur after diseases and injuries of the somatosensory nervous system and spread within a neuroanatomical innervation area.

PCT Patent Cooperation Treaty, an international patent law treaty, concluded in 1970. It provides a unified procedure for filing patent applications to protect inventions in each of its contracting states.

Peptide Short chains of amino acids linked by peptide bonds.

PICK1 A protein that interacts with C-kinase 1.

Plasmid Small, extrachromosomal DNA molecule within a cell that is physically separated from chromosomal DNA.

Preclinical study In vitro and in vivo studies carried out before the clinical development (see above) with the objective to make sure that the new therapy is safe and has the intended effect.

Proof-of-concept Documented evidence that a potential product or method has the intended effect.

Viral vector Viral vectors are tools that are used to deliver genetic material to cells. Examples of viral vectors are lentivirus, adeno-associated virus (AAV), retrovirus and adenovirus. AAV vectors are non-hazardous viruses that can infect human cells without causing disease and can be used to deliver genetic material into human cells.

We are now looking forward to a really busy spring with continued development of all our projects. Even though we recently entered into the collaboration with our colleagues at Zyneyro for the further development of the pain program COZY, we will continue our efforts to find new projects that can add further value to CombiGene.

Our next quarterly report will be published on May 12, 2023, but there will ample opportunities to follow the development of CombiGene before that date. You are always welcome to visit our web site and to follow us on LinkedIn, Facebook, and Twitter. We will also be presenting at a number of shareholder events during the coming months and publish at least one new issue of our magazine *Ingeneious*. You can find detailed information on our web. We wish you all the best until next time.

The CombiGene Team

CombiGene's vision is to provide patients affected by severe life-altering diseases with the prospect of a better life through novel gene therapies. CombiGene's business concept is to develop effective gene therapies for severe life-altering diseases where adequate treatment is currently lacking. Development assets are sourced from an external research network and developed to achieve clinical proof of concept. Drug candidates for common diseases will be co-developed and commercialized through strategic partnerships, while the company may manage this process on its own for drugs targeting niched patient populations. The Company has an exclusive collaboration and licensing agreement for the CG01 project with Spark Therapeutics. The company is public and listed on the Swedish marketplace Nasdaq First North Growth Market and the company's Certified Advisor is FNCA Sweden AB.

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