STATUS REPORT

CERENO SCIENTIFIC

CERENO SCIENTIFIC – EXPANDED POTENTIAL IN CARDIOVASCULAR DISEASE

INTRODUCTION

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Cardiovascular disease is the number one killer in the world, and better treatments are in high demand. Trying to answer that call is Cereno Scientific, a biotech company developing new treatments for both common and rare cardiovascular diseases. In 2020, the company took important steps towards advancing its lead candidate CS1 to the next stage of development. After receiving orphan drug designation for CS1 from the FDA for the treatment of pulmonary arterial hypertension, Cereno Scientific has, in collaboration with world-leading experts, defined a strategy and an action plan to make sure that CS1 has a path to market for this rare disease. In 2021, so far, the company has obtained patents for CS1 in two major markets, Japan and Russia, adding to the already approved US patent as well as presented a timeline for the phase II clinical trial initiation this coming September. In parallel, the company has continued to build on its pipeline through an exclusive option to in-license a preclinical development programme and through two collaborative development agreements with the University of Michigan aimed at making the two preclinical programmes CS585 and CS014 ready for phase I within 24 months.

According to the World Health Organization (WHO), cardiovascular disease (CVD) is the most common cause of death worldwide and a huge burden on the individual and society. CVD is an umbrella term referring to a wide range of disorders that involve the heart and the blood vessels, and the majority of such disorders, including the most common like heart attack and stroke, are caused by thrombotic events – the formation of occluding blood clots inside the blood vessels. The number of people expected to suffer from such events is increasing, and current treatments, some of which are aimed at preventing blood clots, often lead to bleeding problems, which, in itself, could be life-threatening. Thus the need for better treatments in CVD is obvious.

With the ambition of developing innovative drugs with better efficacy and fewer side effects than today's alternatives, as well as seeking to improve the lives of patients with CVD, Cereno Scientific is aiming to position itself in a highly competitive environment by initially addressing the rare and progressive CVD pulmonary arterial hypertension (PAH), a disease that puts a very heavy burden on patients and still lacks effective treatment. However, the company's overarching goal is to become a staple in the CVD space by addressing a wide range of CVD indications, both rare and common.

Strong foundation built for the long-haul

To reach this goal, Cereno Scientific relies on a robust business model, a well thought out strategy, and a solid organisation.

Pipeline

A key component of the company's business model is having a well-diversified pipeline of three drug development programmes: lead programme *CS1*, and two preclinical programmes *CS585* and *CS014*. Two of Cereno's projects, a phase II clinical programme with CS1 and the preclinical programme with CS014, are HDACis (histone deacetylase inhibitors) and built on a visionary therapeutic approach based on the potential of epigenetic modulation – a way of regulating the expression of certain genes without an actual alteration of the genetic material. This approach seeks to unravel significant potential therapeutic benefits for patients suffering from CVD through antifibrotic, anti-inflammatory, pressure-reducing as well as antithrombotic properties that has been demonstrated in preclinical and clinical studies done by both Cereno and peer researchers.

The other preclinical programme, CS585, is based on the newly entered option agreement of a prostacyclin receptor agonist that has demonstrated potential to significantly improve on mechanisms relevant to selected cardiovascular diseases through initial *in vivo* animal models.

Organisation

Cereno Scientific's strength as a biotech company, however, also derives from having built a solid organisation over the years based on key competencies in the areas of scientific research, intellectual property rights, drug development and commercialisation.

This is evidenced by a highly experienced Executive Management Team, a dedicated Board of Directors, and a Scientific Advisory Board (SAB) comprised of high-profile CVD experts that have international recognition in the field, chaired by Dr **Bertrand Pitt**, Professor Emeritus at the University of Michigan. Overall, Cereno has built up a strong team of employees, long-term consultants and advisors working towards a common goal of improving treatments for patients with CVD.

INTRODUCTION

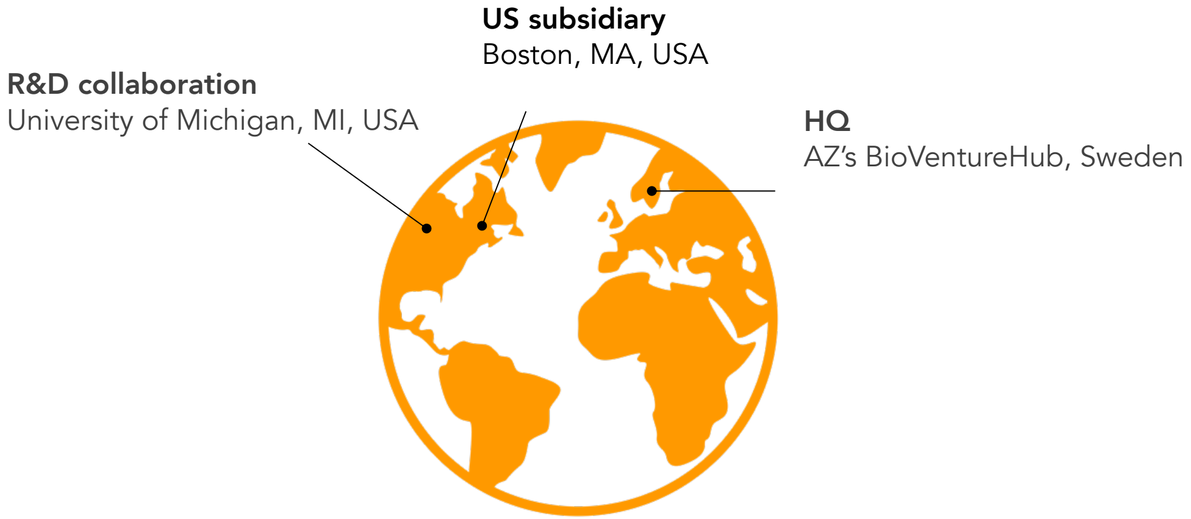
International footprint

To generate even more value, part of Cereno's business strategy has been to expand beyond the Nordic region and establish a global presence. While the company's headquarters is located at **AstraZeneca**'s *BioVentureHub* in Gothenburg, Sweden, in 2019, a US-based subsidiary, **Cereno Scientific Inc.**, was set up and is located at the biotech centre in Kendall Square, Boston, Massachusetts.

