EQUITY RESEARCH – SPONSORED RESEARCH
Research report prepared by DNB Markets, a division of DNB Bank ASA
Health Care
Initiating coverage
This report was completed and disseminated at 18:10 CET on 25 October 2018

25 October 2018

NEUROVIVE PHARMACEUTICAL

Mighty mitochondria

Mitochondrial diseases are chronic and in many cases life-threatening. No effective treatments are available, hence a significant unmet medical need exists. Although these diseases are rare individually, in aggregate 12.5/ 100,000 individuals are affected globally. KL1333 is one of NeuroVive's most advanced assets, and in our view is an interesting drug candidate since it is directed to a scientifically validated target that could potentially modify several mitochondrial diseases. We expect clinical development of KL1333 to speed up in next few years. We initiate coverage with a fair value of SEK3–9/share.

Significant unmet medical need. NeuroVive aims to address the unmet medical need that exists for patients with mitochondrial diseases such as MELAS, Alper's disease, CPEO, PEO, KSS, MERFF and Pearson syndrome. These are all severe conditions for which no approved disease-modifying drugs exist.

KL1333 targets a validated mechanism… In preclinical studies, it has been shown that KL1333 elevates the intracellular levels of NAD+, leading to upregulation of PGC-1α, which is considered a therapeutic target in many mitochondrial diseases.

… providing an interesting opportunity. The target indications of KL1333 are rare, orphan indications. However, many of the mitochondrial diseases have close similarities in the disease-causing mechanism. We believe that KL1333 has the potential to become a blockbuster product, if it can be shown to benefit patients with various mitochondrial diseases. NeuroVive is about to initiate a phase Ib study with KL1333, due to be finalised in 2019, following which a pivotal phase II/III study could be initiated in 2020.

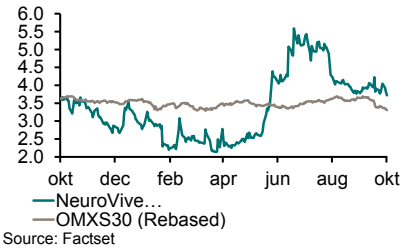
NeuroSTAT targets traumatic brain injury. The cost associated with traumatic brain injury (TBI) is estimated to be in the region of USD400bn/year globally. There is currently no treatment available which can protect brain cells from damage during TBI, but this is exactly what NeuroVive intends to provide with its drug candidate NeuroSTAT, by protecting the mitochondria in brain cells. This is an acute treatment given directly after TBI occurs. The active product ingredient has been proven safe in TBI patients as well as in hundreds of thousands of patients in other indications. Furthermore, numerous studies in various animal species have demonstrated that NeuroSTAT fills a protective function when these animals have been exposed to brain injuries that simulate TBI.

Initiating coverage with a SEK3–9/share fair value. We have used a risk-adjusted DCF model to calculate fair values in a bear-case and a bull-case scenario. In our bear case, KL1333 constitutes 65% of the total value, while it is 78% in our bull case.

Year-end Dec	2014	2015	2016	2017	2018e	2019e	2020e
Revenue (SEKm)	8	3	0	0	nm	nm	nm
EBITDA adj (SEKm)	-45	-91	-72	-71	-58	-94	-147
EBIT adj (SEKm)	-46	-93	-73	-73	-60	-97	-153
PTP (SEKm)	-46	-93	-73	-73	-60	-97	-153
EPS rep (SEK)	-1.53	-3.01	-1.67	-1.33	0.00	-4.42	-3.15
EPS adj (SEK)					-3.15	-4.42	-3.15
Revenue growth (%)	20.2	-63.7	-96.1	133.1	nm	nm	nm
EV/Sales adj (x)	130.02	47.00	nm	nm	nm	nm	nm

Source: Company (historical figures), DNB Markets (estimates)

NVP versus OMXS30 (12m)



Source: Factset

SUMMARY

Share price (SEK)	3.72
Tickers	NVP SS, NVP.ST

CAPITAL STRUCTURE

NIBD adj end-2018e (SEKm)	-45
Net debt/EBITDA adj (x)	0.77

Source: Company , DNB Markets (estimates)

Note: Unless otherwise stated, the share prices in this note are the last closing price.

NEXT EVENT

Q3 2018 report	22/11/2018

This report has been commissioned and paid for by the company, and is deemed to constitute an acceptable minor non-monetary benefit as defined in MiFID II

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Please see the last two pages for important information. This research report was not produced in the US. Analysts employed by non-US affiliates are not registered/ qualified research analysts with FINRA in the United States.

Overview

Valuation fair value range per share SEK3-9

Source: DNB Markets

Valuation methodology

- We have used a risk-adjusted DCF approach with a bull case and a bear case scenario. We discount the value with a WACC of 10% and apply a tax rate of 22% on all future sales.
- In our bull case, we assume an LOA of 15% for KL1333 in MELAS and 5% in other target indications.
- In our bear case, we assume an LOA of 10% for KL1333 in MELAS and 5% in other target indications.

Source: DNB Markets

Downside risks to our fair value

- We believe the key risks are the outcomes of future efficacy trials. Today, there is very limited clinical data supporting the efficacy of either NeuroSTAT or KL1333.
- Delays in clinical development could have a major share price impact.
- There is a high execution risk in both scenarios since all of the company's assets are in early-stage development.

Source: DNB Markets

DNB Markets estimates

- For KL1333 we assume a price per patient per year of USD50,000 in EU and USD100,000 in the US. We assume the same price for a one-time treatment with NeuroSTAT.
- In our bull case, we estimate a peak penetration of 50% in both the US and EU for MELAS. We estimate off-label usage of 15% and 35% in other target indications.
- In our bear case, we estimate a peak penetration of 35% in both the US and EU for MELAS. We estimate off-label usage of 15% and 35% in other target indications.

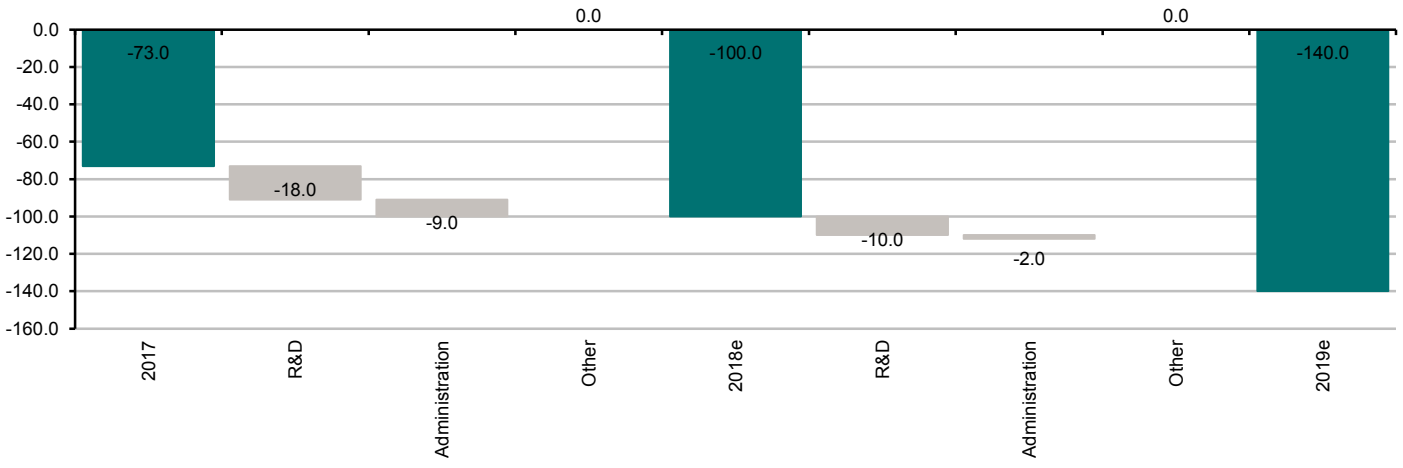
Source: DNB Markets

Upside risks to our fair value

- Higher sales of KL1333 and/or NeuroSTAT due to a higher price being charged if promising outcomes are shown in pivotal trials.
- Clinical development can be speeded up if patients can be recruited to trials faster than anticipated or due to a potential breakthrough designation.
- The company, or one of its assets, is acquired by a large pharma company.

