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June 2019

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Erik Kinnman
CEO

As summer approaches, we can now look back on a successful first half of the year. Our important KL1333 project has now commenced its important Phase Ia/b study with healthy volunteers and patients. The first test subject was screened at Covance’s Clinical Research Unit in Leeds, in the UK, and we anticipate being able to present the first results from the study at the end of 2019.

The objective of the NV354 project is to develop an alternative energy source for genetic mitochondrial disease. The initial experimental results are positive and we are now continuing preclinical development. We expect to present further experimental data during the year, with the goal of starting clinical trials in 2020.

The NeuroSTAT project is also moving in a positive direction. In May, the FDA approved our IND application (Investigational New Drug), which makes it possible to conduct clinical studies with NeuroSTAT in the US. We already presented very exciting biomarker data earlier.

NeuroVive’s development was very positive during the spring and I am already looking forward to the remainder of 2019. I want to take this opportunity to wish everyone that follows NeuroVive in one way or another a long and pleasant summer!

Erik Kinnman, CEO

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Spreading the word



The clinical phase Ia/b study with candidate drug KL1333 started in the UK in March.

KL1333 in clinical study – how does it work?

In March this year, NeuroVive started its clinical phase Ia/b study with candidate drug KL1333 in the UK. KL1333 is in development for chronic treatment of genetic mitochondrial diseases, a group of diseases with a critical unmet medical need. NeuroVive’s Matilda Hugerth – Director of Clinical and Regulatory Affairs, together with Magnus Hansson – Chief Medical Officer, visited the clinical site in Leeds when the drug was given to the first healthy volunteer. Amongst other things, in this interview, Matilda talks about how the study is conducted and about her role in the company.

Hi Matilda! Could you talk a little about your background?

“I am a pharmacist by trade, so I have worked at a number of pharmaceutical companies in clinical development in different roles, on different projects and in different therapeutic areas, including Novartis, UCB Pharma, a Belgian company, and then for quite a few years in Denmark at Lundbeck.”

You have worked at big companies, but what is the main difference in working for a small pharmaceutical company like NeuroVive?

“At NeuroVive, we are incredibly driven and passionate about what we do. There are some organizational differences; in a small company like this, we don’t have the same access to internal resources, so we use our



Matilda Hugerth

network to a large extent and work with outside experts in a wide range of areas.”

Could you give us an example of the network you describe? I understand that you also collaborate with your competitors, which is a little unusual.

“We work in the area of mitochondrial medicine, and there are just a handful of companies that work with mitochondrial diseases. We all share a common goal of developing new treatments for those patients who do not have treatment alternatives today. We raise awareness of these diseases in the process, we work with government entities to increase their interest in the diseases, and we create interest in the field. In this way, we are partners more than we are competitors. Some other examples of experts we work with are patient organizations. They are experts in what it’s like to

live life as a patient with these diseases. There are also experts with more technical knowledge, such as statisticians, who know how to carry out trials in the smartest way. It could also be clinical experts, who know how to best treat these patients, or government agencies with experts who know how to best navigate through the regulatory maze.”

You are developing drugs for people with very serious illnesses, where there currently aren't many options for these patients. Can you talk a little about the research?

“It has to do with genetic defects in the DNA that have an impact on the mitochondria in the cells. The mitochondria are the so-called organelles of the cells that help provide the body with energy. If one has defects in the mitochondria, the organs that demand the most energy will be affected first. It can be different for different patients. It can lead to blindness, problems with the heart or muscles, muscle weakness or that you get extremely fatigued, so tired that you have a hard time getting out of bed in the morning.”

How does the drug development process work, up until you have a finished product, with all the different phases in clinical trials?

“Clinical trials are performed in human subjects and you usually divide them into three phases. In phase I you investigate, in healthy volunteers, the drug efficacy, how the drug works and is metabolized in the body. In phase II you look at the efficacy of

the drug in a small clinical trial to see how the illness you want to treat is ultimately affected by the drug. Then you move on to phase III, where you do slightly larger confirmatory trials. Finally, you assemble all of this information and make an application to the Medical Products Agencies who will do a risk/benefit analysis for the patient group who will be treated.”

Recently, you were in England to look over your clinical trial. What is your take on what's going on there?

“The study, underway in England, is a phase I study and we started in healthy volunteers. The day we were there we had dosed the first healthy volunteers, and we got to meet the healthy volunteers and the team, which is a highly skilled team who knows how to best conduct trials like these in accordance with all ethical and regulatory rules, which is very important for us and for those who participate in the trials - that this is done in the best possible way.”