In 2020, Cereno expanded its US footprint even further by starting a development collaboration with Dr **Michael Holinstat** at the **University of Michigan**. Since then, the collaboration has expanded significantly through two collaborative development agreements aimed at bringing the preclinical assets CS585 and CS014 into phase I studies in about 24 months.

Furthermore, four out of six SAB members are based in the US at prestigious institutions, e.g., University of Michigan, **Harvard Medical School** and **Ohio State University Wexner Medical Center**. Additionally, the company's upcoming phase II study with CS1 in PAH will be conducted in the US.

Cereno's global presence



INTRODUCTION

Looking ahead

Overall, Cereno has created an extensive network of high-profile experts in the field of CVD who contribute to a high level of experience and are involved in both clinical strategy and drug development in the company. These collaborations with advisors enable close contact with the clinical reality, ongoing research and open doors to a large network of researchers and opinion leaders that is valuable for the company's development.

Thanks to a diversified project portfolio with broad therapeutic potential, Cereno's initial aim is to first establish drug candidates in rare diseases. An alternative path to development within more common CVDs is provided through partnerships with major pharmaceutical companies. Thus, in a future out-licensing or deal with a major pharmaceutical company, Cereno will be able to rely on clinical data, a strong patent portfolio and potential regulatory market exclusivity. This is why the opportunities for increased commercial value of the company and its drug candidates are continuously expanded through further secured market exclusivity with expanded patent protection and other regulatory pathways such as *orphan drug designation* (ODD).

Cereno is a research and development company with no current sales. The company is financed mainly via the capital market or through future out-licensing or sale of projects. Activities to achieve financing via the capital market are ongoing in parallel and in interaction with processes to be able to enter into agreements on out-licensing or sales.

INTRODUCTION

Approaching phase II

Several years of research out of **Sahlgrenska Akademin** at the **University of Gothenburg** led to the founding of Cereno Scientific in 2012 and later to a successful phase I trial that ran between the fall of 2017 and the spring of 2018 with drug candidate CS1. CS1, an innovative formulation of a promising histone deacetylase inhibitor (HDACi) called valproic acid (VPA), is now Cereno Scientific's lead candidate. Thanks to the promising phase I results and the significant need for new treatments in PAH, CS1 was granted ODD by the **FDA** in March 2020 for the treatment of PAH and is now being prepped for a phase II study.

So far in 2021, Cereno Scientific has initiated an *Investigational New Drug* (IND) application to send to the FDA seeking approval for initiating the phase II trial, where the aim will primarily be to demonstrate CS1's safety and tolerability but also evaluate dose and pharmacokinetics, validated risk scores and exploratory efficacy endpoints in PAH patients. The study will be conducted under the ODD, and it will be run at approximately six different clinical sites in the US and include a total of 30 patients. The company expects to begin the trial in September this year.

Preparation for the phase II trial has been done in collaboration with **Worldwide Clinical Trials**, a global CRO with whom Cereno partnered earlier this year. Thanks to Worldwide's expertise in clinical trials and dealing with a number of regulatory bodies, including the FDA, this partnership has been essential not only for support and guidance in the final preparatory steps towards the phase II study but will also be important for the execution of the trial.

The preparations for the phase II trial have also included Cereno's work with its formulation partner **Galenica**, an established pharmaceutical development company based in Malmö. The work is aimed at scaling up the production of CS1 in the form of oral capsules in line with regulatory requirements to be used in the study.

Expanding pipeline

CS1, being based on an HDACi, is considered an important epigenetic modulator with therapeutic potential thanks to its anti-thrombotic, anti-inflammatory, anti-fibrotic and pressure-relieving properties. Epigenetic modulation with HDACi has been previously explored in oncology, however, Cereno Scientific is one of the first to explore its clinical and commercial potential in CVD. Now, the company is expanding on this therapeutic potential by broadening its project portfolio by initiating a full preclinical development programme for another epigenetic modulator, CS014.

CS014 was originally acquired by Cereno Scientific in 2019 from **Emeriti Bio**, and then, in June 2020, Cereno partnered with Dr Holinstat at the University of Michigan to further explore CS014's therapeutic potential. This year, Cereno Scientific announced that it has extended its collaboration with the University of Michigan, which has extensive experience of successfully collaborating with the pharmaceutical industry, to include a full preclinical development programme for CS014 with the goal of meeting the regulatory requirements to be able to start first-in-man, phase I studies, within about two years.

Cereno's collaboration with Dr Holinstat, who leads the translational programmes in drug development in Hemostasis and Thrombosis in the Department of Pharmacology at the University of Michigan, has been going strong since the start of the collaboration last year. In fact, in March of this year, Cereno added a third project to its development portfolio through the collaboration: CS585 - a stable, selective, and potent IP (prostacyclin) receptor agonist that in initial in vivo animal models has demonstrated potential to significantly advance treatments within selected CVDs. Through an option agreement with the University of Michigan, Cereno will have the rights to in-license CS585 for further clinical development and commercialisation if the preclinical evaluations were to be successful following the 24-month development programme.

The start of the development programmes for both CS014 and CS585 plays a key role in Cereno Scientific's ambition to both expand and diversify its portfolio.

INTRODUCTION

Financial status

Financially, the company carried out a directed share issue last September bringing 60 MSEK to the company along with a bridge loan of 10 MSEK. Cereno also issued two warrants, the first to be exercised in September 2021 and the second warrant will be exercised a year later, in September 2022. The two warrant programmes could potentially bring around 200 MSEK to the company, securing funding for the phase II trial and further development of the preclinical projects.

Any other funding opportunity that would arise, would be interpreted as an increased interest in Cereno, which would be beneficial for all long-term investors.

Cereno could choose to go market with CS1 in PAH on their own, but would probably be invited to discuss license agreements and partnerships with pharma and biotech companies as the project advances.

Significant increase of company valuation

In October 2020, BioStock published a company update of Cereno Scientific, describing the potential and advancement of the CS1 project. By then, the market value of the company was 142 MSEK on the **Spotlight Stock Market**. Now, about seven months later, the market cap has increased to 248 MSEK, an appreciation 116 MSEK or 82 per cent.

The CVD area is one of the largest segments of the pharmaceutical market with a high unmet medical need for better treatments. Since October, Cereno has taken steps with their lead candidate towards an expected initiation of the phase II trial in September, and an expanded preclinical pipeline including a solid set up of two collaborative development agreements with University of Michigan providing the possibility of taking these two new promising programmes to the clinic within about two years, have all driven value upward.

