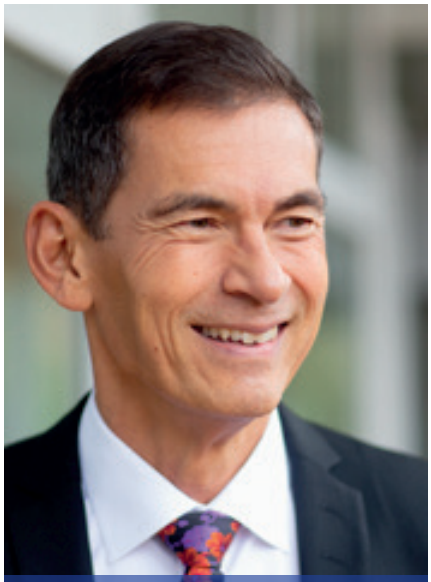
NeuroVive PHARMACEUTICAL

Newsletter

April 2019



Erik Kinnman
CEO

As planned, NeuroVive has now commenced the very interesting and important Phase Ia/b trial with KL1333. The first two parts of the trial will be conducted in healthy volunteers, the third and final part in patients with mitochondrial diseases. It will be very exciting to follow the results of this trial, which represents a significant milestone for the project.

Genetic mitochondrial diseases can cause many different types of disorders and disabilities, as well as a shortened lifespan, and for the vast majority of these diseases, no effective drugs are currently available. That is exactly what inspires everyone working at NeuroVive. With our drug development, we want to develop treatments with the potential to improve the lives of people living with mitochondrial disease.

In this newsletter, you can read an interview with Roger Kjell who suffers from MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes). Mitochondrial diseases are relatively rare, which means that knowledge about them is generally scarce. In the interview, Roger tells about his experience of living with MELAS.

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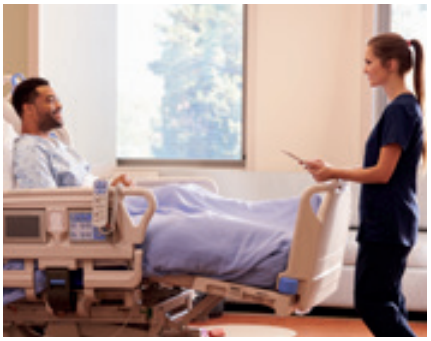

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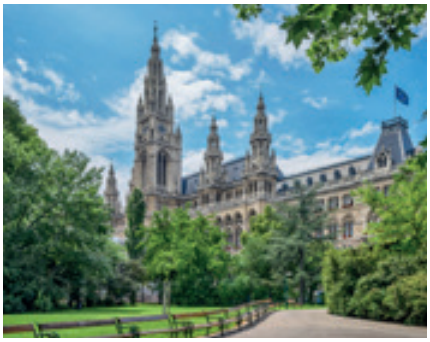