This is a hybrid trial where you are working with very smart solutions to move things forward faster. Tell us a little about that.

“We have opted to do it, so we have both healthy volunteers and patients in the same trial, which is a way to move things along more quickly and to earlier get information on how the drug works in patients as well. This is something one would usually expect in phase II, so that means we get the maximum amount of information from the same trial, which will help us forward in the development of KL1333.”

How do you decide which trials you are going to do and when?

“That is a rather fun part of the job, making a strategic plan, a development plan. Then you take a look at exactly which regulations apply as well as the guidelines for this, but above all, you look at KL1333 in this therapy area and how to best proceed. In general, you want to do as few trials as possible; the fewer trials, the lower the cost and the faster you get things out to the patients. At the same time, you want to be sure to perform enough studies to be able to evaluate whether the drug is effective and safe to use.”

What drives your company, and what are you working on right now?

“The biggest thing that drives us, is developing a drug that improves patients' overall lives and day to day lives. It is quite natural to feel this way about this therapeutic area since there are no treatments available for patients with mitochondrial diseases today. Right now, I am working on getting this phase I trial completed. In parallel with that, we are preparing for the next trial, which is a phase II trial in patients.”

See the complete video interview here: <https://cornelianews.com/deep-talk/nytt-godkannande-for-neurovive/>



Erich Gnaiger, CEO, and Verena Laner, COO of Oroboros Instruments, in front of their eye-catching entrance in Innsbruck, Austria.

NeuroVive and Oroboros in exclusive agreement on novel research compounds

In February 2019, NeuroVive announced that the company has entered into an exclusive agreement with Oroboros Instruments, a leading global supplier of mitochondrial research technologies. NeuroVive and Oroboros share a long history collaborating in mitochondrial research, and the current agreement will promote NeuroVive’s new research compounds and help to elucidate the role of mitochondria in disease. We met with CEO Erich Gnaiger and COO Verena Laner for an interview at their facilities in Innsbruck, Austria.

Earlier this year, you entered an exclusive agreement with NeuroVive to commercialize and distribute two of their succinate/malonate prodrugs to the mitochondrial research community. Can you briefly explain the applications for these new research tool compounds and what opportunities you think they will give for better understanding mitochondrial physiology?



Erich

“The NeuroVive compounds that attracted our attention are cell membrane-permeable succinate and malonate, which are now available from Oroboros Instruments as MitoKit-CII. With the MitoKit-CII reagents, we can modify respiration in living cells by supply of succinate (NV118) or inhibition of respiratory Complex II (CII) by malonate (NV161). In addition to evaluation of inherent or drug-induced CI dysfunction in living cells, two important questions can now be addressed with the MitoKit-CII: (1) When adding succinate to living cells, a specific transporter protein may transport

succinate across the cell membrane and exert a stimulatory effect on respiration. This transporter-effect can be evaluated in relation to controlled succinate delivery to the cell using NV118 followed by CII-inhibition by NV161. (2) In many living cells, external succinate does not pass the intact cell membrane. In these cells treated with the Complex I inhibitor rotenone, stimulation of respiration by succinate is a sensitive test of cell viability, if the action of the transporter can be excluded. After selective cell membrane permeabilization, succinate becomes accessible to mitochondria and stimulates the respiratory Complex II. Integration of the MitoKit-CII in these protocols allows us to separate the effects of loss of cell membrane barrier function - which is cell death - versus transporter activity. Thus, a highly selective respirometric cell viability test is available, as well as a test for inherent or drug-induced dysfunction of respiratory Complex I of the mitochondria.”

Oroboros and NeuroVive have a long history of research and skill exchange. NeuroVive’s Eskil Elmér, CSO, and Magnus Hansson, CMO, together with Erich Gnaiger, started to build a solid collaboration already more than 13 years ago. What makes the people in the two companies work so well together?



Verena

“Both teams are highly motivated to contribute to a better understanding of mitochondrial disease. Eskil Elmer’s group – a high-level laboratory in the mitochondrial research field - with innovative driving force is in continuous conversation with our team and was looking for a possibility to provide the newly developed prodrugs to the scientific community. Our company, Oroboros Instruments, has implemented the concept of Open Innovation and appreciates opportunities for innovation. Our collaboration creates scientific and entrepreneurial synergies.”

NeuroVive has communicated that their revenues will be modest and that the primary value is that the outcome of this partnership is part of their mission to promote the development of mitochondrial medicine research. If you look ahead, what do you predict this new opportunity will mean for mitochondrial medicine at large?