Source: DNB Markets

Operating cost base bridge 2017–2019e (SEKm)



Source: DNB Markets (forecasts), company (historical data)

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Summary of positives

KL1333: Targets a validated mechanism in mitochondrial diseases

It has been shown in a preclinical study that KL1333 efficiently modulates the NAD+/NADH ratio in cells and elevates the levels of NAD+. Elevated NAD+ levels will lead to activation of SIRT1, AMPK and subsequently activation of PGC-1α. PGC-1α is considered an attractive therapeutic target in many mitochondrial diseases since it plays a central role in mitochondrial biogenesis, mitochondrial protein expression, and mitochondrial respiratory function[1].

NeuroSTAT: TBI is a multi-billion dollar market

With 50–60 million new cases globally per year, traumatic brain injury (TBI) is estimated to remain the most common cause for neurological disability globally until at least 2030[2]. A significant portion of patients living with disabilities caused by TBI are young individuals who could have lived normalised lives with high productivity. Instead, these individuals, their families and society have to carry a significant burden that translates into suffering and huge healthcare costs – it is estimated that the costs associated with TBI is USD400bn per year globally[3]. Hence, we believe a drug which had any benefit in improving the productivity, cognition or quality of life for these patients would likely become a blockbuster.

New management and new board

NeuroVive has a history of failure in clinical development. A large phase III trial was carried out with CicloMulsion in acute myocardial infarction; the study did not meet its primary clinical endpoint and development was discontinued. Then, the company changed the route of development to acute kidney injury; yet this was also discontinued in this indication after a phase II study showed that no benefits could be proven over placebo. However, the company has since undergone a transformation; all current drug candidates in the pipeline except NeuroSTAT are new. In addition to this, the majority of management, including the CEO, are new and the board of directors has changed completely over the past year.

Significant unmet medical need in mitochondrial diseases

With KL1333, NeuroVive targets the mitochondrial diseases Alper's disease, CPEO, PEO, KSS, MELAS, MERFF and Pearson's syndrome. These are all severe diseases for which there are currently no approved therapies on any market. The only treatment options available today aim at treating the symptoms associated with these diseases. Likewise, no approved therapies exist for traumatic brain injury, which NeuroVive targets with its other clinical drug candidate, NeuroSTAT.

Strong competence and network in mitochondrial medicine

TRACK-TBI, Karolinska Institutet, The Children's Hospital of Philadelphia, the University of Pennsylvania, UCL, and the University of Florida are some of NeuroVive's partner organisations included in its broad network of mitochondrial medical research. In addition to its experienced in-house team, it also has several external experts in relevant therapeutic areas.

[1] Lehman JJ, et al. (2000). Peroxisome proliferator-activated receptor g coactivator-1 promotes cardiac mitochondrial biogenesis. Journal of Clinical Investigation
[2] Maas et al. (2017) Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research
[3] Maas et al. (2017) Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research

Summary of negatives

Limited efficacy data on KL1333

Today, our knowledge of KL1333 regarding its clinical significance is limited, and it is when KL1333 enters a phase II trial that we could get any data indicating if it could have any effect at all in patients. One animal study has been carried out, but these results have not been published in a peer-reviewed journal and only extracts from the study are available. Furthermore, the only data we have indicating that KL1333 modulates NAD+ levels are from one patient sample from one healthy cell which showed that KL1333 modulated the NAD+/NADH ratio in-vitro.

Uncertainties over what patient groups would benefit from KL1333

Mitochondrial diseases are very heterogeneous. The cause of disease and how the diseases are expressed in term of symptoms varies greatly. Even if the company communicates that KL1333 could have benefits for many different mitochondrial diseases, this is only based on their hypothesis. No pre-clinical disease model studies have been carried out for any mitochondrial disease other than MELAS.

Previous clinical trials with cyclosporine in TBI have demonstrated discouraging results

The active product ingredient in NeuroSTAT, cyclosporine, has been evaluated in many preclinical and clinical studies of traumatic brain injury (TBI). In our review of relevant publications on cyclosporine in TBI, our summarised view is that many preclinical studies, especially animal models, have shown very impressive efficacy results for cyclosporine. However, results from clinical studies are less appealing. In human TBI patients, cyclosporine appears to be safe; however, as for efficacy, all TBI studies with cyclosporine we have identified conclude that TBI patients do not benefit from it. For instance, multiple studies have shown that cyclosporine has no effect on improving cognitive function or consciousness. Furthermore, studies concluded that mortality or other adverse events was not significantly different from placebo in TBI patients who received cyclosporine at doses up to 5mg/kg/day within eight hours after injury.

Cyclosporine is a generic compound

The formulation of NeuroSTAT is unique and patented; however, its active product ingredient is not. Today, there is only vague evidence suggesting that the NeuroSTAT formulation would be safer for TBI patients than generic cyclosporine formulations. If NeuroSTAT makes it all the way to market indicated for TBI, it is very likely that healthcare providers will use a cheaper generic version of cyclosporine to treat patients.

NeuroVive will likely need several years and tens of millions in dilutive financing before it could get a drug on the market

Several of the company's assets are in early-development phase, and even though orphan indications can be speeded through clinical development faster than for other indications, it will take until at least 2022 before NeuroVive could have a product on the market. It should be stressed that while a launch in 2022 is estimated, it is more common than uncommon that the timing lapses for projects in early-stage development, since a myriad of both regulatory and development hurdles have to be passed before a potential launch.

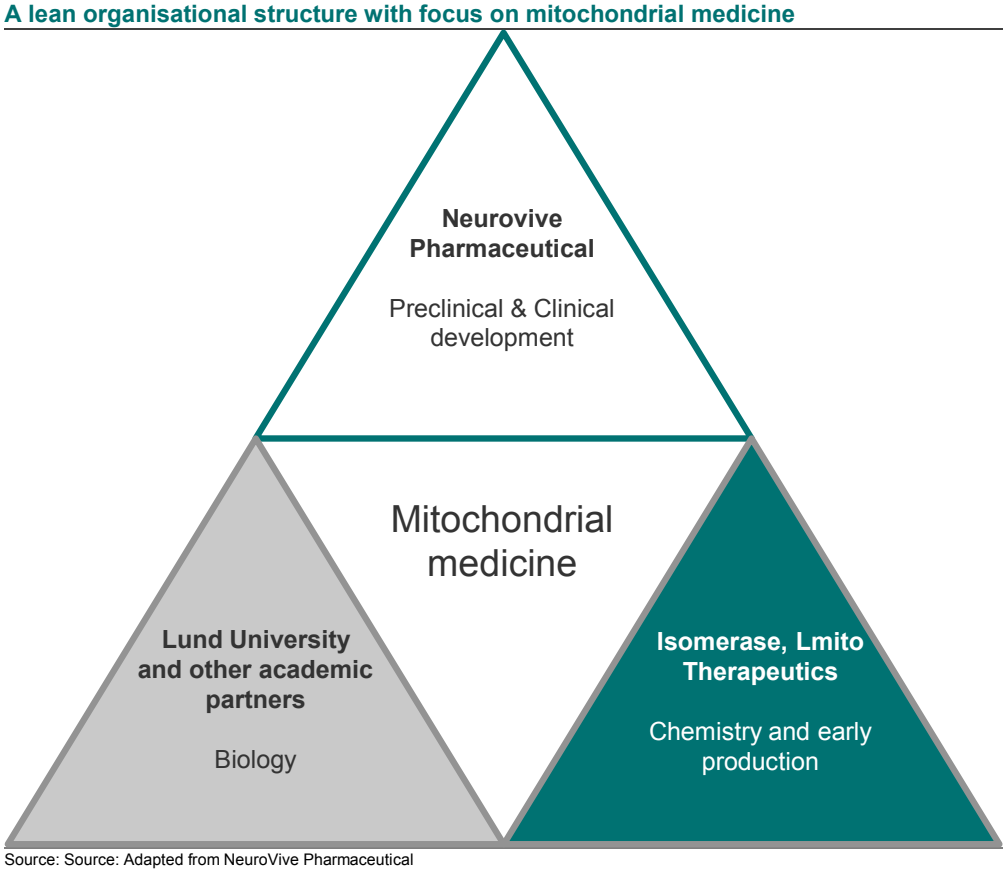
Company overview

NeuroVive Pharmaceutical ('NeuroVive') is a biotechnology company developing several drug candidates, of which two (NeuroSTAT and KL1333) are currently in clinical development. The company's focus is within mitochondrial medicine. Mitochondria have a central role in the disease-causing mechanism in many common as well as rare diseases. NeuroVive's core strategy is to develop drugs for both common and rare mitochondrial diseases. For rare diseases such as genetic mitochondrial diseases and moderate-to-severe traumatic brain injury (TBI), NeuroVive aims to develop drug candidates all the way to market. As for the more common diseases such as NASH and liver cancer, the company aims to out-license assets prior to clinical development.