Spreading the word

KL1333 clinical study

THE STARTING PISTOL HAS BEEN FIRED

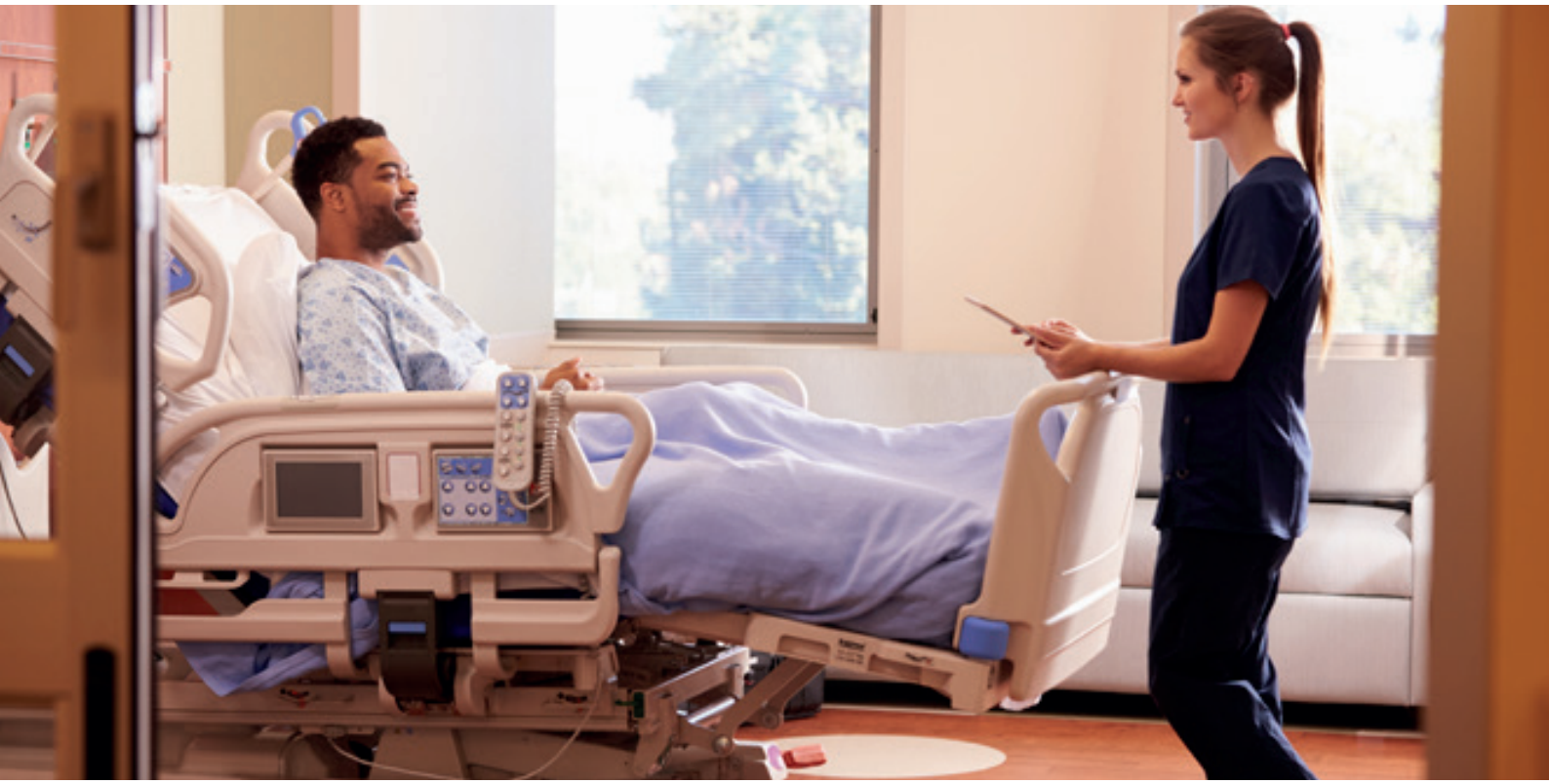
NeuroVive's clinical phase Ia/b study with KL1333 in the UK has now started. The first healthy volunteer has been screened and will be enrolled. The current study contains three parts, of which two will be conducted in healthy volunteers and the third in patients with genetic mitochondrial disease.

In the first part, the effect of food intake on the uptake of KL1333 will be evaluated after a single dose. In the second part healthy volunteers will be dosed with KL1333 during 10 days, and in the third part patients with genetic mitochondrial disease will be treated. All dose levels will include a placebo arm, i.e. the persons enrolled in the study will not know if they get the active drug or the inactive version. This is the first time repeat doses of KL1333 are tested, and also the first time KL1333 is given to patients.

The main aim of the study is to further examine the safety profile of KL1333 and how the drug is metabolized, the so-called pharmacokinetic profile. In addition, possible efficacy endpoints will be explored, to provide the basis for how the upcoming efficacy studies will be designed. These endpoints include both blood biomarkers, different scales evaluating symptoms, and a test measuring functional capacity.

