NeuroVive PHARMACEUTICAL

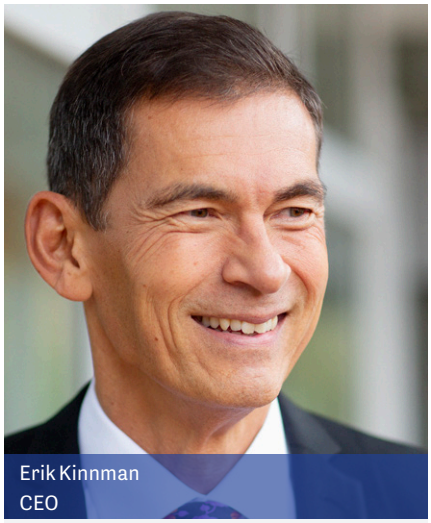
Newsletter

January 2019

NeuroVive has ambitious goals for 2019.

New pharmaceuticals can revolutionize the care of severely ill patients.

Read the exciting interviews with some of the people behind the latest successes at NeuroVive.



Erik Kinnman
CEO

NeuroVive has a very exciting – and promising! – year ahead.

NeuroVive has substantial research experience in mitochondrial function with focus on genetic mitochondrial disorders. Knowledge about these diseases is relatively new and so far only one drug has been approved in the area. This means progress in research and drug development has great potential to change the life situation for people, often children and young people, who currently suffer from severe mitochondrial disorders. Additionally, this means we – if we are successful in developing new drugs for the affected patients – can create substantial value for our shareholders.

NeuroVive's project portfolio in clinical phase research consists of two drug candidates, KL1333 and NeuroSTAT®. Both exhibit major potential to satisfy important unmet medical needs in traumatic brain injury and in rare genetic mitochondrial disorders, respectively, and for which there is no medication currently available. In 2019, we expect to make significant progress in both of these projects. At the same time, we have projects for common illnesses where there are opportunities to out-license projects to companies with large amounts of resources for further development and the market. To find out more, please feel free to read the interviews in this issue of our newsletter.

Key persons in this issue

Matilda Hugerth
Director Clinical and Regulatory Affairs. Coworker since 2016. Has 17 years of experience with project management in clinical and regulatory development in large pharmaceutical companies, such as Lundbeck.

Magnus Hansson
Chief Medical Officer & Vice President Preclinical and Clinical Development. Coworker since 2008. Has 15 years of experience in academic research within mitochondrial medicine, is a specialist physician and has been working in different stages of pharmaceutical development.

Mark Farmery
Vice President Business Development. Coworker since 2017. Has more than 15 years of industrial experience in leading positions within business development from e.g AstraZeneca.

Alvar Grönberg
Director of Preclinical Development. Coworker since 2014. Has 30 years of experience from key positions in big and small pharmaceutical companies, e.g Pharmacia.

Erik Kinnman
Chief Executive Officer. Coworker since 2016. Has broad experience in clinical development, business strategy, business development, investor relations and the financial industry as well as many years in leading positions in pharmaceutical companies, such as AstraZeneca.

Fredrik Nicklasson
Owner, Scius Pharma Support AB. NeuroVive's partner since 2016. Has 18 years of experience within pharmaceutical development, whereof 5 years as a consultant in his own company.

KL1333

A UNIQUE CHANCE TO MAKE A DIFFERENCE

Genetic mitochondrial diseases are metabolic diseases that affect the ability of cells to convert energy. An estimated 12 in every 100,000 people suffer from a mitochondrial disease. KL1333 has in preclinical models been demonstrated to increase mitochondrial energy output, reduce lactate accumulation, diminish the formation of free radicals and to have long-term beneficial effects on energy metabolism. The drug candidate is intended for chronic oral treatment of genetic mitochondrial disorders.

Precision medicine

Launch 2024

1.8 BUSD peak year sales

Read the interview with Magnus Hansson, Matilda Hugerth and Fredrik Nicklasson on the following page.

The clinical Phase I trial of your drug candidate, KL1333, developed for long-term oral treatment of genetic mitochondrial disorders, was completed in South Korea in 2018. What were the principal results, and why are they important for the future development of KL1333?