NeuroVive's core strategy is to develop drugs for both common and rare mitochondrial diseases

There are currently 12 employees in the company, of which the majority are working full time. The organisational model is lean and complemented by carefully chosen strategic partners. The lean model allows optimal scaling to meet the company's needs; the University of Lund is an important strategic partner that fuels NeuroVive with innovative ideas and research. Isomerase has been a partner to NeuroVive for many years; Isomerase is responsible for chemistry and early manufacturing of drug candidates, which is key in upscaling of clinical projects. Lmito is another partner which fills a complementary function to discovery and chemistry. NeuroVive's own resources are key when it comes to conducting pre-clinical and clinical studies, yet the company also hires contract research organisation (CRO) to complete the value chain.

A lean organisational structure with focus on mitochondrial medicine



Source: Source: Adapted from NeuroVive Pharmaceutical

Popular science summary

Mitochondria are the powerhouses of the human body. They are the part of the cell responsible for effective energy production and, in addition, protect the cell from potential harmful calcium levels and are involved in the regulation of cell death. When the mitochondria do not function properly, cells die, which can lead to organ failure and in the worst case death. One of the most advanced projects that NeuroVive is currently developing is NeuroSTAT. This drug candidate aims to treat patients with moderate-to-severe traumatic brain injury (TBI), a severe state which can be caused by trauma such as car accidents, sports injuries and other accidents. Many individuals who suffer from moderate-to-severe TBI die, and of those who survive, the majority will develop permanent and lifelong handicaps which put a lot of burden on patients and entail significant healthcare costs. The direct healthcare costs associated with TBI have been estimated at SEK2.5m per patient.

Mitochondria are the powerhouse of the human body

There is currently no treatment available which can protect brain cells from damage during TBI, but this is exactly what NeuroVive intends to provide with NeuroSTAT, by protecting the mitochondria in brain cells. NeuroSTAT is an acute treatment given directly after TBI occurs. The active product ingredient has been proven safe in TBI patients as well as in hundreds of thousands of patients in other indications. Furthermore, numerous studies in various animal species have demonstrated that NeuroSTAT fills a protective function when these animals have been exposed to brain injuries that simulate TBI. The most promising effect data which NeuroVive has demonstrated are from a recent animal model on pigs. Data from the study showed that NeuroSTAT contributed to a decrease of damage in the brain cortex of 35% compared to placebo if the pigs received NeuroSTAT consecutively for five days.

There is currently no treatment available which can protect brain cells from damage during TBI…

… but this is exactly what NeuroVive intends to provide with NeuroSTAT

Another condition in which mitochondria are involved is genetic mitochondrial disease. Genetic mitochondrial disease can have many symptoms and the disease is characterised by what type and how many mutations individuals have. Even if patients have varying symptoms, large organs such as the brain, skeletal muscles, heart, liver, kidneys, bowel and more are commonly affected since these organs require a lot of energy. Genetic mitochondrial diseases are rare and often affect children. Children with these diseases can often live for several years with the disease but they will experience a continuous worsening of the function of the affected organs as the body's ability to produce energy decreases.

In 2017, NeuroVive in-licensed the clinical drug candidate KL1333, which aims to increase the body's ability to produce energy and could enable the production of new mitochondria. KL1333 acts by increasing the availability of a component that is essential in the process of energy production, which we need, for instance, to be able to move or for our organs to function. Patients with mitochondrial disease often have low levels of NAD+ and by modulating it, i.e. making it more available in the process of energy production, KL1333 could help many patients to generate more energy. Recently, NeuroVive's partner, Yungjin Pharm., finalised a safety study in healthy Asian volunteers. NeuroVive is now preparing for the initiation of a safety study in a Caucasian population, to be conducted in Europe. It aims to launch KL1333 in 2023.

In 2017, NeuroVive in-licensed the clinical drug candidate KL1333…

…it aims to increase the body's ability to produce energy and could enable the production of new mitochondria

If individuals with genetic mitochondrial diseases get a cold, influenza or other common diseases, many will not be able to produce the amount of energy required for the immune system to attack the disease. In these patients, common diseases can result in acute metabolic crises, a very severe condition associated with life-threatening stroke, heart attack and liver failure. With NV354, the lead compound of the NVP015 programme, NeuroVive aims to address the unmet medical need that exists for patients with genetic mitochondrial diseases who suffer from acute metabolic crises. Approximately half of all individuals with mitochondrial disease have a dysfunction in the first complex of the mechanism in mitochondria that is responsible for producing energy. The succinate prodrug NV354, aims to restore energy production in these patients by skipping the first complex and provide a source of energy directly to the second complex. The company intends to rapidly scale up development of this asset by conducting trials in animals and then quickly move into clinical trials, hopefully in 2019.

Scientific introduction

Mitochondria

In the cytoplasm of cells, there are a number of very small structures known as organelles. Organelles found in almost all eukaryotic cells include for instance the endoplasmic reticulum, golgi apparatus and cell nucleus, another very important organelle is mitochondria. The primary function of mitochondria is to produce a sufficient amount of energy allowing organisms to maintain vital functions such as muscle contraction and for organs to function. The source of energy required in these processes is known as adenine triphosphate (ATP). Mitochondria exist in vast numbers in all cells except in red blood cells, where there are no mitochondria at all. In addition to the production of ATP, there are a few other cellular processes where mitochondria have a central role, which include calcium homeostasis, iron–sulphur cluster biogenesis and apoptosis.

Mitochondria produce adenine triphosphate (ATP), the 'energy currency' of cells

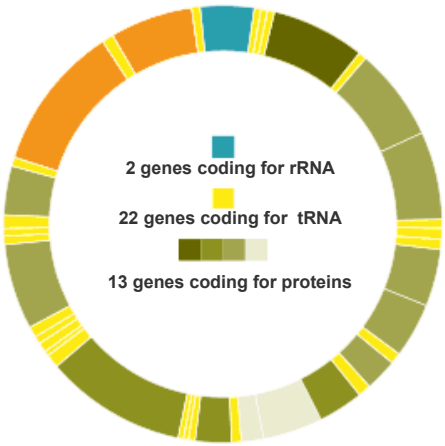
Mitochondria stem from bacteria that coexisted with eukaryotic cells throughout evolution; the symbiotic relationship led to mitochondria subsequently becoming an integrated part of cells around 1 billion years ago. Important evidence in the mapping of mitochondria to its origin is mitochondrial DNA (mtDNA). In fact, mtDNA is the only DNA in humans that is not nuclear DNA. mtDNA is circular, 16.6-kbp long and is always passed on through the mother. The most vital function of mtDNA is the encoding of various components such as tRNA and proteins, which together constitute oxidative phosphorylation (OXPHOS). Mitochondria are constituted by approximately 1,500 proteins, but only 13 of these are coded by mtDNA: the remaining proteins are coded by nuclear DNA.

Mitochondria are dynamic structures that communicate with other cellular components through signalling, and they are also key in regulating signalling between cells and tissues. They have two membranes that separate them from the cytoplasm, one outer membrane and one inner membrane. The outer membrane is porous, and various molecules, including large structures such as proteins, can easily be transported over the outer membrane. The inner membrane on the other hand, is much more selective and specific membrane transport proteins are required for molecules to pass this barrier. The inner membrane consists of double-layer phospholipids with hydrophobic tails facing each other and hydrophilic heads facing outwards. The inner membrane has wrinkled/ folded structures known as Cristae which are the site for OXPHOS. Vital components required in OXPHOS, including complex I, II, III, IV, cytochrome c and ATP synthase, can all be found in the Cristae. It has been shown that 94% of ATP synthase and complex III are located in the Cristae[4].

