

Developing the “missing link” biomarker test for cardiovascular disease

Company

CardiNor AS is a Norwegian biotech company established in June 2015 to develop and commercialise assays for secretoneurin (SN), an important new biomarker for cardiovascular disease (CVD).

The use of SN for CVD is based on research carried out by world leading cardiac authorities at Akershus University Hospital, Oslo University Hospital and Akademiska Sjukhuset in Uppsala, Sweden. Patents have been granted in the US and Europe.

SN is the only biomarker shown to be associated with biological processes linked to cardiomyocyte Ca²⁺ handling (1). This unique biological function explains why SN presents as an independent and strong predictor of mortality in all major patient cohorts, including **ventricular arrhythmia, acute heart failure, acute respiratory failure** patients with CVD and **severe sepsis**.

We are currently developing an easy to use ELISA (enzyme-linked immunosorbent assay) blood test to address the vast and untapped market potential in CVD patient diagnosis, risk stratification and monitoring. This will also involve clinical documentation, regulatory filing and market awareness programs.

Medical need

Cardiovascular disease (CVD) is the leading cause of death worldwide (2). A large proportion of

these patients ultimately die from sudden cardiac death (SCD). The predominant causes of SCD - ventricular tachycardia and ventricular fibrillation (VT/VF) – have been shown to be key determinants of survival in patients both with CVD and the general population.

Cardiomyocyte Ca²⁺ imbalance is at the core of most triggered arrhythmias in CVD, but current biomarkers (troponins and BNP) do not reflect Ca²⁺ regulation. Accordingly, methods to identify and monitor patients with cardiomyocyte Ca²⁺ imbalance and increased risk of VT/VF are highly warranted. As the only biomarker associated with Ca²⁺ status, SN is ideally suited for this purpose. Moreover, high SN concentrations are also a strong indication of the need to follow up with ECGs, echocardiography, and other examinations (angiography, cardiac MRI, PET-CT, etc.) to determine whether there are signs of structural or functional heart disease.

In addition to front line CVD testing, there is a potential major role for SN testing in patient selection for cardiac rhythm management. Current criteria both lack the desired sensitivity and specificity. As an example, as many as 70% (3) of patients with an ICD (implantable cardioverter-defibrillator) will never need the device. Conversely, a large proportion of sudden cardiac death patients do not fulfil current criteria for ICD implantation. Thus, there is an urgent need to better target and select patients who will benefit from an ICD. The arrhythmia-ICD market is massive: It is estimated that > 30 million people suffer from arrhythmias and

>100.000 ICDs are implanted in the EC alone with yearly device treatment costs exceeding €2 billion.

CardiNor solution

Our solution to this problem is a new biomarker test – SN. Data recently published in the high-ranking Journal of the American College of Cardiology (JACC) and several other publications clearly show that elevated levels of SN in blood are associated with increased risk of cardiovascular mortality. The importance of these results and potential of SN was emphasized in the JACC editorial: **Will Secretoneurin Be the Next Big Thing?** Implying a potential future role of SN alongside BNP and troponins for risk stratification in patients with cardiovascular disease.

CardiNor is now developing an easy-to-use blood test for SN to help identify patients with heart disease who will benefit from ICD treatment. The current technology available for measuring SN is an RIA (radioimmunoassay) not suitable for routine or clinical use. We are developing a new test based on ELISA technology that is very well established in both clinical research and routine and can easily be adopted on high-throughput platforms such as Cobas by Roche and Architect by Abbott.

The opportunity

The market for CVD biomarkers exceeds USD 5 billion, with BNP and troponin both selling for approx. 2 billion annually. Our forthcoming ELISA, Secretoneurin is the only biomarker shown to be associated with biological processes linked to cardiomyocyte Ca²⁺ handling.