Read more about the study:
https://clinicaltrials.gov/ct2/show/NCT03888716?term=NCT03888716&rank=1

One of the target groups for treatment with an approved KL1333 drug is patients with the mitochondrial disease MELAS. On the next page, you can read about Roger Kjell who speaks about how it is to live with the disease.



INTERVIEW WITH ROGER KJELL WHO HAS THE GENETIC MITOCHONDRIAL DISEASE MELAS

Today, some 12 people out of every 100,000 are living with some form of mitochondrial disorder. The symptoms are often varied, with different degrees of severity; they usually involve several different organs, with gradual deterioration. At present, there is only one approved drug, in Europe, for the mitochondrial eye disorder LHON (Leber's hereditary optic neuropathy). Roger Kjell suffers from the genetic mitochondrial disorder MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) which, according to the Swedish National Board of Health and Welfare, some 100–150 people in Sweden are living with today.

Roger Kjell

What is MELAS?
"It is a mitochondrial disorder in which there is a genetic error in all the body's cells that causes other diseases as symptoms."
How does MELAS manifest itself for you?
"I have hearing loss, a type of diabetes and impaired kidney function. All due to MELAS."
When did you discover you had this disorder?
"Eight years ago, I began having problems with my eyes. So I went to the eye specialist. They thought it was inflammation of the optic nerve, and told me to go to the ER the next day. The emergency neurologist examined my eyes and said it wasn't an inflammation."
"Then they started taking blood samples and running tests. After eight hours, they decided to admit me for elevated blood sugar. They said they couldn't see that I had diabetes, but I had elevated blood sugar."
When did they determine it was MELAS?
"It took nearly three years for them to figure out what it was. Everyone wondered how it was possible to have diabetes without having the tiny antibodies in the blood that indicate Type 1 diabetes. And how do diabetes and hearing loss go together, along with the eye problem?"
"I had CAT scans and x-rays, I went to a thoracic clinic, an infectious disease specialist, and a neurophysiologist and had a number of tests. As I said, after three years they concluded that it was indeed MELAS."
How did your life change when you got the diagnosis?
"It was really just another handicap because I'd had hearing loss from the beginning, so it probably wasn't as big a change as it would be for someone who had been completely healthy and suddenly got diabetes."
Is the hearing loss a symptom of your MELAS?
"Yes, apparently. I got it when I was around ten years old. The eardrum and ossicle on my right side broke apart. I had several ear infections as a child, so they thought the hearing loss was due to that."
How does your hearing loss affect you?
"Most of the hearing loss is now in the range of human speech. It's hard to hear someone calling from behind me. I can't determine the direction of a sound behind me, either. It's hard to hear s, v, p and t outside of a quiet environment."
Is it tough for you, having this disorder?
"Sometimes it's mentally difficult to know that I have to go around all the time with two different disabilities and a medical handicap. I'll never be able to do certain things that regular people do anymore — like eat candy. I have to watch what I eat all the time, and how much I move. I have to have a fixed sleeping routine. I can't be up as late as I want, because then my body starts acting strangely."
What does your medication look like?
"I take insulin, and medicine to increase my blood pressure and to decrease my lipoproteins and potassium. Potassium apparently accumulates in my blood. It hardens the arteries, which can cause a stroke. I also try not to eat things that contain potassium, such as bananas, spinach, broccoli or citrus fruits."
How many doctors are you seeing?
"I'm seeing a kidney doctor, a doctor for the diabetes, a neurologist and an eye doctor, who are all keeping tabs on my different symptoms and disabilities. I'd like it if they had another doctor coordinating them."
Are there other symptoms you think you might suffer due to MELAS?
"I hope there won't be any more symptoms. Though I'll probably need a kidney transplant in the future, but I'll be far down on the list. But I'm trying not to worry about that now. I have 30% of my kidney capacity left."
Are you worried that the disorder will give rise to more symptoms?
"MELAS first manifested as hearing loss at age ten, then high blood sugar and diabetes at age 30. Three years later, they found I was also having problems with my kidneys. The hearing loss and kidney problems go together with MELAS. I hope my kidneys won't be that much worse, since I've changed my diet. There really isn't anything to do about my hearing. It's probably just going to get worse. I hope there will be better hearing aids in the future. They're doing a lot of research into diabetes, but the question is whether I'll be cured of it or if they'll solve the problem with insulin."
How do you think MELAS impacts your life, in general?
"I suppose it's the different illnesses MELAS causes. They're what make you change your life and find new routines: how you eat, how you move, if you play games and sports or go to the gym, how you work — that is, how much energy you spend, mostly for the sake of the diabetes. You have to adapt your existence in accordance with your disabilities."