Mitochondria are dynamic structures that communicate with other cellular components through signalling…

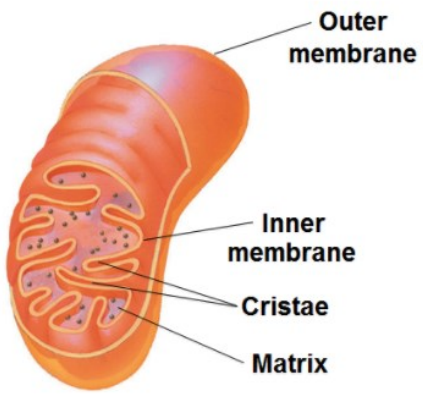
… they are also key in regulating signalling between cells and tissues

Genetic composition of human mtDNA



Source: Adapted from Socialstyrelsen.se

Schematic illustration of mitochondrion



Source: Collin College

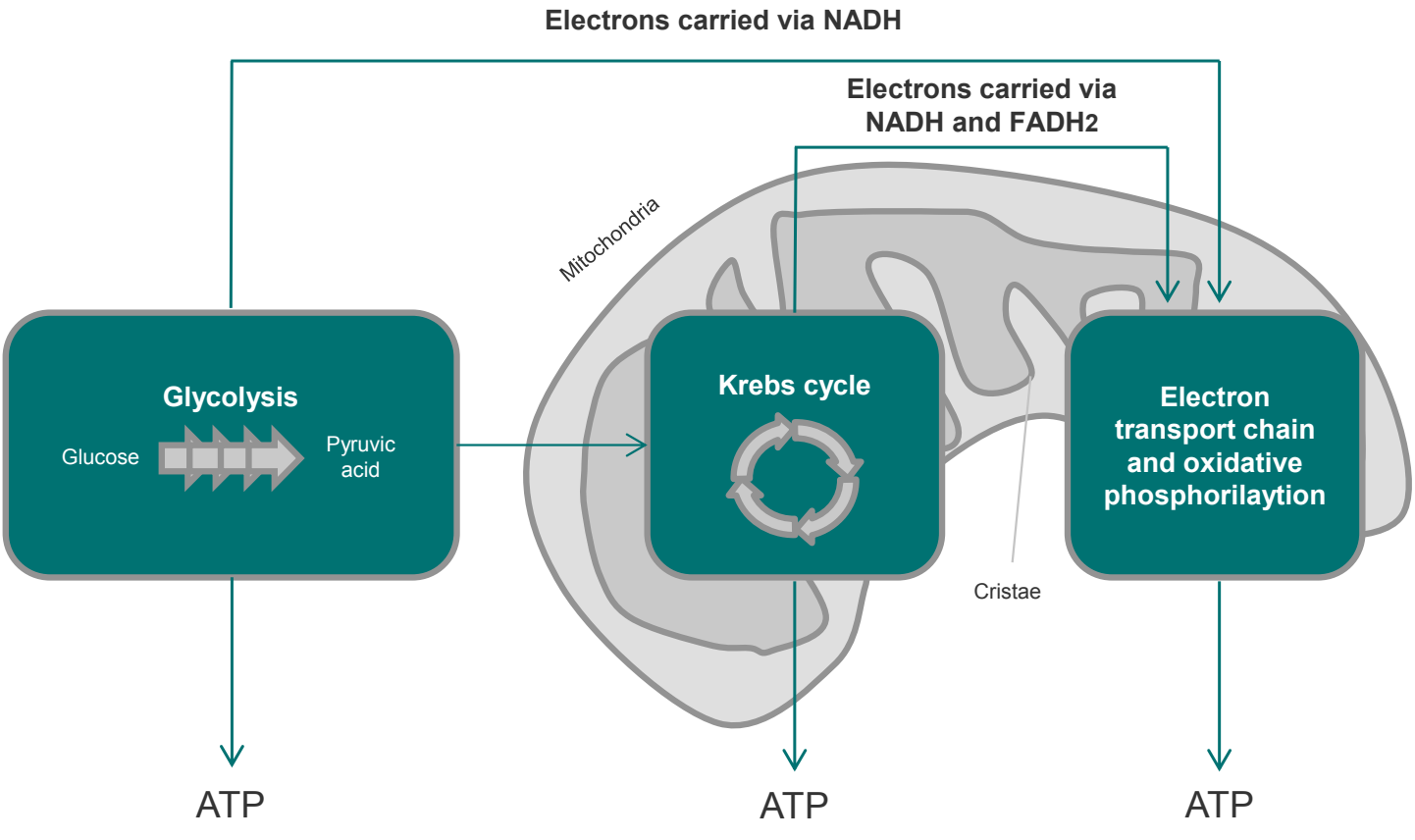
[4] Gilkerson R.W.et al. (2003) The Cristae membrane of mitochondria is the principal site of oxidative phosphorylation (OXPHOS). FEBS Lett. 2003; 546: 355-358

Generation of ATP from cellular respiration

It is estimated that the average adult male generates and consumes more than 50kg of ATP every day; it is a constantly ongoing mechanism, occurring in all eukaryotic cells. ATP is generated through three essential mechanisms, glycolysis, Krebs cycle and the electron transport chain / oxidative phosphorylation (OXPHOS). The last two mechanisms mentioned occur in the mitochondria, of which the last one, the electron transport chain / OXPHOS, is responsible for generating most ATP. The first mechanism, glycolysis, occurs in the cytoplasm; it is basically a way for the body to consume glucose in order to produce ATP, NADH and pyruvate; this way of generating ATP is anaerobic, meaning that no oxygen is required in order to generate ATP; this process can only generate a limited amount of ATP, but products from glycolysis can be utilised in other ATP-generating processes. For instance, pyruvate from glycolysis can be converted to acetyl-CoA by pyruvate dehydrogenase. Acetyl-CoA can in turn enter the Krebs cycle, which is another mechanism in which ATP can be generated. The Krebs cycle takes place in the matrix of mitochondria and is essentially a series of reactions where acetyl-CoA is oxidised resulting in the products NADH and $FADH_2$. A basic rule in the Krebs cycle is that 1.5 ATP is generated for every NADH and $FADH_2$. NADH and $FADH_2$ are essential for carrying electrons into the electron transport chain. NADH generated from both glycolysis and the Krebs cycle is responsible for carrying electrons into the electron transport chain, where the majority of ATP generation will take place through OXPHOS.

The average adult male generates and consumes more than 50kg of ATP every day

Schematic illustration of cellular respiration



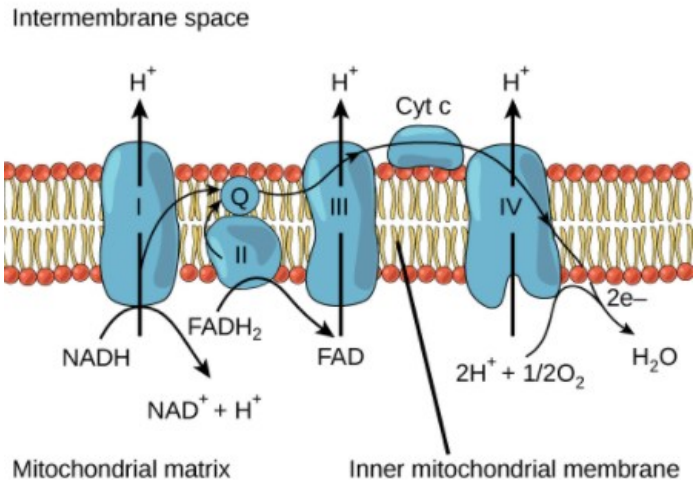
Source: Adapted from figure by Indiana University

The electron transport chain and oxidative phosphorylation

In summary, the electron transport chain constitutes a number of proteins in the inner mitochondrial membrane which undergo conformational change when fuelled with electrons. The conformational changes in these proteins enable the formation of a hydrogen ion gradient which is essential for generating ATP. In this section, we briefly touch upon the steps which cause the electrons to move through complex I, II; III and IV and how these steps generate ATP by utilising the hydrogen ion gradient.