UPCOMING TRIGGERS

UPCOMING TRIGGERS

Key milestones

- Preparations for the phase II trial CS1 in PAH (Q2-Q3 2021)
- Initiation of phase II with CS1 in PAH (September 2021)
- Exercise of the warrant TO1 (15-29 September 2021)
- Advancements of the 24-month development programmes CS585 and CS014
- Top line data from the phase II trial with CS1 (H2 2022)

THE COMPANY IN BRIEF

THE COMPANY IN BRIEF

Cereno Scientific was founded in 2012 by Niklas Bergh, Sverker Jern and Pia Larsson and is based on research from the Wallenberg Laboratory, Sahlgrenska Academy at the University of Gothenburg.

Cereno Scientific is headquartered at the AstraZeneca BioVentureHub in Mölndal, Sweden. In May 2020, the company opened a new office located at Kendall Square in Boston, Massachusetts, US. This comes as a strategic advantage with closeness to several of the company's scientific advisors, leading research institutions and the US being the largest market for CVD therapies in the world.

Cereno Scientific' has been collaborating with University of Michigan, Ann Arbor, Michigan, US, resulting in the two development programmes CS585 and CS014.

Cereno Scientific's organisation has been greatly strengthened thanks to recent new additions to the team. Dr Raymond Benza, a global thought leader within PAH and who has been working as an advisor to the company's phase II programme with CS1 in PAH, is the latest addition to the company's SAB.

For all ongoing and future clinical studies, Cereno picked up **Tiina Seppä** as Director of Clinical Research & Regulatory Affairs. Seppä has more than 14 years experience in the pharmaceutical industry acting as a regulatory lead in both early- and late-stage clinical development.

Meanwhile, for all preclinical affairs, Cereno appointed the aforementioned Dr Holinstat as Director of Translational Research. Dr Holinstat has played a key role in helping Cereno expand its preclinical programmes through the company's collaboration with the University of Michigan.

Ten largest sharholders as of 2021-03-31	**Capital (%)**	**Votes (%)**
Avanza Pension	8.53	7.82
Milad Pournori	4.96	4.55
Peyman Pournori	3.56	3.27
Ivar Nordqvist	2.94	2.70
Myrlid AS	2.78	2.55
Formue Nord Fokus AS	2.69	2.47
GU Ventures AB	2.17	1.99
Dory Gevryie	2.14	1.97
Sverker Jern (privately and through companies)	1.70	4.23
Niklas Bergh (privately and through companies)	1.66	4.17
Total ten largest shareholders	**33.14**	**35.71**
Other shareholders	66.86	64.29
Total (3,145 shareholders)	**100.00**	**100.00**

Market	Spotlight Stock Market	**Number of shares**	71 819 312
Ticker	CRNO B	**Share price 2021-06-11**	SEK 3.46
ISIN	SE0008241558	**Market cap 2021-06-11**	SEK 248 494 820

THE COMPANY IN BRIEF – BOARD OF DIRECTORS

Catharina Bäärnhielm
Chair of the Board

- Chair since 2015
- Pharmacist, PhD in pharmacokinetics and drug metabolism
- Experience from all phases of drug development
- Board member GU Ventures
- Prev. VP Global project manager, AstraZeneca

Björn Dahlöf
Board member

- Board member since 2012
- M.D., Associate professor of cardiovascular prevention at Sahlgrenska Academy
- Experience as an advisor for small and large pharmaceutical companies in all phases of drug development

Jonas Faijerson Säljö
Board member

- Board member since 2012
- PhD in neurobiology and licensed pharmacist
- Senior IP Business Consultant and CEO of Synergon

Sverker Jern
Board member

- Board member since 2012
- Professor of cardiovascular physiology at the Sahlgrenska University Hospital
- Jern's research is the basis for Cereno Scientific's new treatment

Anders Svensson
Board member

- Board member since Oct 2018
- Licensed physician, medical doctor and lecturer with over 20 years of experience in academic medicine focusing of CVD
- VP clinical development of cardiovascular, Astra Zeneca

Rein Piir
Board member

- Board member since June 2021
- Many years of experience in business and acquisition analysis, capital market matters, investor relations and alliance management towards global companies.
- Head of Analysis, Carnegie Investment Bank
- CFO/Head of Investor Relations at Medivir

Klementina Österberg
Board member

- Board member since 2014
- CEO of GU Ventures, University of Gothenburg's holding company
- Significant experience within venture financing and business development