Erich

“In our collaboration, our mission as a driving force in mitochondrial physiology plays the most important role. Over the past decade it has become increasingly evident that mitochondria are central in numerous diseases, both acquired and inherited, including diabetes, cardiac myopathies, various neurodegenerative diseases, and cancer. Mitochondria may in this context be a downstream element with impaired functionality which primarily aggravate the existing disease condition. Alternatively, mitochondrial defects may act a driving force, e.g., by supporting accelerated tissue growth as observed in cancer, or by damaging structures through enhanced production of reactive oxygen species, as can be detected in some neurodegenerative diseases. In either case, to better understand the role mitochondria play in the disease and to eventually develop therapeutic approaches, it is essential to know which element(s) of the mitochondrial metabolic machinery have changed. To address this question, elaborated experimental protocols have been developed by Oroboros that allow to dissect the electron transfer pathways fueling respiratory complexes and driving oxidative phosphorylation (OXPHOS). Numerous diseases can be well correlated with metabolic reprogramming of mitochondrial pathways or specific defects of the OXPHOS system. For OXPHOS analysis, however, cells must be permeabilized to make all chemicals accessible to the mitochondria, as required in respirometric titration protocols. The intact cell membrane is a selective barrier through which only few of the numerous chemicals required for analysis can penetrate. The MitoKit-CII will help us to apply specific OXPHOS analyses to living cells, without disturbing the cellular signaling network by cell membrane permeabilization. This opens up new research opportunities to analyze mitochondrial function in health and disease. While the permeabilized cell-approach will retain its importance as the method of choice for detailed OXPHOS analysis, the combination with using living cells and cell membrane-permeable chemi-

cals provides a state-of-the-art approach to accelerate progress in the scientific understanding of mitochondrial and cellular energy metabolism. This is fundamental for the development of therapeutic approaches involving mitochondria as important targets.”



Oroboros' mythological logotype. The dragon feeding on its own tail, forming a cycle, symbolizes the divine process of creation and the evil backlash of destruction.

Oroboros Instruments has developed the Oroboros O2k-FluoRespirometer, advanced high-resolution laboratory equipment which is considered the 'gold standard' in measuring the mitochondria's ability to convert oxygen and nutrients into metabolic forms of energy. Can you tell us a little bit about how you started to explore this science field and what it is that has made you succeed?



Erich

“High-resolution respirometry started with the specific aim to measure mitochondrial respiration accurately over a large range of oxygen levels, thus fighting the artefact prevailing in the literature on oxygen kinetics of mitochondrial respiration. These methodological developments opened the door to a variety of biomedical applications, cutting down the size of muscle biopsies required for the diagnosis of mitochondrial function, reducing the number of cells needed for respirometric assays, and providing an unparalleled reproducibility. Continued innovation was another key to our success. Respiration can now be monitored at controlled oxygen levels combined with measurement of mitochondrial membrane potential, hydrogen peroxide production, ATP production, pH, Ca²⁺ and nitric oxide levels. For combining polarographic oxygen measurements with fluorometric assays in the O2k-FluoRespirometer, we received the prestigious B&C Houska award in 2012. Our next step is the integration of a Q-redox sensor, NADH-autofluorescence, and a PhotoBiology module in the NextGen-O2k”.

We recently heard the news that you have received a € 2.4 million EU research grant. Congratulations! How will you use the grant, and what does it mean to a company like yours?



Verena

“Yes, these are great news for our team and customers. With this project we are able to push the current development of the NextGen-O2k and ensure a fast launch. Besides the fact that we received the grant, it is highly prestigious to be selected out of approx. 1,500 applications, and to be one of only two Austrian companies who received the H2020 SME Instruments Grant in this round.”

Can you describe the Oroboros business model and how you see the company evolving over the next few years?



Erich

“Being one step ahead with instrumental innovations on a global scale is the key for our success. We include the users in the early stages of the development, and the concept of Open Innovation is therefore crucial. Importantly, we have a long-term partnership (WGT Elektronik GmbH & Co KG). Two years ago we have begun another promising collaboration with an innovative start-up company for software development (SH Tech). Beside this project we also have other developments in the pipeline, which will ensure our position on the market.”

In terms of sales/distribution rate of the NeuroVive research compounds, how has the interest from the research community been so far, and what are your estimations for the coming year and also further ahead?



Erich

“Based on previous experience with the respiration medium MiR05-Kit developed by Oroboros, we know that once we advertise a well-tested new product through our established routes, i.e., customer newsletters, conference presentations, workshops and training courses, interest will gain significant momentum. In addition, we have the biggest network of mitochondrial research leaders (> 600 labs), which will help us to disseminate the new product. Once first applications are published using the MitoKit-CII, sales are expected to increase exponentially. This will support key developments in mitochondrial medicine.”