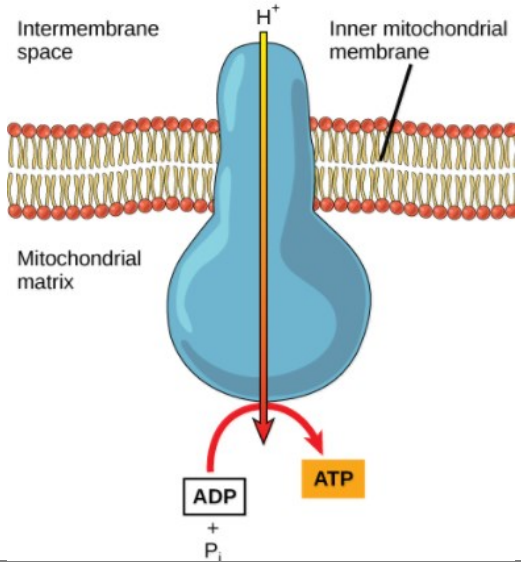
- **Complex I (NADH dehydrogenase).** Dysfunctions in complex I are associated with several genetic mitochondrial diseases. In complex I of the electron transport chain, NADH will be oxidised by the enzyme NADH dehydrogenase. This means that NADH will disrupt its binding to a hydrogen ion which will be released through a hydrogen ion pump located in the inner membrane of the mitochondria. Simultaneously, two electrons will be released; the 2 electrons produced from complex I will enter into ubiquinone in the electron transport chain.
- **Complex II (succinate dehydrogenase).** The second complex will be fed with electrons from $FADH_2$, then, succinate dehydrogenase will convert succinate to fumarate and 2 hydrogen ions and electrons will be funnelled into ubiquinone through FAD. Unlike in the other complexes, no hydrogen ion gradient is created in complex II, however, it is still essential for carrying electrons further through the chain.
- **Complex III (cytochrome-c-reductase).** In complex III, cytochrome-c-reductase transport electrons from ubiquinone to cytochrome c; this allows hydrogen ions to be transported into the intermembrane space.
- **Complex IV (cytochrome-c-oxidase).** Just like complex I, dysfunctions in complex IV are associated with several mitochondrial diseases. In complex IV, cytochrome c transports two electrons to the mitochondrial matrix, which will lead to the reduction of oxygen and subsequently generation of water. The two electrons traveling to the matrix will allow pumping of two hydrogen ions into the intermembrane space, creating a hydrogen ion gradient.
- **ATP synthase.** In the last step of the electron transport chain, the enzyme ATP synthase utilises the hydrogen ion gradient in order to generate ATP from ADP and Pi. ATP synthase is responsible for generating the most ATP in our bodies. A general rule is that 3 hydrogen ions are required to enter from the inter membrane space and into the ATP synthase in order to generate one ATP molecule.

The electron transport chain



Source: courses.lumenlearning.com

Generation of ATP by ATP synthase



Source: courses.lumenlearning.com

Disease overview

Genetic mitochondrial diseases

Mitochondrial diseases are characterised by the inability of mitochondria to produce a sufficient amount of ATP. The diseases can be expressed in many ways throughout the body; this has to do with heteroplasmy, which basically entails how many of the mitochondria are affected by the disease causing mutation. The most frequently occurring symptoms are seen in large organs such as the brain and muscles which require a lot of ATP to function. Below, we have listed the most studied genetic mitochondrial diseases. Many have similarities in terms of symptoms and/or disease-causing mechanism, they are all rare and genetically caused by mutations in either nuclear DNA and/or mtDNA that code for genes which are essential for mitochondria. Several of the genetic mitochondrial diseases affect children, who may suffer from severe complications. Unfortunately, there is no current drug indicated for any of the diseases we have listed below, hence a significant unmet medical need exists.

Mitochondrial diseases are characterised by the inability of mitochondria to produce a sufficient amount of ATP…

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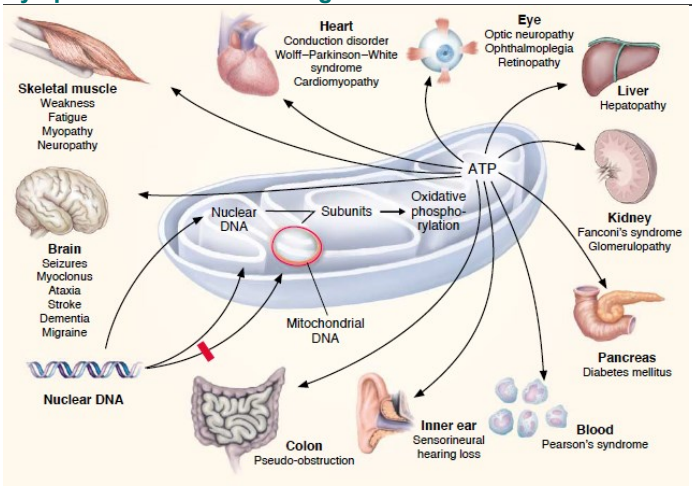
Diagnosis in clinical practice

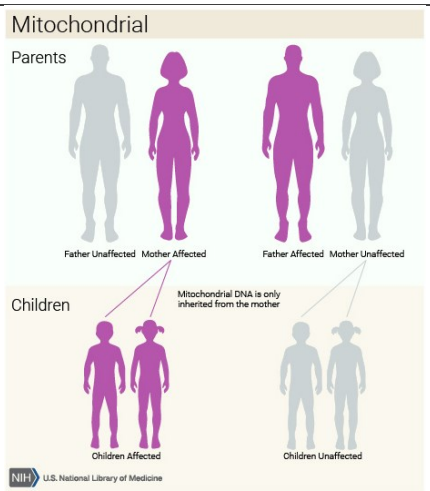
Today, genetic analysis is the standard for diagnosing mitochondrial disease. Before genetic testing was available, other procedures such as the modified Bernier criteria, the Nijmegen criteria and the Morava criteria were used. The procedures include a wide range of tests ranging from review of family history, biochemistry assays and neuro-imaging.

Symptoms associated with genetic mitochondrial diseases



Source: *Courtesy of SIMD NAMA, originally published by Johns DR. N Engl J Med 1995;333:638-44)*

Inheritance of mtDNA



Source: NIH

Alper's disease

The first symptoms of Alper's disease are typically manifested in children before age four. Symptoms include epilepsy, brain damage, complications in the liver, gastrointestinal tract and in the peripheral nervous system. As the disease progresses, patients can also develop dementia, loss of vision and paralysis.

Symptoms include epilepsy, brain damage, complications in the liver, gastrointestinal tract and in the peripheral nervous system

- **Prevalence.** It is far from clear how many patients suffer from Alper's disease, but the estimated prevalence is 2 in every 100,000 individuals. According to literature, the incidence rate is 1 in every 100,000 to 250,000 births.
- **Cause.** In most cases, the disease is caused by a mutation in the POLG1 gene, which is located on chromosome 15. The gene is responsible for coding the protein DNA-polymerase gamma, which is required for duplication and reparation of mtDNA. Mutations in POLG1 can cause disturbances in the reparation mechanism of mtDNA, a state which is known as depletion. Depletion will in turn affect mitochondria negatively and its ability to produce ATP becomes limited. Another mechanism which has been linked to brain damage and liver symptoms in Alper's patients is the absence of selenium. Selenium is one of the components in glutathione peroxidase, an enzyme that protects cells from ROS. Absence of selenium and

subsequently glutathione peroxidase could be a reason why neurons in the grey matter of the brain are damaged and potentially also liver cells.

- **Treatment.** There is currently no available disease-modifying treatment, only drugs aiming to treat symptoms of the disease are available. The epilepsy which is characteristic for Alper's is treated with anti-epileptic agents. Liver complications can in some cases be eased through carnitine supplementation. Patients could also be given vitamins such as folic acid and coenzyme q10, which are essential leading up to – and in OXPHOS. However, there is currently a lack of evidence supporting the clinical significance of treatments with i.e. folic acid and coenzyme q10 in Alper's disease.