THE COMPANY IN BRIEF – MANAGEMENT

Sten R Sörensen
Chief Executive Officer

Daniel Brodén
Chief Financial Officer

Björn Dahlöf
Chief Medical Officer

Niklas Bergh
Chief Scientific Officer

Jonas Faijerson Säljö
Chief Intellectual Property Officer

Tiina Seppä
Director Clinical Research & Regulatory Affairs

Michael Holinstat
Director Translational Research

Jan-Peter Idström
Senior Director Development

Tove Bergenholt
Director Communications & IR

Stine Birk Hansen
Project Director

THE COMPANY IN BRIEF – SCIENTIFIC ADVISORY BOARD

Dr Bertram Pitt, Chair

Professor Emeritus in Medicine,
University of Michigan School of Medicine

Dr Deepak Bhatt

Professor of Medicine,
Harvard Medical School

Dr. Raymond L Benza

Professor of Medicine,
Ohio State University

Dr Gunnar Olsson

MD, PhD in Medical Sciences,
Karolinska Institute

Dr Gordon Williams

Professor of Medicine,
Harvard Medical School

Dr Faiez Zannad

Professor of Therapeutics and Cardiology,
Université de Lorraine

University of Michigan Medical School

HARVARD MEDICAL SCHOOL

THE OHIO STATE UNIVERSITY

KAROLINSKA INSTITUTET ANNO 1810 Karolinska Institutet

HARVARD MEDICAL SCHOOL

UNIVERSITÉ DE LORRAINE

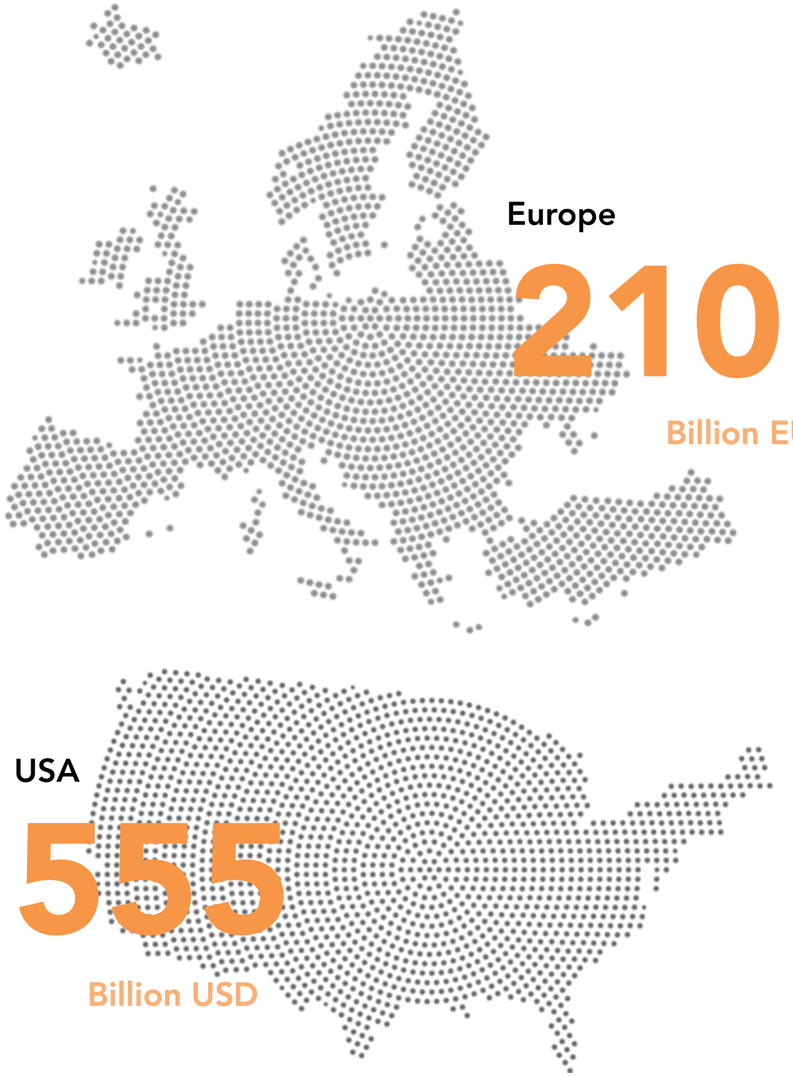
BUSINESS MODEL AND THERAPEUTIC PLATFORM

Cardiovascular disease

An estimated 17.9 million people die annually from CVD, and WHO forecasts suggest that 22.2 million people will die from CVD by 2030. CVD deaths are almost twice those of global cancer death, and the number of people suffering from severe conditions resulting from CVD in combination with insufficient treatments is increasing. CVD is also causing significant societal costs; 210 billion USD is spent per year in the EU to cover CVD-related costs, and an estimated 555 billion USD per year is spent in the US. These numbers are expected to double by mid-2030.

As alluded to in the introduction, CVD refers to a wide range of disorders that affect the heart and the blood vessels. Heart attack and stroke are some of the most common forms of CVD, and they are normally caused by the formation of occluding blood clots (thrombosis) inside the blood vessels that lead to a lack of oxygen in either the heart or the brain, respectively. The lack of oxygen causes the surrounding tissue to die leading to irreversible damage and eventually death.

Currently, the best way to counteract thrombotic events is through blood thinners. Some of the most common include *Warfarin*, *Heparin* or *NOACs*. However, such treatments have a major side-effect – risk of excessive bleeding. Being able to develop a treatment that restores balance in the body's fibrinolytic system (the interplay of molecular mechanisms that prevents clot formation as well as excessive bleeding in normal situations), has been a major challenge for bio and pharma companies.



Associated economic and societal burden for CVD.
Source: Cereno Scientific

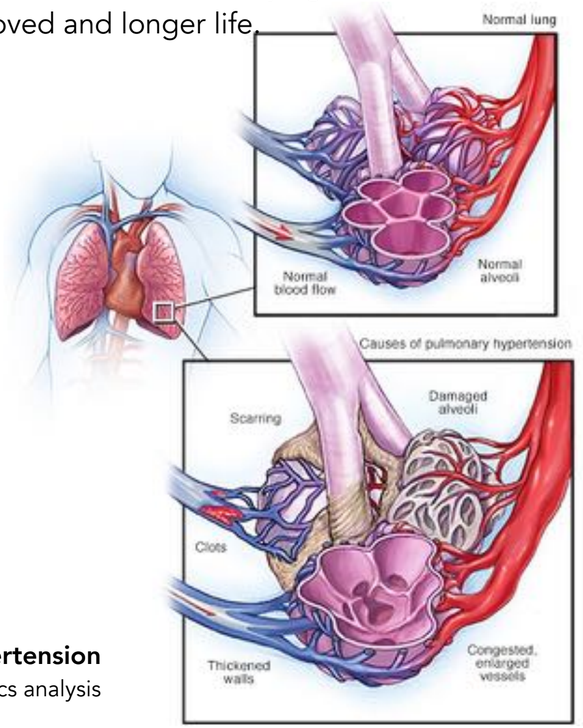
Pulmonary arterial hypertension (PAH)

Not all CVDs are common, in fact, some are categorised as rare, affecting fewer than 200 000 patients in the US or fewer than 1 in 2000 patients in Europe. This is the case with PAH, which has been classified as a rare CVD in both Europe and in the US since it affects about 5-15 per 100,000 people globally. The categorisation is quite important because, thanks to the *Orphan Drug Act* of 1983 passed in the US, drug developers dealing with such diseases are given better incentives to focus on diseases that would be otherwise considered orphan diseases, or abandoned diseases, since pharma companies would previously ignore them because of a much smaller market potential.

The pathophysiology of PAH is characterised by high blood pressure in the arteries of the lungs. The narrowing of the blood vessels caused by the high blood pressure makes it harder for the blood to flow through the arteries, which causes the heart to work harder and harder. With time, the heart muscle weakens, making heart failure a likely consequence.

Seeing the potential of developing a treatment for PAH with CS1, Cereno Scientific filed for ODD with the FDA in 2019, and was later granted this designation in 2020. Benefits of the ODD include, among other things, regulatory fee waivers, eligibility for research grants and tax credits for clinical trial costs. An approved orphan drug is also granted seven years of market exclusivity in the US and 10 years in Europe.