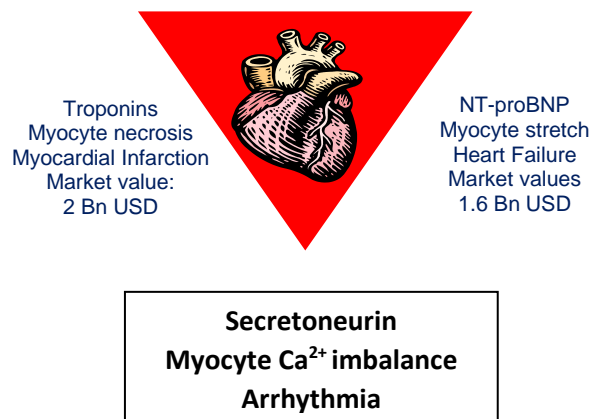
The company will market and sell its first product for research use (RuO) through a network of local and global distributors covering the major markets in Europe and the US, followed by the

as mentioned, will be designed in such a way that it easily can be adopted to these platforms.

This unique biological function explains why SN acts as an independent and strong predictor of mortality in several patient cohorts, including, **ventricular arrhythmia, acute heart failure, acute respiratory failure** patients with CVD and **severe sepsis**.

SN is thus addressing a vast and untapped market potential for CVD patient diagnosis, risk stratification and monitoring, such as BNP/NT-proBNP and cardiac troponin.

Fig 1



The biomarker market for CVD is dominated by the major IVD companies such as Siemens, Roche and Abbott with their proprietary high-throughput platforms. Our forthcoming ELISA, as mentioned, will be designed in such a way that it easily can be adopted to these platforms.

Business model

introduction of a CE marked product. The next face in our commercialization strategy will be to seek collaborations with major IVDs players such as Abbott, Roche, Siemens or medical device companies such as Boston Scientific, to support the US regulatory submission and market introduction. Collaboration and/or out licensing

to adopt the SN test on the high throughput diagnostic platforms of these companies will secure a global market and access to high volume facilities. In parallel, CardiNor will pursue opportunities to adopt its SN test to point of care (PoC) platforms to facilitate market uptake and gain access to the near patient testing segment. CardiNor will sell key reagents and collect royalties from such agreements.

The team

The CardiNor team consists of Dag Christiansen, CEO, Olav Steinnes Chair with Ronny Hermansen and Torbjørn Omland as board members. The team have extensive experience from the IVD industry, covering every aspect of a company's life cycle, from start-up phase to exit. This includes high-level business negotiations, licensing agreements, scientific marketing and successful trade sales

The team also has in-depth know-how of the CVD biomarker field, both from a business and scientific perspective. Professor Omland was involved in the early clinical validation of BNP and NT-pro-BNP and played a key role in documenting the clinical value of these very important biomarkers for heart disease. He also did pioneering work on the use of high sensitivity troponins. Professor Omland served as a scientific advisor for Biosite and is currently advisor for several major IVD and pharma companies. He is an Associate Editor in Circulation and member of the International Federation of Clinical Chemistry (IFCC)'s Task Force on Clinical Application of Cardiovascular Biomarkers.

In addition, CardiNor has signed on several external consultants to gain access to the know-how vital for the development of an SN ELISA: Frank Franzen VP R&D Alere (former Axis-Shield) – Mats Stridsberg Akademiska Sjukhuset, Uppsala Sweden and Tom Soriano, CEO Docro on regulatory affairs US.

Major future milestones

- Development of a prototype ELISA, H2-18
- Commercial launch of RuO, H2-19
- CE marking of SN ELISA, 2020
- Partner major IVD, 2020
- US regulatory clearance, 510k, 2022

Partners

CardiNor has teamed up with several leading technology partners to secure access to world leading expertise and know-how vital for a successful assay development. We also have access to world leading expertise on CVD biomarkers. Combined this provides CardiNor with a complete value chain from basic R&D through to production of final product.

- ✓ **Bioventix** is a listed company on LSE. It is a world leading supplier of antibodies and among its customers we find Abbott, Roche, Siemens and bioMèriux. Bioventix has also made investments in CardiNor
- ✓ **Mizar Bio** (former Axis-Shield lab in Bodø Norway) is supporting our assay development. The Mizar scientists have extensive know-how of and a long track record in assay development and technology transfer of several important IVD biomarker assays to proprietary IVD platforms, including PoC instruments
- ✓ **Kaivogen** is a Finnish company specializing in the development and production of ELISA components and finished Kits. The company is currently supplying customers in the US and Europe. Kaivogen Oy is certified according to the Quality Management System standard ISO 9001:2008 and ISO 13485:2003 by DNV GL