CPEO

Progressive external ophthalmoplegia (CPEO) is a group of diseases characterised by impairments in the extrinsic muscles involved in eye movements. Other symptoms include epilepsy, impairments in the peripheral nervous system, myopathy, ataxia. The first symptoms are seen in children and the disease progresses from early childhood to adolescence. PEO becomes CPEO when the disease progresses to a chronic state.

CPEO) is a group of diseases characterised by impairments in the extrinsic muscles involved in eye movements

- **Prevalence.** Just as in the case of Alper's disease, there is no exact data on how many individuals are affected; the worldwide prevalence has been estimated at 1 or 2 per 100,000 individuals.
- **Cause.** A deletion (loss of a large DNA sequence) in mtDNA is the most common cause of the disease. The frequently identified deletion in PEO patients is a deletion of 4,977 base pairs in the DNA. PEO can also be caused by mutations in nuclear DNA; specifically two genes POLG1 on chromosome 15 and TWINKLE on chromosome 10 have been linked to PEO. Mutations in these genes can cause misfolding or lack of protein expression, which affects the repair process of mtDNA. The mutations also affect complex I and IV in OXPHOS, which caused impairments in the mitochondria's ability to synthesise ATP.
- **Treatment.** There have been case reports suggesting tetracycline could delay the muscle-weakening effects in the eyes, however, clinical evidence is limited[5]. There is currently no disease-modifying treatment, only symptomatic treatment such as mechanical eyelid openers and pacemakers to cope with the muscle-weakening effects that come with the disease.

Kearns-Sayres syndrome

Just as with many other mithochondrial disorders, Kearn-Sayres syndrome (KSS) is a rare neuromuscular disorder with onset in early childhood. Common symptoms include abnormal pigmentation and/or loss of cells in the cornea of the eyes, and disturbance in the electrical conduction system of the heart. Complications in the central nervous system followed by dementia, depression and ataxia are also common in these individuals. Individuals with KSS may also develop PEO later in life.

Symptoms include abnormal pigmentation and/or loss of cells in the cornea of the eyes, and disturbance in the electrical conduction system of the heart

- **Prevalence.** In a case report by Leal M et al. (2016), it is stated that only 226 cases have been reported in literature since 1994. However, the global prevalence has been estimated to 1–3 in every 100,000 individuals, hence the rate of underdiagnoses should be significant.
- **Cause.** The disease-causing mechanism in KSS is very similar to that of PEO. Deletions ranging between 1,000 to 10,000 base pairs have been linked to KSS. Just as for PEO, a 4,997 base pair deletion causing a loss of 12 important mitochondrial genes is a common cause of the disease. If 80–90% of the mtDNA is mutated, it is very likely that OXPHOS will be affected, especially the complex I and IV. Unlike many other mitochondrial diseases, KSS is not inherited but the deletion occurs spontaneously in individuals[6].
- **Treatment.** It has been reported that treatment with coenzyme Q10 and supplementation with carnitine could be of help for the symptoms caused by disturbance in OXPHOS, more specifically, it has been reported that these treatments improve the conditions related to the heart. Supplementation with vitamins could have a protective effect for symptoms related to ROS, but this has not been demonstrated in clinical trials.

[5] http://n.neurology.org/content/68/14/1159
[6] http://www.childneurologyfoundation.org/disorders/mitochondrial-diseases/

Pearson syndrome

A very severe condition with a high mortality rate

Pearson syndrome is a very severe condition and the mortality rate is high. The bone marrow and pancreas are two organs frequently affected in individuals suffering from Pearson syndrome. Both organs are affected since individuals with Pearson become anaemic as haemoglobin end up in mitochondria instead of in red blood cells where it belongs. The anaemia is associated with vacuolisation of bone marrow precursors and also leads to dysfunctions in the exocrine system of the pancreas[7]. Furthermore, dysfunctions of the kidneys, liver and central nervous system have also been linked to the disease.

- **Prevalence.** Pearson syndrome is very rare, perhaps the most rare genetic mitochondrial disease we touch upon in this report. The overall global prevalence has been estimated to 1 in every 1,000,000 individuals.
- **Cause.** Just like in the case of PEO and KSS, large deletions in mtDNA causes Pearson's syndrome. Approximately 20% of all patients will have deletion of 4,997 nucleotides.
- **Treatment.** Frequent blood transfusions are important to avoid the anaemia. Replacement of pancreatic enzyme may also be useful to cope with the exocrine functions that do not work properly in patients.

MELAS

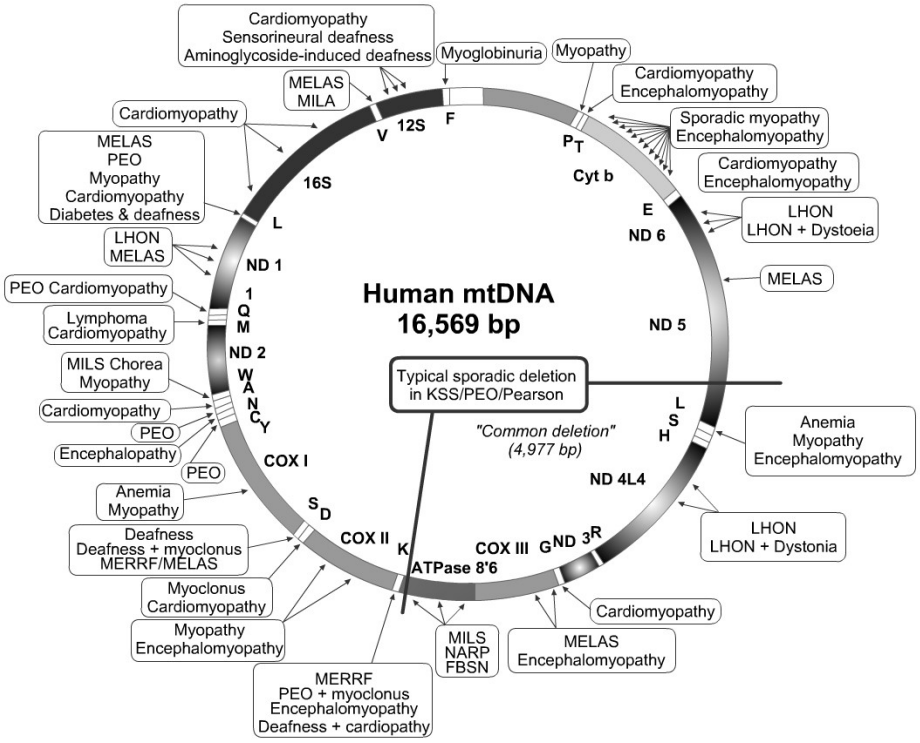
A chronic disease characterised by progressive neurodegeneration and organ failure

The term MELAS is an abbreviation for mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). It is a chronic disease characterised by progressive neurodegeneration and organ failure due to dysfunction in OXPHOS; more specifically in complex I, III and IV. Individuals suffering from MELAS have no symptoms at the time they are born. However, in more than half of individuals, the first symptoms appear between the ages of five and 15 years, and almost always before the age of 40. Other medical conditions frequently associated with the disease are: stroke-like episodes, dementia, headache, vomiting, seizures, lactic acidosis, deafness, growth retardation, and myopathy.

- **Prevalence.** The estimated prevalence in available literature suggests an incidence rate of approximately 1–2 per 100,000 people.
- **Cause.** In most cases, the disease is caused by a mutation in mtDNA. The most common site for mutation is the MT-TL1 gene, more specifically the m.3243A> mutation in the MT-L1 gene, which has been suggested to cause about 80% of all cases of MELAS disease. The MT-TL1 gene codes for a transport RNA (tRNA), which is essential for the translation of proteins required in OXPHOS, and more specifically, the mutation affects the enzymatic activity in complex I in OXPHOS, but some patients also have defects in complex II. Another gene often associated with MELAS is MT-ND5, which, as if it is mutated, can cause disease. It has been estimated that mutations in MT-ND5 are responsible for about 15% of all MELAS cases. The MT-D5 gene encodes a subunit of the protein NADH-ubiquinone oxido-reductase[8]. Overall, more than 30 mutations in mtDNA have been linked to MELAS. Just as in most genetic rare mitochondrial diseases, the proportion of the mutated mtDNA (hetero-plasmic) often determines how the disease is expressed, as well as its severity.
- **Treatment.** Several studies, including a recent publication by Hattab A et al. (2017) suggests treatment with arginine and citrulline can have therapeutic effect for individuals with MELAS since arginine and citrulline are precursors to nitric oxide. Studies have confirmed that administration of arginine or citrulline, either orally or intravenously, increases nitric oxide availability and since deficiency of nitric oxide has been suggested to play a major role in the pathogenesis of MELAS, increasing nitric oxide levels could be beneficial. However, Hattab A et al. (2017) stress the clinical effects for citrulline have not been studied and the evidence that supports clinical effects of arginine is limited to heart-related complications.