Oroboros' website: www.oroboros.at



Interview with Magnus Persson – new Board member

Welcome to NeuroVive! Can you tell us about yourself?

“I have a background as a doctor and researcher, though I co-founded a startup company in health technology while still a postdoc in the 1990s, and have therefore worked with leadership, strategy and financing in innovation-driven small companies in the life science sector. I was a partner in two venture capital companies, one in Sweden and one in San Francisco in the US.”

Why did you agree to join the NeuroVive Board?

“There were two main components: the focus on orphan drugs and the fact that the company’s management is highly experienced and familiar to me. Taken together with the company’s values, I believe NeuroVive has a strong potential to create value for shareholders and by extension for patients suffering from disabling mitochondrial diseases.”

Looking at NeuroVive’s various projects, is there a particular area that you find especially interesting or exciting?

“Difficult to say, all mitochondrial diseases are so serious that even if NeuroVive could only solve one of the diseases it is studying it would still be an enormous achievement, and a relief for the families affected.”

In light of your background, which issues do you expect to focus on in your work on the Board?

“As a Board member of several listed companies, not only in Sweden but also abroad, I consider general corporate governance as one key issue. In more company-specific terms, I believe I can use my experience to contribute in strategy discussions and issues concerning organizational structures.”

Which challenges and opportunities have you identified so far, both in the industry as a whole and specifically for NeuroVive?

“As always in small, life science companies, the main challenges are access to capital and talent. Specifically for NeuroVive, the project portfolio is so broad and promising that it will be a challenge to choose which projects should be out-licensed and which should be developed in house.”

Where do you think NeuroVive will be in five years?

“If the company remains independent, and is not acquired, I hope we will have several projects in the late clinical phase. Perhaps one of our projects will be about to receive marketing authorization.”

Spreading the word



Covance's clinical site: Leeds, UK, on 15 – 16 April 2019

Matilda Hugerth, NeuroVive's Director, Clinical and Regulatory Affairs, and **Magnus Hansson**, Chief Medical Officer & VP Preclinical and Clinical Development, visited the clinical site in Leeds when the first healthy volunteer in NeuroVive's phase Ia/b clinical study was given KL1333, the company's candidate drug for chronic treatment of mitochondrial diseases.



BIO KOREA International Convention: Seoul, South Korea, on 17 – 19 April 2019

NeuroVive's VP Business Development, **Mark Farmery**, and CEO **Erik Kinnman** attended this conference and met with old and new contacts in the Asian biotech- and pharmaceutical industry.



The 9th Annual Traumatic Brain Injury Conference: Washington, DC, US, on 16 – 17 May 2019

Magnus Hansson, NeuroVive's Chief Medical Officer & VP Preclinical and Clinical Development, and Kevin K.W. Wang, Center for Neuroproteomics & Biomarkers Research at the University of Florida, talked about *Traumatic Brain Injury Biomarkers in Therapeutic Trials: Pharmacodynamic Perspectives*.



BIO International Convention: Philadelphia, US, on 3 – 6 June 2019.

CEO **Erik Kinnman** attended this conference that gathered more than 16,000 participants from 74 countries with expertise including brain health, business development, orphan drugs and the financial industry, as well as participated in interesting partnering meetings. Interview with Erik: <https://cornelianews.com/live-talk/neurovive-intensifier-ar-jakten-pa-en-partner/>



LHON-dagarna och konferens – ”Lev här och nu”: Södertälje, Sweden, on 6 – 7 June 2019

Magnus Hansson, NeuroVive's Chief Medical Officer & VP Preclinical and Clinical Development, talked about the company's strategies to improve the energy metabolism in primary mitochondrial diseases, like LHON

Upcoming

UMDF Mitochondrial Medicine: Washington DC, USA, on 26 – 29 June 2019

This annual international symposium organized by the *US United Mitochondrial Disease Foundation* gathers researchers, caregivers, patients and families as well as patient organizations and companies. The goal is to spread knowledge about the latest research and to strengthen the mitochondrial medicine networks and enable interactions between the different target groups.

In addition to meeting with leading persons in mitochondrial medicine, NeuroVive will present important preclinical NV354 data on the poster *The succinate prodrug NV354 demonstrates positive effects on motor function and metabolic blood parameters in a model of rotenone-induced complex I dysfunction* and participate at a patients/families workshop where the ongoing phase Ia/b clinical KL1333 study will be presented.

Further reading at www.neurovive.com