Matida

The trial examined single doses of KL1333 and showed two important things. Firstly, that KL1333 is well tolerated in the dose range of interest, and secondly, the blood concentrations after the different doses. A "first-in-human" study like this provides answers about the metabolic changes of the drug candidate in the human body. Therefore it is an important milestone to complete a successful "first-in-human" study, as it reduces uncertainty in a development program.

The clinical Phase Ia/b study will be conducted in the UK, and involves both healthy volunteers and patients with genetic mitochondrial disorders. What do you expect to understand from this study, and when do you expect to start up and obtain the initial results?

We plan to begin the study in 2019, and the results will come in throughout the year. The main aim of the study will be to examine the safety profile of KL1333 and how the drug is metabolized following multiple doses — that is, under conditions that are more similar to clinical treatment — in healthy volunteers and in patients. We will gather as much information as possible about how the patients' illness reacts to the drug, which will facilitate the design of our next study focusing on gauging the effects.

What needs to be in place to begin this kind of study?

It requires both approval from the local drug authority and approval from the ethics committee. We have these approvals in place, which are important steps on the path to beginning the study. Another important part of this kind of study is the methods of analysis in order to measure the concentrations of KL1333 in the test subjects. Optimizing and validating these methods is something we worked intensely on over the winter in order to begin this study. In addition, a functional scaling up of production of the drug being studied is required, which was successfully managed by our consultant Fredrik Nicklasson.

One of the consultant companies NeuroVive employs is Scius Pharma Support AB, which is based out of the same building in Lund as NeuroVive. The owner and operating consultant, Fredrik Nicklasson, was responsible for the chemistry, manufacturing and controls (CMC) work in the production of KL1333. We have seen the finished product, in the form of red tablets. How has production worked, and how far have you come?


Fredrik

Production has worked well, in general — both the manufacture of drug substance KL1333 and the manufacture of the KL1333 tablets to be used in the clinical study. We now have the finished tablets packed in bottles, ready to be used, which is an extremely tangible delivery for the project.

If everything goes as planned, KL1333 will reach the market as one of the first drugs approved for the treatment of genetic mitochondrial disorders such as MELAS. What effects do you expect in general as regards quality of life for patients, the view of mitochondrial medicine and the company's future?


Magnus

We are developing KL1333 for disorders such as MELAS and mitochondrial myopathy, which in principle currently completely lack effective treatments aimed at the defective mitochondrial function. Our collaborations with various patient organizations have been productive, and it is obvious how great the need is for new treatments when we talk with them. By improving mitochondrial functions, we hope that our product can result in a crucial improvement in muscle function and the function of other affected organs and thereby also in quality of life. If we succeed, it will naturally be an important milestone for us and people with mitochondrial disorders, but it will also indicate the potential of starting out from the function of the mitochondrion in the development of drugs.

What will be the most important milestone for the KL1333 project in 2019?


Matida

The start of our clinical study in the UK will be an important milestone, as will the readouts from the first cohorts. We are also very much looking forward to later in the year, when we will be recruiting and dosing the first patients with mitochondrial disorders for the latter part of the study, where we will also try to find different ways of measuring the effect of our drug in the patients.

NEUROSTAT

CLEAR STEPS TOWARDS THE MARKET

Traumatic brain injury (TBI) is caused by external force to the head resulting in immediate damage to nerve cells. The damage continues to worsen for several days after the acute trauma. The most common causes for TBI are trips and falls, traffic accidents and assault and battery.[1] With more than 50 million new cases occurring each year, TBI is estimated to cost the global economy nearly 400 billion dollars annually in direct and indirect healthcare costs.[2] A large number of patients suffer moderate to severe functional disabilities requiring intensive care and various forms of lifelong support.

50 million patients per year

€ 340,000 patient care cost

400 BUSD global societal cost per year

Read the interview with Matilda Hugerth and Erik Kinnman on the following page.

1) www.internetmedicin.se/page.aspx?id=1178
2) Maas A Et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. The Lancet Neurology. 2017 Nov; 16(12):987.