NeuroVive wants to help patients with mitochondrial diseases

Published by BioStock April 10, 2019

The number of individuals affected by mitochondrial diseases may be low, but there is every reason to conduct research and drug development in this area. This is because, for those actually affected, the disease entails extensive physical and mental suffering and an everyday life that constantly needs to be adapted to their disease. For Swedish company NeuroVive Pharmaceutical, the driving force and objective is to help this patient group to have a better life.

Mitochondrial disorders are a collective term for a group of diseases attributable to mitochondrial dysfunction. The mitochondria are located inside our cells and are necessary for us to be able to function optimally. They are usually called the powerhouses of the body because they generate the energy that is needed for us to be able to move, grow and think.

When mitochondria don't work

When mitochondria don't work as they should, the person affected can present a number of different symptoms, which can all have major consequences. The symptoms are numerous and varied, but one of the more common ones, according to the Swedish National Board of Health and Welfare, is hearing problems. The other symptoms include muscular dystrophy, a weakened heart muscle, epilepsy, dementia and vision problems.

Some organs are particularly sensitive to mitochondrial diseases, such as nerve cells, muscles (including the heart) and hormone-producing organs. The consequences for the individual are serious and far-reaching resulting from weakened organ function and shorter life expectancy.

Difficult diagnosis

In addition, the road to diagnosis is often long. The onset of mitochondrial diseases occurs at various times; for some, symptoms begin during childhood, while for others, they may arise during adulthood. In many cases, diagnosis takes several years, which is obviously mentally stressful.

The difficulty in establishing a diagnosis is based on the fact that mitochondrial diseases lead to a number of different symptoms and in many patients, several organs are affected at the same time. It does not help the situation either that there are many different combinations of symptoms and the symptoms vary from person to person.

There is thus no simple test that can identify mitochondrial diseases, but instead, a muscle biopsy is required and often highly comprehensive investigations to establish the correct diagnosis.

A life adapted to the disease

When the diagnosis has been confirmed, the life that follows is dominated by the symptoms and the gradual deterioration of the organs, which the diseases entail. For many patients, mitochon-

drial diseases entail innumerable visits to physicians and many different medications. Since the diseases affect various organs, a patient may need to make regular visits to, for example, a kidney specialist, diabetes specialist, neurologist and ophthalmologist.

The person affected is compelled to organize their life according to the disease, not only in terms of frequent doctor's visits and many different types of medication, but also in relation to nutrition, sleep and exercise. For many, the diseases entail that it is difficult to live a normal life and they perceive the diseases as considerably reducing their quality of life. It is mentally stressful to have an everyday life that is dictated by disability, which can lead to a sense of isolation.

NeuroVive – part of a brighter future for patients

There is currently no cure for mitochondrial diseases and the reality is that there is only one approved treatment for one single mitochondrial disease – a therapy for the eye disease, Leber's hereditary optic neuropathy (LHON).

However, the future looks somewhat brighter as a number of research groups are now focusing on mitochondrial diseases. One of the companies that is active is Lund-based NeuroVive Pharmaceutical, one of the leading companies in mitochondrial medicine. KL1333, the company's oral drug candidate for congenital mitochondrial diseases, has just commenced a clinical Phase I trial and has already received orphan drug designation in both Europe and the US. The first results from the study are expected at the end of the year.