[7] Morris A A M (1997) Pearson syndrome without marrow involvement, BMJ Journals
[8] http://www.socialstyrelsen.se/ovanligadiagnoser/melas

Genetic mapping of disease related to mutations in mtDNA



Source: Originally published by Drs. DiMauro and Schon

Traumatic brain injury (TBI)

50–60 million new cases globally per year

With 50–60 million new cases globally per year, traumatic brain injury (TBI) is estimated to remain the most common cause for neurological disability globally until at least 2030[9]. A significant portion of patients living with disabilities caused by TBI are young individuals who could have lived normal lives with high productivity. Instead, these individuals, their families and society have to carry a burden that involves suffering and huge healthcare costs. A significant unmet medical need exists for this condition; the pharmaceutical industry has invested billions of dollars in drug development; however, no effective treatment exists yet.

Traffic accidents, falls among the elderly and sports-related accidents are all common causes of TBI

Traffic accidents, falls among the elderly and sports-related accidents are all common causes of TBI currently driving its growth. However, the global epidemiology for TBI is changing and the cause of trauma is very much related to socioeconomic factors. For instance, in low-income countries, traffic accidents are by far the most common cause for TBI, and unfortunately it is a growing trend. For instance, a study looking at incidence rates for TBI in India between 2004 and 2015 showed that accident-related deaths increased by 49% over the period, while the increase of the overall population was 16.4% for the same period. Also, it is estimated that 60% to 70% of all TBI cases in India are related to traffic accidents. In high-income countries, traffic-related TBI incidence is falling; instead there has been a documented rise among TBI in the elderly. In this population, falls are the most common cause for trauma. Elderly individuals are at higher risk of TBI, but most notably, the morbidity rate is much higher compared to the overall population. The elderly are estimated to represent 10% of all TBI cases, but of those who die from TBI within 10 years of trauma, the elderly represent 50%.

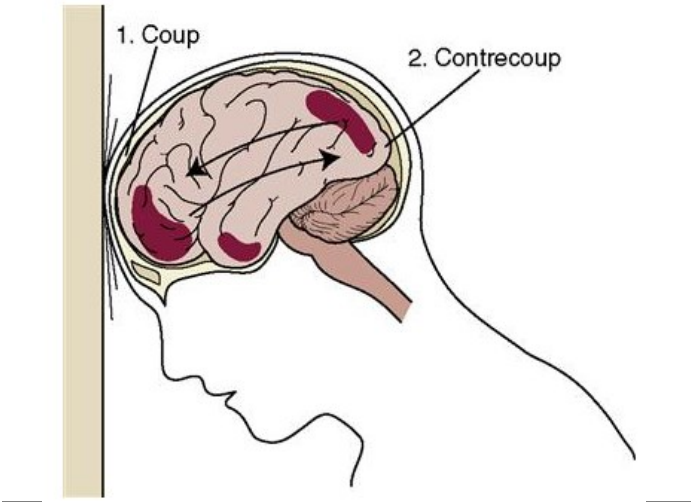
Several studies have reported TBI could be a risk factor for neurodegenerative diseases such as dementia, Alzheimer's disease and Parkinson's disease

Several studies have reported that TBI could be a risk factor for neurodegenerative diseases such as dementia, Alzheimer's disease and Parkinson's disease. A meta-analysis of 15 studies investigating the possible linkage of comorbidity showed an odds ratio of 1.58 to develop Alzheimer's disease, however, the odds ratio was only true for men[10]. Other studies suggest that TBI is associated with non-AD type dementia; especially in the moderate-to-severe patient group where it has been confirmed to be a risk factor.

The brain is surrounded by cerebral spinal fluid and the skull. When an external force causes trauma to the head, it moves along with the skull while the brain sits still; this causes the skull to directly impact the brain in one direction, causing a coup injury. What happens afterwards is that the head snaps back, causing a force in the contrary direction that will make the skull impact the brain again but on the other side, this causes a contrecoup injury. Depending on the trauma, there are many different complications that can follow from coup and contrecoup injuries associated with TBI; below, we list some of the most common.

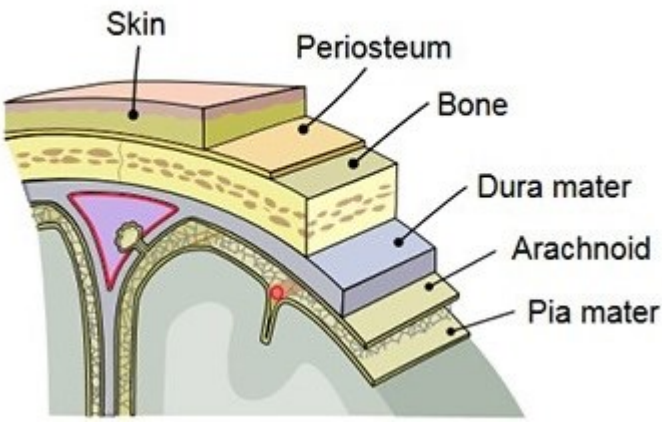
[9] Maas et al. (2017) Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research
[10] S Fleminger1, D L Oliver1, S Lovestone2, S Rabe-Hesketh3, A Giora1 (2003) Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication

Illustration of coup and contrecoup injury



Source: Nurse Key

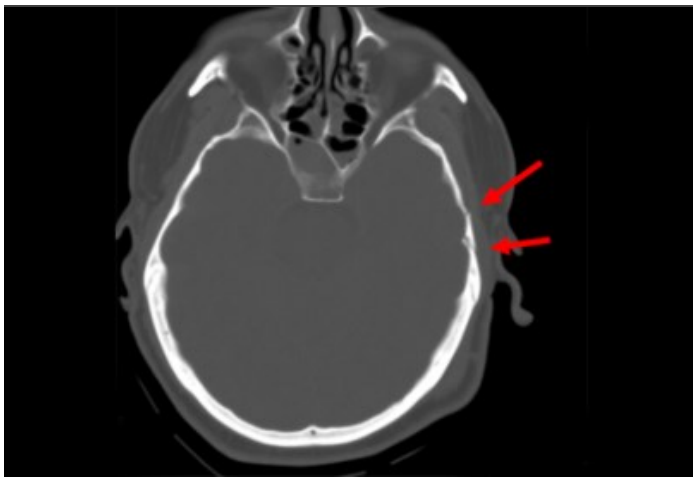
Meninges = Dura mater, Arachnoid & Pia mater



Source: ALUS Medical solutions

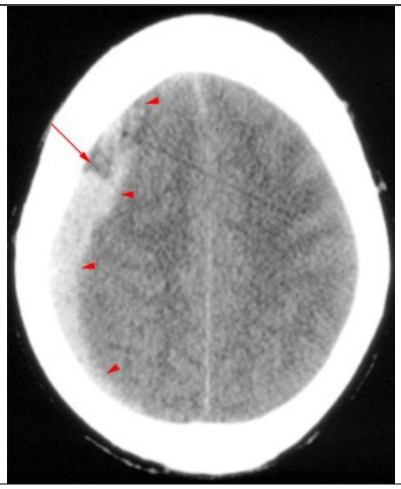
- **Skull fractures.** Large forces can lead to a depressed skull, which has a direct impact on the brain and injures it. But very small fractures can also be devastating since they can allow bacteria to move through small tears in the skull and potentially cause meningitis.
- **Epidural hematoma.** A type of injury commonly seen in TBI patients, these are basically arterial bleeds in the meninges of the skull (see figure above). Since hematomas are arterial bleeds, blood can accumulate very quickly and build up enormous pressure inside the skull that will compress the brain tissue and damage it.
- **Subdural hematoma.** Another type of hematoma is subdural hematoma, but contrary to epidural hematomas, the subdural type is caused by venous bleeding. Compared to epidural hematomas, blood will accumulate slower in subdural hematomas; but over time, accumulation can result in a life-threatening state similar to that of epidural hematomas.
- **Cerebral contusion.** Contusion is a bruising of brain tissue that kills neurons. After severe injury, contusion will lead to an inflammatory reaction known as gliosis. During gliosis, glia cells will proliferate to replace the damaged neurons, forming a glial scar.
- **Diffuse Axonal Injury (DAI).** The result of traumatic shearing forces that happen when the head is exposed to extreme acceleration. Brain tissue consists of both grey and white matter; grey matter has lower density than white matter which is stiffer. In between these two matters there are a large amount of neurons; accelerating forces can cause the grey matter to slide across the white matter and lead to axonal shearing. The degree of DAI injury is most commonly seen at the junction of grey/white matter and is the most extensive in areas where density differs the most.