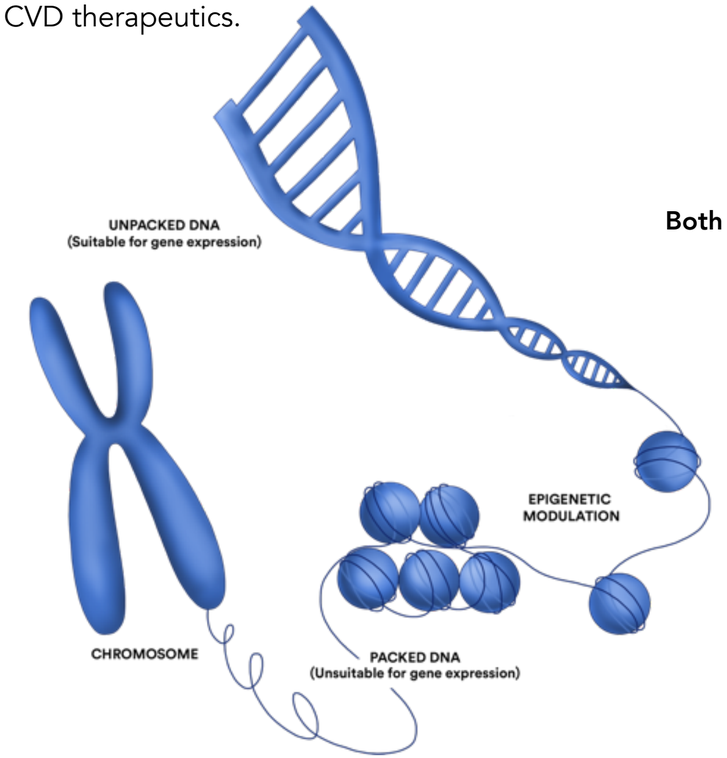
There are approximately 6 000–8 000 rare diseases, affecting more than 300 million people worldwide. Yet, about 95 per cent of these diseases have no approved pharmaceutical drug treatments. There is currently no cure for PAH besides lung transplantation, which patients are often too seriously ill to undergo. Furthermore, the treatments offered today are only focused on improving the patient's overall function and involve, at best, a moderate slowdown in the progressive development of the disease. There is thus a great need for new disease-modifying treatments that can give patients an opportunity for an improved and longer life.



Pulmonary Arterial Hypertension
Source: Hibiscus BioVentures, MSC Nordics analysis

Epigenetic modulation

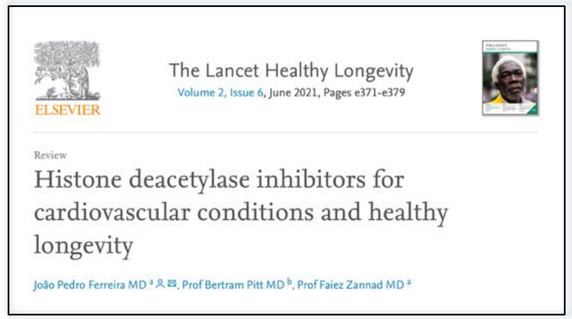
The balancing act engaged by the fibrinolytic system to keep clots from forming all while avoiding excessive bleeding is dictated in large part by gene expression, which happens inside our cells. Over the years, researchers have found ways of regulating the expression of certain genes without an actual alteration of the genetic material. This type of modulation is called epigenetic modulation, and it has played an important role in new treatments for cancer, however, until recently, it has not been much explored in CVD therapeutics.



Both CS1 and preclinical CS014 act as epigenetic modulators
Source: Cereno Scientific

One of the most common epigenetic modulators is a class of enzymes called histone deacetylases (HDACs). HDACs are found in most cells throughout the body, and their stimulation through environmental factors, e.g., diet and exercise, can lead to changes in how an individual's DNA is expressed within the cells. This can affect key cellular mechanisms and thus increase the risk of disease. Researchers have discovered ways of regulating certain disease-causing epigenetic changes as a form of treatment using inhibitors. HDAC inhibitors (HDACis) are epigenetic modulators with a full range of disease-modifying effects, which has caught the interest of many pharmaceutical and biotech companies in various disease areas.

This application of HDACi in CVD therapy has recently received external validation from a review article published in **The Lancet Healthy Longevity**. The review describes several mechanisms associated with the antithrombotic, antifibrotic, anti-inflammatory and pressure-reducing properties of HDACi in the cardiovascular system, and how such mechanisms could impact a large number of CVD indications, including PAH. This represents a paradigm shift in CVD therapeutics, and Cereno is in the driver's seat.


The Lancet Healthy Longevity
Volume 2, Issue 6, June 2021, Pages e371-e379

Review

Histone deacetylase inhibitors for cardiovascular conditions and healthy longevity

João Pedro Ferreira MD [a], Prof Bertram Pitt MD [b], Prof Faiez Zannad MD [a]

Clinical programme

Over the years, Cereno Scientific developed ways of exploiting the immense potential of epigenetic modulation. In fact, two of the company's three portfolio projects use an epigenetic modulation platform based on HDACis – lead programme CS1, which is now in the clinic, and the preclinical program CS014.

CS1

Cereno Scientific is one of the first companies to explore the potential of HDACis in CVD. This approach provides an opportunity to develop safer and better treatments for cardiovascular diseases in a completely new way. The Swedish biotech was founded in 2012 on the basis of research by Professor **Sverker Jern** and his team at the *Wallenberg Laboratory*, Sahlgrenska Akademin at University of Gothenburg. Based on that research and in collaboration with the SAB the company discovered that the advanced new reformulation of a common, well-established HDACi, VPA, had anti-thrombotic, anti-inflammatory, anti-fibrotic and blood pressure-relieving properties, thus becoming a drug candidate with commercialisation potential for the treatment of a wide range of CVDs.

At the end of 2015, Cereno stepped into collaboration with Galenica, through which Cereno was able to put more discovery efforts into its new candidate, CS1, and develop it into an innovative new asset with potential for clinical development. Then, in 2016, Cereno was listed on the marketplace now known as Spotlight Stock Market.

After initially focusing their efforts on targeting deep vein thrombosis with CS1 and validating the candidate's safety and tolerability profile in phase I, during spring 2019, the company's then newly formed SAB identified several new promising areas for CS1, including both common and rare CVDs. Given the specific properties of CS1, Cereno Scientific filed for ODD with the FDA for CS1 in PAH.