The development of NeuroSTAT for the treatment of moderate to severe traumatic brain injury (TBI) has made giant strides in 2018. Could you describe the biggest successes in the program, and what they mean for continued development?


Matida

Our interactions with the US Food and Drug Administration about our development program were a significant event last year, since it validated the way forward in the project for us. Late last year, we received some exciting results from the previous clinical study with TBI patients in Copenhagen, which showed that NeuroSTAT could push down the levels of markers for brain injury during treatment. We are using these results to design our next Phase II study. We also published the results from an experimental model conducted at the Children's Hospital in Philadelphia, which showed a drastic reduction in injury volume for NeuroSTAT compared with a placebo.

One of the goals for 2019 is to obtain approval of your Investigational New Drug (IND) application for clinical development in the US. Why is conducting studies in both Europe and the US important?

We intend to market NeuroSTAT in both Europe and the US; for that reason, it is always advantageous to conduct studies in both parts of the world. We also have orphan drug designation in both Europe and the US. But above all, it's because we want to collaborate with the most competent clinics and researchers in this field on both continents. In the US there is a lot of interest in TBI, and a great deal of research in the field is being carried out there. We are collaborating with TRACK-TBI, a network of leading TBI researchers, which is headquartered in the US.

You describe the planned Phase II efficacy study as innovative and limited in size. What do you mean by "innovative"?

The planned study will be innovative in several ways. The efficacy in the study will be measured using biomarkers, with both advanced imaging and with the type of biomarkers we used in our previous study. Another aspect is how the patients participating in the study are selected, in order to obtain a population that yields the least variation and thus the greatest possibility for detecting an effect signal. The study will also have an "adaptive" element, with the possibility of implementing certain modifications while the study is in progress based on preliminary results, which means that we maximize the information we can obtain from the patients included. All this will lead to the study not needing to be as large as a traditional Phase II study.

Which event do you see as the most important for the NeuroSTAT project in 2019?

The start of the planned Phase II efficacy study will clearly be crucial for the project.

Earlier, you said that "soft" money would largely finance the development of NeuroSTAT. What does "soft" money mean, and why is the program being funded this way?


Erik

In our corporate strategy, we wanted to create the possibility of taking several of our promising projects further in order to create as many opportunities as possible for strong value development for our shareholders. NeuroSTAT is regarded by many as a project with great potential, since there are no drugs that protect brain cells, but at the same time it is associated with greater risk than other projects because it deals with brain injuries. For this type of project, there are opportunities to obtain funding for clinical studies that does not entail a diluting effect, facilitating development toward the next important milestone — in this case, proof that the drug works in connection with TBI.

Under your business model, NeuroVive is developing orphan drugs — with or without partners — all the way to the market. How do things look for collaboration around NeuroSTAT?

We have already begun the work on creating interest among possible collaborating partners for NeuroSTAT. We have partnership agreements in China and South Korea. When we obtain the efficacy data from the planned Phase II study, we expect to be able to find additional partners we can share resource needs with in order to bring the project to market.

Finally, what would market approval of NeuroSTAT mean for health care, and for society as a whole?

The direct and indirect costs of TBI are estimated to be USD 400 billion per year globally, and € 340,000 per patient. NeuroSTAT has the potential to save lives and tangibly reduce the risk of severe mental, cognitive and motor handicaps, thereby increasing the chance of returning to work and decreasing the need for qualified hospital care. NeuroSTAT can thus dramatically reduce the costs to society and health care while making an enormous difference for individuals suffering from TBI.

NV354

AWARD-WINNING INNOVATION ON THE RISE

One of the most common causes of mitochondrial diseases relates to Complex I dysfunction, i.e. when energy conversion in the first of the five protein complexes in the mitochondrion that are essential for effective energy conversion does not function normally. This is apparent in disorders including Leigh syndrome and MELAS, both of which are very serious diseases with symptoms such as muscle weakness, epileptic fits and other severe neurological manifestations. The NV354 project is based on a NeuroVive innovation in which the body's own energy substrate, succinate, is made available in the cell via a prodrug technology. A prodrug is an inactive drug that is activated first when it enters the body by the transformation of its chemical structure.