- ✓ **Akershus University Hospital (AHUS)** is home to the research group of professors Torbjørn Omland and Helge Røsjø, who are world leading experts on CVD biomarkers and key scientific advisors to CardiNor. In addition, Akademiska Sjukhuset Uppsala and Stavanger University hospital are supporting our clinical trial collecting blood samples from patients with ICD implants
- ✓ **Boston Scientific**, a world leading supplier of medical devices for the management of heart disease has agreed to grant CardiNor access to their clinical study, MADIT which includes close to 2000 patients with ICD implants for the validation of our SN assay when launched as RuO

The IP position

CardiNor has secured an exclusive license to IP generated on secretoneurin in connection with CVD. The patent was granted in the US territory 30 July 2013, and for Europe last year. This agreement also provides CardiNor rights to sub license to future partners.

It covers the use of SN in relation to heart disease (HD) with a comprehensive list of important claims linked to:

- ✓ **Diagnosing heart disease**
- ✓ **Determine the clinical severity of HD**
- ✓ **Prognosis of HD**
- ✓ **Identify a subject requiring more intensive monitoring**
- ✓ **Identify a subject which might benefit from early therapeutic intervention**
- ✓ **Monitor the progression or severity of HD,**

- ✓ **To assess effectiveness of HD therapy,**
- ✓ **To monitor the progress of HD therapy**

Shareholders

- Inven2 AS: 30,500 (48%)
- Bioventix plc: 13,550 (21,5%)
- Dag Christiansen, CEO: 3,950 (6,3%)
- Torbjørn Omland, inventor and board member 3,500 (5,6%)
- Helge Røsjø, inventor: 3,500 (5,6%)
- Geir Christensen, inventor: 3,500 (5,6%)
- Mats Stridsberg, inventor: 3,500 (5,6%)
- Ronny Hermansen, board member: 1,000 (1,6%)

Funding needs

The initial development work of the ELISA and creation of a biobank for clinical validation of SN was funded by the Norwegian Research Council with approx. 7 MNOK. In addition, the company has in addition secured 2 MNOK I private funding and 0.7 MNOK from Innovation Norway.

To secure the further product development of the SN ELISA assay (research use only), conduct further clinical trials, establish production (OEM) and initiate commercialization activities, the company is initially seeking 16 MNOK in private funding for 2018 -2019, in addition to the public funding.

CardiNor and its partners, AHUS, Bioventix and Kaivogen has been granted Eurostars funding of the project: Secretoneurin, a breakthrough blood biomarker for heart disease and sudden Cardiac Arrest risk. The total funding by EU is € 631,000.

Vocabulary

Arrhythmia: An irregular heartbeat that's abnormally slow (bradycardia) or too fast (tachycardia)

Ventricular tachycardia (VT): A heart rhythm disorder originating in the ventricles. Rapid contractions prevent the heart from filling adequately with blood between beats. Patients may feel faint, become dizzy or collapse. Can be life threatening if not treated.

Ventricular fibrillation (VF): A heart rhythm disorder originating in the ventricles. An abnormally rapid heart rhythm that is unstable and irregular. Electronic signals move through the heart erratically and prevent it from beating properly. Patient may feel faint. If untreated, may cause cardiac arrest

Electrocardiogram: A test that records the electrical activity of the heart, revealing evidence of previous heart attack, enlargement of the heart and abnormal rhythms

Implantable cardiac defibrillator (ICD): A surgically inserted electronic device that constantly monitors your heart rate and rhythm. When it detects a very fast, abnormal heart rhythm, it can deliver an electrical shock to the heart muscle to help the heart beat in a normal rhythm again

Angiography is a medical imaging technique used to visualize the inside, or lumen, of blood vessels and organs of the body, with particular interest in the arteries, veins and the heart chambers

Cardiac MRI, is a medical imaging technology for the non-invasive assessment of the function and structure of the cardiovascular system

References:

1. Ottesen et al (2015) Secretoneurin Is a Novel Prognostic Cardiovascular Biomarker Associated With Cardiomyocyte Calcium Handling. Journal of the American College of Cardiology, 65(4), 339-351. <http://dx.doi.org/10.1016/j.jacc.2014.10.065>
2. WHO (2017) The top 10 causes of death, fact sheet. Available at: www.who.int/mediacentre/factsheets/fs310/en/
3. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352: 225–37.

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