In parallel, the company planned a phase II trial with the aim to prevent venous thrombosis in patients undergoing elective orthopaedic surgery. The trial was scheduled to begin by mid 2020, but in late March, it was postponed due to the Covid-19 pandemic.

At around the same time, the FDA granted ODD to Cereno for evaluating CS1 in PAH. This became a validation of the major unmet clinical needs within the treatment of PAH and that CS1 has fulfilled the criteria of showing a potential to provide significant benefit to these patients. The ODD also brought a strengthened commercial potential and well-defined business case toward potential investors as well as partners for the company, thus opening up new opportunities for Cereno as it moves forward with its development programme.

Given the prospects at hand, in the fall of 2020, Cereno Scientific decided to revise its clinical strategy to initially focus on CS1 in PAH and go into other CVD indications with CS1 at a later time. Now, a phase II trial is planned for initiation this September, and the study aims to demonstrate CS1's safety, tolerability and exploratory efficacy in PAH patients. Other variables include all standard efficacy endpoints for this patient group, validated risk scores, dose-finding and pharmacokinetics. The study will be utilising cutting-edge technology for monitoring pulmonary pressure and will include 30 patients at about six different US clinics.

Preclinical programme and collaboration with University of Michigan

Cereno's other two projects are CS585 and CS014, both preclinical development programmes in their relatively early stages.

CS585 and CS014

Preclinical programme CS585 can be described as small molecules, analogues to the endogenous metabolite 12-HETrE. It comprises stable, selective, and potent IP (prostacyclin) receptor agonists. The programme has demonstrated potential to significantly improve on mechanisms relevant to selected CVDs through initial in vivo animal models.

Meanwhile, preclinical programme CS014 is, like CS1, based on HDACi mechanisms and is being evaluated for the treatment of CVDs. This programme was acquired from Emeriti Bio in March 2019 and has since been developed in a collaboration between the two companies.

What CS585 and CS014 have in common is the fact that both programmes are being developed as part of a collaborative agreement with the University of Michigan, which has been a strong partner for Cereno for more than a year now.

For CS585, Cereno signed an option agreement with the University of Michigan in March of this year that gave exclusive rights to evaluate its market potential, as well as the possibility of in-licensing the candidate for further clinical development during a time period of 27 months. The agreement also gives Cereno the rights to the subsequent commercialisation of CS585.

Through the respective collaborative agreements with the University of Michigan, the aim with both preclinical programmes is to bring them to phase I within 24 months.

Programme	Discovery	Preclinical	Phase I	Phase II	Phase III	Indication
CS1	HDAC inhibitor					PAH
CS585	Prostacyclin analog					CVD
CS014	HDAC inhibitor					CVD

THERAPEUTIC PLATFORM

A strong collaboration

The University of Michigan is a top-ranked public research university in Ann Arbor, Michigan, US, with an extensive track record of successful collaborations with the pharmaceutical industry. The university has one of the largest annual collegiate research budgets of any university in the US with over 1.6 billion USD spent on research and development annually.

One of the key figures of this collaboration is Dr Michael Holinstat, who leads the work on Cereno's two preclinical programmes. Dr Holinstat received his PhD in pharmacology from the University of Illinois, Chicago, and completed postdoctoral training at Vanderbilt University in Nashville. His research interests include thrombosis, pharmacology and haematology, among others. He is currently an Associate Professor of Pharmacology and leads the translational programs in drug development in haemostasis and thrombosis in the Department of Pharmacology at the University of Michigan. In May of this year, Dr Holinstat, joined the team at Cereno and took on the role of Director of Translational Research at the company.

Additionally, the Chair of Cereno's SAB, Dr Bertram Pitt, is Professor Emeritus at the University of Michigan, where he has been active in CVD research for over 40 years.

University of Michigan
Source: Shutterstock

POSITIONING & MARKET POTENTIAL

POSITIONING

Patients diagnosed with PAH are often started on a combination of different treatments to address the pathological mechanisms of the disease. CS1 has shown potential to address several of these mechanisms and could therefore be relevant both in combination with other therapies as well as monotherapy.

Combination treatments are becoming more adopted

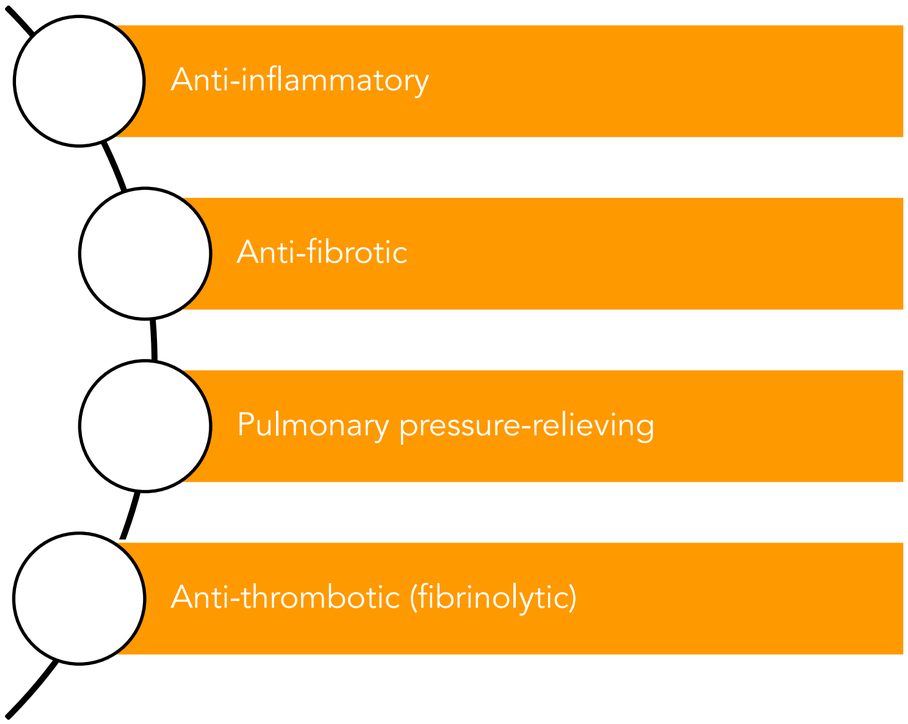
Early stage disease is treated with different classes of drugs following different pathways, such as endothelin receptor agonists (ERAs), PDE5 inhibitors (PDE5i), and depending on response and risk, additional drugs can be added, e.g., prostacyclins (PCA) and soluble guanylate cyclase stimulators (sGC). Only patients with known clinically manifested thromboembolism receive anticoagulants in most countries.