5 MSEK Vinnova grant

Launch 2025

1 BUSD peak year sales

Read the interview with Alvar Grönberg on the following page.

In 2018, you announced a great deal of positive news about the NV354 project for the treatment of congenital mitochondrial disorders such as Leigh syndrome. What were the most important successes, and why are they important for further development?


Alvar

The candidate compound NV354 has proven to have medicinal properties that make oral chronic treatment possible. The most important properties are a high level of uptake from the gastrointestinal tract, and that in addition the compound can pass the blood-brain barrier. The latter is particularly important, since Leigh syndrome leads to neurologically conditioned problems such as epileptic seizures and difficulties with movement.

These successes with NV354 mean that we could expand the goal of the project from acute treatment to chronic illness-modifying treatment of diseases such as Leigh, which is something that is far more promising than we'd hoped. We have also shown that NV354 has the ability to correct certain metabolic and functional defects that arise when experimentally inhibiting the first complex of the respiratory chain.

As Director of NeuroVive's preclinical development, you play a central role in coordinating the activities around NV354. What are you aiming for in 2019, and what will that mean for the project?

In 2019, we will produce several kilograms of NV354 and initiate the necessary toxicological studies in order to start clinical testing in 2020. We will also continue the studies of various disease models in 2019 in order to study in greater detail which doses of NV354 are active and how the course of the illness is affected.

In November 2018, NeuroVive was awarded a total of SEK 5 million in further funding (Step 2) from Vinnova's Swelife call for projects, in order to further develop NV354. A properly implemented project in Step 1 was required to receive this funding. What earned you this increased funding, and what will the money be used for?

The increased funding is confirmation that we have successfully worked on the project since the start, and above all since we had the initial Swelife funding granted. This would not have been possible without the fantastic efforts from all the members of the project team, especially the members from our collaborating partner Isomerase Therapeutics. The funding will allow us to continue our preclinical development work without delays, in order to reach clinics as soon as possible.

Last year, your partner at the Children's Hospital of Philadelphia (CHOP) received a large research grant of around USD 4 million from a division of the US Department of Defense to study compounds as part of the NVP015 project. How will this accelerate the process of taking NV354 to studies in humans, i.e. clinical trials?

The research team at CHOP has the expertise and resources necessary for conducting advanced studies with our compounds in preclinical disease models. NeuroVive has long had a productive collaboration with key persons at CHOP, and the current project will also be conducted in close collaboration with — and involve — people from NeuroVive. The results will yield important knowledge to facilitate future clinical studies with NV354, for example, by identifying relevant effect markers that could provide early information on the clinical benefit of NV354.

Which NV354 milestone do you see as the most important in 2019?

Without doubt, the start of the toxicology study, in which the compound is administered in multiple doses over a longer period. These types of studies require large amounts of compound, particularly if it is tolerated well; indirectly, this means that we have also succeeded in manufacturing a larger amount of NV354 that meets our requirements. These studies are important steps when we move to clinical development in 2020.

If we look ahead all the way to the market, how do you think the finished drug with NV354 could make the most difference in daily life for a patient with Leigh syndrome, for example?

My hope is that NV354 means these patients will have access to a drug that is easy to take and markedly improves their daily lives. If NV354 functions as intended in these patients, there is a chance that they could experience rapid relief of certain symptoms — fatigue, for example — and over the long term reduce or even prevent permanent neurological damage caused by chronic lack of energy.

TOGETHER WE'RE STRONG

NeuroVive is cooperating with a number of leading stakeholders in academia and industry. For example, NeuroVive is collaborating in the KL1333 project with the Korean pharmaceutical company Yungjin Pharm, with Fortify Therapeutics in the US on developing compounds from the NVP015 project for local treatment of LHON, and with Karolinska Institute in Stockholm in studies into experimental mitochondrial myopathy models. NeuroVive's business model also contains projects for larger patient groups. These are run to preclinical stage for subsequent out-licensing to a large pharmaceutical company for clinical development and commercialization. NeuroVive is therefore able to enter major pharmaceutical markets.