KL1333 regulates levels of cellular NAD+. This is a co-enzyme that plays a crucial role in the energy metabolism of the cell. Preclinical studies have demonstrated that KL1333 has several positive effects. The candidate increased the mitochondrion's energy production, reduced lactate accumulation, and was able to convey long-lasting positive effects on energy metabolism.

The company's portfolio also contains other projects for genetic mitochondrial diseases and it is worth noting that, in June 2018, the company licensed molecules from its NVP015 project for targeted treatment of LHON to Fortify Therapeutics.

BioStock spoke with **Magnus Hansson**, Chief Medical Officer and head of preclinical/clinical development at NeuroVive Pharmaceutical.

You are developing therapies for genetic mitochondrial diseases, a condition that entails a significant decline in quality of life for patients. Can you tell us more about how patients are affected by the diseases?


Magnus

"The diseases can manifest very differently depending on the organs in which the genetic defects are located. Mitochondrial diseases often present in early childhood and can lead to severe symptoms, such as stunted growth, heart failure and rhythm disturbances, dementia, movement disorders, stroke-like episodes, deafness, blindness, droopy eyelids, limited mobility of the eyes, vomiting and seizures.

"But the symptoms can also present later in life, as in the case of the mitochondrial eye disease LHON, which often presents in the age range of 20 to 40, when there is a strong deterioration initially in one eye and then in the other."

Today, there is no cure for mitochondrial diseases and there is only one approved therapy. Why do you think that it has been so difficult to develop successful therapies?

"Congenital mitochondrial diseases are, as I said, a rare set of diseases and, similar to other rare disorders, they have often been neglected by the large drug companies. However, to support and encourage the development of drugs for rare disorders, medical products agencies can provide orphan drug designation and orphan drug status for drugs intended for the treatment of life-threatening or chronically disabling rare disorders, wherever no therapy alternatives have been approved or the new drug offers significant benefits to those affected. The designation entails, for example, reduced application fees, assistance in preparing protocols and market exclusivity, for ten years in the EU and seven years in the US, after approval for sale. This often entails a shorter time to market.

"Our candidate, KL1333, has received orphan drug designation in both Europe and the US, and there are favorable possibilities that our other projects in congenital mitochondrial diseases will also receive orphan drug designation."

In what ways can your therapy help patients?

"Both our drug candidate KL1333 and our substance candidate NV354 are aimed directly at the cells' mitochondria, meaning the place where the genetic defects in patients causes the initial damage. The mechanisms of action differ, but what they have in common is that, in different ways, they support the mitochondria to produce the energy the body needs. In this way, we hope to be able to improve muscle function and function in other affected organs and, accordingly, the quality of life of those affected."

Can you tell us something about how your Phase I trial with KL1333 is progressing?

"Recruitment has commenced and on March 18 this year, the first study participants' initial visit was conducted to our Phase Ia/b study with KL1333 in the UK. The main aim of the study will be to examine the safety profile of KL1333 and how the drug is metabolized in the body 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."

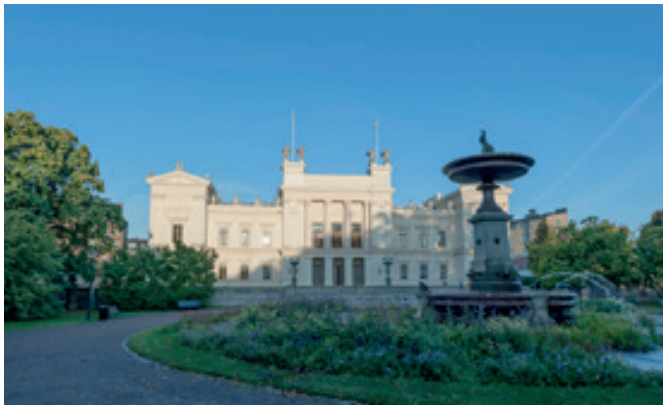
Do you think that people with mitochondrial diseases can expect any significant progress in the next few years and, if so, what will this be?