CS1 represent a new class of drugs to treat PAH

A key advantage of CS1 is the four-fold efficacy profile outlined in the figure to the right. This profile was thoroughly described in a review article recently published in The Lancet Healthy Longevity, which is a strong validation of the fact that therapeutics based on HDAC inhibition, such as CS1, have significant potential in a number of CVD indications, including PAH.

Furthermore, CS1 is an oral, daily treatment offering a convenient alternative for patients. It is proven to be safe and well tolerated, which indicates suitability as a potential long term therapy.

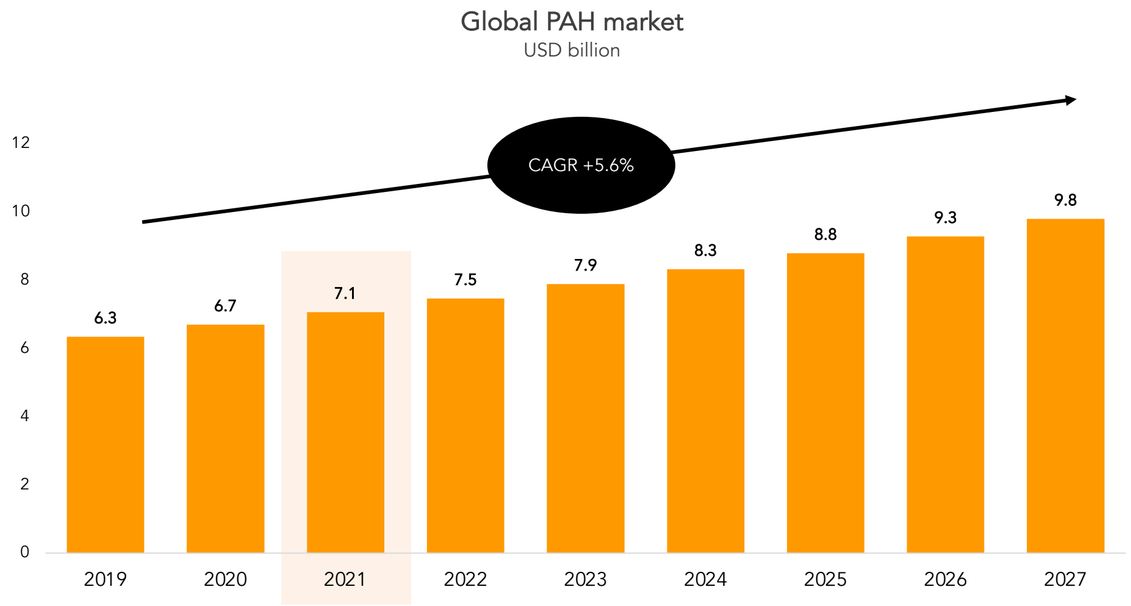
CS1's four-fold efficacy, all relevant for PAH



MARKET POTENTIAL

Despite being a rare disease, the prevalence of PAH in the world is expected to grow and the market is estimated to increase by 5.6 per cent annually according to American market analyst **Grand View Research** in a report published in 2020.

By 2027, the market size is estimated to 9.8 BUSD, with the US, Europe and Japan accounting for 50 per cent of the patients and 60 per cent of sales, according to **MSC Nordics Analysis** and **Informa Pharma Intelligence Datamonitor Healthcare**.



Competitive landscape

In the table below, a number of the marketed drugs are listed; their class, name and how much they generated in sales in 2020. Some drugs are off patent, but still generate steady sales revenues. Actelion, originally a Swiss pharmaceutical company, acquired by **Johnson & Johnson** in 2017, is marketing a portfolio of PAH therapies. Tracleer and Opsumit have generated sales of 5 billion USD each since 2014.

Letairis/Volibris was approved by FDA in 2007 – an ERA, once-daily oral treatment of PAH. The total sales in the US for Letairis has been reported to reach almost 6 BUSD in the 2010s, according to **Gilead Sciences**'s annual reports. The patent for Letairis expired in 2020.

Adempas is a drug commercialised by **Bayer** and approved by FDA in 2013 to treat PAH and chronic thromboembolic pulmonary hypertension (CTEPH) – a condition that is also characterised by hypertension in the pulmonary artery, but of different origin than PAH. Since approval up to 2019, Adempas has sold for 1.6 BEUR globally, driven mainly by the US market. The Adempas patent is valid until 2027.

A table with marketed drugs used in PAH treatment can be found on the following page.

Marketed drugs used in PAH treatment

Class	Name	Molecule	Company	Sales* 2020 (MUSD)	Patent expiry
ERA	Letairis	ambrisentan	Gilead Sciences	314	Dec 2020
	Opsumit	macitentan	Actelion	1639	Dec 2025
PDE5i	Adcirca	tadalafil	Eli Lilly	67	Aug 2018
sGC stimulators	Adempas	riociguat	Bayer	628	Sep 2002
PCA	Uptravi	selexipag	Actelion	1093	Oct 2026
	Remodulin	treprostinil	United Therapeutics	517	Jun 2018
	Tyvaso	treprostinil	United Therapeutics	483	Jan 2026
	Orenitram	treprostinil	United Therapeutics	293	Feb 2030

* Sales figures from annual reports

COMPETITIVE LANDSCAPE

Deals in the PAH space

The market for PAH therapies is of considerable size and is growing steadily. Cereno Scientific strongly believes that CS1 will be able to enter this competitive market and will help transform how PAH is treated in the future.

Several deals in the PAH space have been struck during the past decade, particularly in recent years, indicating a growing interest for the area. Given the underlying medical need for new therapies, projected market growth, new deals are likely to be announced in the coming years.

An ODD status has historically been a value driver for licensing deals, which gives Cereno Scientific a good position in future negotiations.