Read the interview with Erik Kinnman and Mark Farmery on the following page.

You differentiate between partnership and licensing. What does licensing entail, and what advantages do the different forms of collaboration have for a company of NeuroVive's size?


Erik

We have a number of promising projects we would like to have the opportunity to develop as far as possible. The breadth of our portfolio creates good conditions for further development. Since drug development takes time, costs money and is associated with risk, we would rather develop several projects in collaboration with other companies than go in completely on a single project. We are focusing on orphan drugs that proceed more quickly, cost less, and are associated with less risk. We would be glad to develop these projects in partnerships. At the same time, we have projects for common illnesses in which the investments up to the preclinical phase are limited, and at the same time there are opportunities to fully license them to companies with large amounts of resources for further development and the market.

In 2018, you licensed compounds in the NVP015 project to BridgeBio's subsidiary, Fortify Therapeutics, for local treatment of the mitochondrial disorder Leber's hereditary optic neuropathy (LHON). How did that turn out, and why Bridge Bio specifically?


Mark

The NVP015 project is highly novel and innovative and targets a relatively unexplored area of mitochondrial biology and aims to provide a ground-breaking therapy to patients. BridgeBio approached us approximately two years ago, after we published the NVP015 concept in Nature Communications, to explore collaboration. The BridgeBio business model is centred on developing new and better medicines for patients with genetically driven diseases. This is done through establishing subsidiary companies made up of hand-picked experts and focused on a single asset. In this case, BridgeBio were interested in applying and developing a small subset of NVP015 chemistry to the targeted treatment of Leber's hereditary optic neuropathy (LHON), a rare mitochondrial disease that causes blindness in, primarily, men aged 20-40. This partnership is very important for NeuroVive's continued development and success for several reasons. Firstly, the fact that a high-profile partner such as BridgeBio has entered into a deal with us validates our approach and the quality of research. Secondly, through exploring an additional indication and route of administration with a partner in parallel with our internal activities in the NV354 project we expect to learn much more about this biology than if we did this on our own. Finally, we need to focus as a business and having the opportunity to work with a partner in this space allows us, because of these synergies, to broaden this project without additional risk or cost.

Dr. Todd Kilbaugh (right) and his team at the Children's Hospital of Philadelphia, received in 2018 a substantial US research grant for the evaluation of NeuroVive's compounds from the NVP015/NV354 project. Here together with NeuroVive's Magnus Hansson (left).

You announced that the goal for the projects in NASH and liver cancer is to license them out in the preclinical phase. Who would be a suitable licensing partner for these projects, and what would a collaboration of this kind mean for development to market?

The non-alcoholic steatohepatitis (NASH) development regulatory and commercial landscapes are highly complex. Currently, there are no approved therapies for this progressive fatal liver disease that is expected to become more and more common in coming years. A handful of programs are in late stage clinical development and are expected to read-out in 2019. These clinical trials are large and very expensive. Additionally, multiple programs are in earlier stage development, including several programs that have not yet entered the clinic. All these programs are targeting different stages of disease and different mechanism of action. In parallel, the regulatory landscape is evolving and changing. Taking all of this together creates an extremely dynamic environment. NV556 is a differentiated and innovative preclinical NASH therapy targeting liver fibrosis. To move this program through preclinical development into the clinic and, ultimately, to the market requires skills, expertise and resources that are outside of NeuroVive's capacity and focus. Consequently, we have actively sought to partner NV556 since publishing promising pre-clinical efficacy data in early 2018. This involves identifying the right partner and reaching an appropriate agreement and is a process that takes time, especially in relation to an early asset. We are working hard, pursuing multiple parallel conversations and are confident in our ambition to partner the program by the middle of the year.

As regards projects for the development of orphan drugs against rare diseases — in your case, genetic mitochondrial disorders and moderate to severe traumatic brain injury, you as a company wish to bring these to the market with or without partners. What could a potential partner bring to these projects?


Erik

Apart from financial muscle and general resources, a partner can bring important expertise in orphan drug development in various regions of the world; market, pricing and discount preparations as well as sales resources.

Read more about all our projects at www.neurovive.com