"Fortunately, interest in mitochondrial medicine has increased in recent years. However, it must be remembered that drug development takes time, for obvious reasons. We must ensure that the drugs are safe to administer, that they have no serious side-effects and that they genuinely make a difference for patients compared with existing therapies.

"If we can succeed in this, for example, with KL1333, which has shown excellent properties to date, persons with mitochondrial diseases can hopefully expect to collect their medication from their local pharmacy in the foreseeable future."

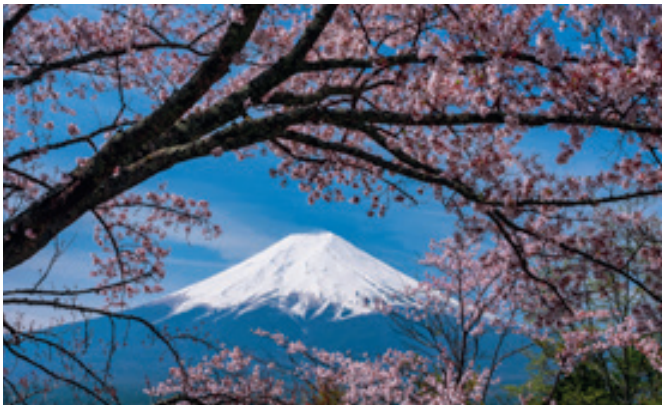
Spreading the word

NeuroVive is continuously engaged in the vibrant community of mitochondrial scientist as well as the world of investors and potential partners. Over the past few months alone, NeuroVive has attended and presented at conferences in Sweden, Japan, Canada and Austria.



The 1st EANS Trauma & Critical Care Update Meeting: Lund, Sweden, on 13 – 14 December 2018

Matilda Hugerth, NeuroVive's Director, Clinical and Regulatory Affairs,and Magnus Hansson, Chief Medical Officer & VP Preclinical and Clinical Development, took part in the meeting and presented a poster entitled *Altered brain injury biomarker kinetics in cerebrospinal fluid during ciclosporin treatment in severe TBI patients.*

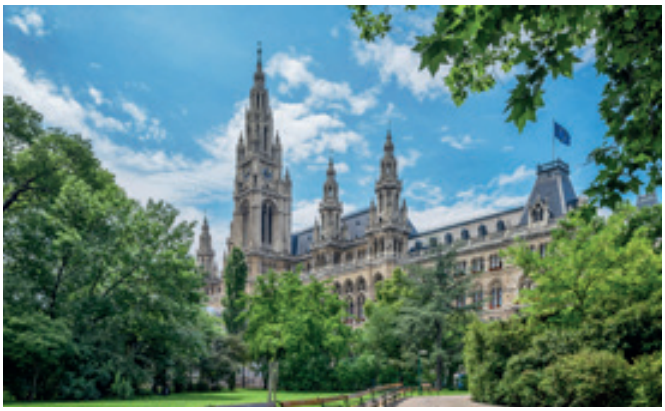


BIO Asia International Conference: Tokyo, Japan, on 5 – 6 March 2019

NeuroVive's VP Business Development, Mark Farmery, attended this conference which brings together the global biotechnology and pharmaceutical industry to explore licensing collaborations and investor engagement in the current Asia-Pacific business environment.

The 13th World Congress on Brain Injury: Toronto, Canada, on 13 – 16 March 2019

NeuroVive's team presented the exciting NeuroSTAT biomarker data from the CHIC study and the company's approach to utilize biomarkers for effective clinical development in Traumatic Brain Injury.



BIO-Europe Spring 2019: Vienna, Austria, on 25 – 27 March 2019.

NeuroVive's team met with key decision makers from the bio-tech, pharma and finance segments during three days of partnering meetings.

Further reading at www.neurovive.com

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