Date	Licensee	Licensor	Candidate/drug	Phase	Region	Total deal value (USD)	Upfront (USD)
15 Nov 2018	United Therapeutics	Arena Pharmaceuticals	APD811	III	Worldwide	1.2 B	800 M
5 Dec 2017	Everest Medicines	Arena Pharmaceuticals	APD811	II	China, Hong Kong, Macau, South Korea	224 M	12 M
2 Oct 2017	Gossamer Bio	Pulmokine	GB002	I	Worldwide	303.5 M	5.5M
6 Jan 2017	VIVUS	Selten Pharma	VI0106	II	Worldwide	40 M	1 M
5 Jun 2014	Merck & Co	Bayer	Adempas	Marketed	Worldwide excl US	2.1 B	1 B
17 Feb 2010	Nippon Shinyaku	Actelion	Uptravi	II	Worldwide	50 M*	30 M

* Before the compound had been granted ODD

IP-SITUATION

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For pharma and biotech companies, a viable strategy for their intellectual property rights is of vital importance to achieve scientific and commercial success. Cereno Scientific is actively strengthening their IP protection, continuously evaluating new findings in their preclinical and clinical research.

For the drug candidate CS1, Cereno has three patent families, of which two of them combined cover issued patents for the most important global markets, including the US, Japan and Canada. The company has ongoing patent processes in several strategic countries and regions that will add market exclusivity upon approval.

The expansion of the patents in the new geographic areas, e.g. the patents announced this year in Russia and Japan, is a significant addition to the long term value of the CS1 project.

Patent family number	Patent family for CS1	Status	Application filed	Estimated patent expiry
WO2012/120262	For the use of various HDACi to increase t-PA production	Granted	2011	2032
WO2016/055797	For the use of VPA to reduce PAI-1, including dosing, formulations and optimal efficacy	Granted	2014	2035
WO2017/175013	To expand protection around formulation and use of CS1	Pending	2016	

FINANCIAL STATUS

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In the latest financial report, the first quarter results for 2021, the company reported a loss of 3.9 MSEK for the quarter and the cash balance amounted to 60 MSEK.

In September 2020, Cereno carried out a directed share issue to which the company raised a total of 60 MSEK together with a bridge loan of 10 MSEK. In connection with the funding in September, the company also issued two warrants, series TO1 and series TO2.

Added funding in 2020	**MSEK**
Directed issue	60
Loan facility	10

Potential funding		**Start of subscription period**
Warrant series TO1	98.4	15 September 2021
Warrant series TO2	114.8	14 September 2022

Warrants to fund the company

The warrant TO1 will be exercised in 15-29 September 2021, a total of 34 519 281 TO1 has been issued. The subscription price will be at 30 per cent discount to the volume weighted average during 30 August to 13 September 2021, with a maximum subscription price of 2.85 SEK per share. Based on this price, series TO1 can potentially add 98.4 MSEK to Cereno before costs.

The series TO2, will be exercised in September 2022. TO2 has similar conditions as TO1, only the maximum subscription price will be 3.33 SEK per share, potentially adding 114.8 MSEK.

Both TO1 and TO2 are traded on the Spotlight Stock Market.

BIOSTOCK'S COMMENTS

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This year, the stock market has started to appreciate the efforts made by Cereno Scientific. Compared to last October, the increase is large in percentage change but it is still modest in terms of absolute value, given the company's future market potential.

Since last October, Cereno has been able to tick a number of value enhancing boxes, as the company is approaching initiation of the phase II trial with CS1 in PAH. The company has not only achieved a successful pre-IND meeting with the FDA, they have attracted world-leading clinical expertise to their scientific advisory board and reached an agreement with a renowned CRO to collaborate with during the trial, strengthened the IP position and recruited key personnel for the next step in development.

In addition, the collaboration with the University of Michigan, where Cereno's SAB Chair Dr Bertram Pitt, is Professor Emeritus, has provided Cereno with the expansion of its pipeline with CS585 and the agreed development plan for CS014 and CS585. The two 24-month development programmes are giving Cereno a defined plan for these projects and, if successful, will lead to two new clinical programmes; ultimately, establishing a firm position in a field characterised by strong competition and significant markets.

With Dr Holinstat as member of Cereno's management team and Director of Translational Research, the company's pipeline development will be led by an authority in the field and in collaboration with a world-leading research institute at the University of Michigan.

Financially, the shareholders have the opportunity to fund the company through subscription of shares via the two warrants TO1 and TO2, potentially adding around 200 MSEK in two years. The first warrant will be exercised by mid-September 2021 and the second one year later.

Any additional funding activities should be seen as an increasing investor interest for Cereno, beneficial to all shareholders in the long term. The company can choose to go to market by themselves with CS1 in PAH, but a natural development would be to engage in talks with big pharma and biotech companies along the way, evaluating possible licensing and partnering deals as the phase II programme advances and the development programmes evolve.

Long-term, a change of list in Stockholm or a US listing would significantly increase the company's funding opportunities, giving larger exposure to institutional investors.

In conclusion, Cereno Scientific is now a biotech company with a portfolio of projects with the lead candidate soon in phase II. Accordingly, the company is stronger, poised to claim its position within cardiovascular diseases - a large field where the medical need is great and the commercial opportunities for a new approach are promising.

Key points

- *Initiation of phase II with CS1 in PAH in September 2021*
- *Collaboration with University of Michigan regarding CS585 and CS014*
- *Expansion of management and clinical expertise*
- *Subscription of TO1 15-29 September 2021 could add 98.4 MSEK*
- *Acknowledged and supported by world-leading experts*
- *Cereno Scientific is positioning itself within CVD with a portfolio of projects*

APPENDIX

ABBREVIATIONS

AZ	AstraZeneca
CRO	Contract Research Organisation
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
CVD	Cardiovascular Disease
DNA	Deoxyribonucleic acid
DVT	Deep Vein Thrombosis
ERA	Endothelin Receptor Agonist
EUR	Euro
FDA	Food and Drug Administration
HDAC	Histone Deacetylase
HDACi	Histone Deacetylase inhibitor
IND	Investigational New Drug
NOAC	Novel Oral Anticoagulant
ODD	Orphan Drug Designation
PAH	Pulmonary Arterial Hypertension
PAI-1	Plasminogen Activator Inhibitor-1
PCA	Prostacyclin Analog
PDE5i	phosphodiesterase 5 inhibitors
SAB	Scientific Advisory Board
SEK	Swedish Kronor
sGC	soluble Guanylate Cyclase
t-PA	tissue Plasminogen Activator
USD	US Dollar
VPA	Valproic Acid
WHO	World Health Organization

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