Hairline thin skull fractures



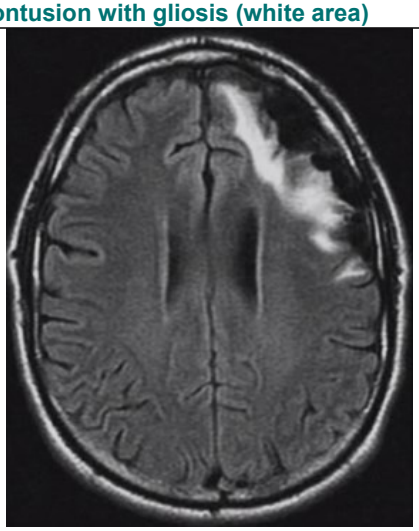
Source: BMJ Best practice

Epidural hematoma



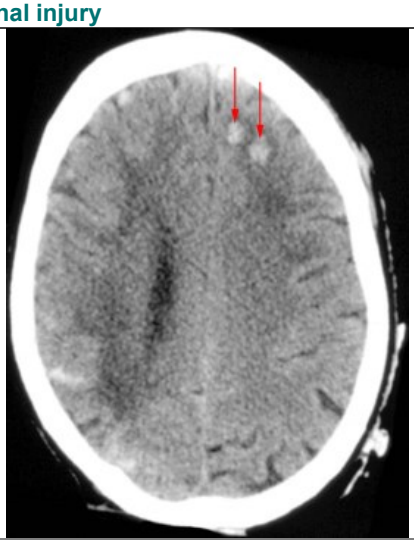
Source: University of Virginia

Result of contusion with gliosis (white area)



Source: Dr. David Mikulis – Director, Functional Neuroimaging Lab. Deot. Of Medical Imaging – Toronto Western Hospital

Diffuse axonal injury



Source: University of Virginia

TBI can affect individuals in many different ways, the location of the injury and the extent of the injury are two broad factors that often determine what type of long-lasting symptoms patients get. For instance, a long-term follow-up of patients who suffer from severe TBI shows that the majority of patients experience fatigue, have problems concentrating and have memory issues. Depression, irritability, communication issues and sleep disturbances are other common physiological issues that these patients have.

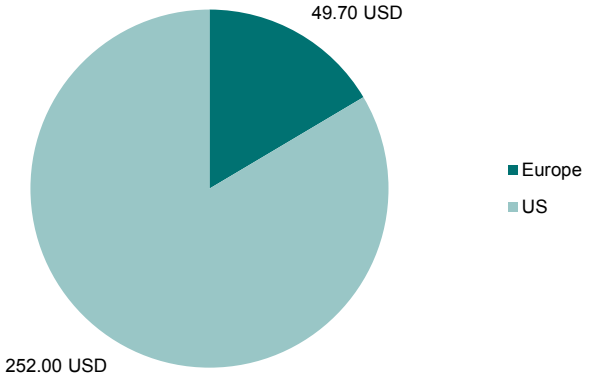
TBI can affect individuals in many different ways

Impairments after 2–11 years follow-up in patients with severe TBI

Psychological functions	Participants n=51	Percentage	Physical functions	Participants n=51	Percentage
Fatigue	42	82%	Weight gain	21	41%
Concentration problem	37	73%	Arm motor impairment	19	37%
Memory problem	36	71%	Leg motor impairment	18	35%
Depression	25	49%	Chronic pain	18	35%
Irritability	23	45%	Hearing impairment	18	35%
Communication problem	23	45%	Visual impairment	17	33%
Sleep disturbances	19	37%	Impaired touch sense	17	33%
Impotence (men, n=38)	14	27%	Problem talking (n=50)	17	33%
Reduced libido (n=50)	18	35%	Dizziness	15	29%
Anxiety	17	33%	Impaired smell sense	14	27%
Smoking addiction	16	31%	Diabetes/cardiovascular disease	11	22%
Alcohol/drug abuse	14	27%	Epilepsy	10	20%

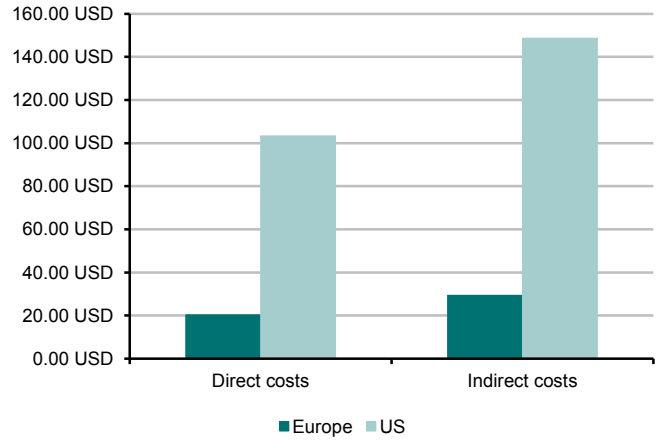
Source: Ulfarsson T et al. J Neurotrauma. 2013.

Estimated total costs related to TBI (USDbn)



Source: Orman J, Kraus J, Zaloshnja E. Epidemiology. In: Silver JM, McAllister TW, Yudofsky SC, eds. Textbook of traumatic brain injury, 2nd edn. Washington, DC: American Psychiatric Association. Publishing, 2011: 3–22.
Gustavsson A, Svensson M, Jacobi F, et al, and the CDBE2010 Study Group. Cost of disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 2011; 21: 718–79
Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jönsson B, and the CDBE2010 Study Group and the European Brain Council. The economic cost of brain disorders in Europe. Eur J Neurol 2012; 19: 155–62

Cost split by direct and indirect costs (USDbn)



Source: Orman J, Kraus J, Zaloshnja E. Epidemiology. In: Silver JM, McAllister TW, Yudofsky SC, eds. Textbook of traumatic brain injury, 2nd edn. Washington, DC: American Psychiatric Association. Publishing, 2011: 3–22.
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Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jönsson B, and the CDBE2010 Study Group and the European Brain Council. The economic cost of brain disorders in Europe. Eur J Neurol 2012; 19: 155–62

Significant economic impact of TBI on society

It has been estimated that the global cost associated with TBI is USD400bn per year. As seen in the two graphs above, we have identified literature where estimates have been made on TBI-related costs in the US and Europe. There is also literature estimating the costs split between direct and indirect costs, in these studies; direct costs relate to all resources consumed within the healthcare sector and out-of-pocket expenses for patients. For indirect costs, these represent all foregone resources, such as loss of productivity and intangible costs such as quality of life and care efforts by family members.

Global cost associated with TBI estimated at USD400bn per year

Diagnosis of TBI

TBI is defined as an alteration in brain function or other evidence of brain pathology caused by an external force. TBI can be classified as mild, moderate or severe; when applying this classification, diagnosis is usually based on the Glasgow Coma Scale, which includes three diagnostic measurements: (1) the individual's ability to speak, (2) mobility, and (3) if the person can open his or her eyes when asked. In addition, it is important to know for how long the person was unconscious after the trauma, and thirdly, for how long the patient had memory loss. Other important diagnostic tools include intracranial pressure (ICP) monitoring and neuroimaging techniques such as computerised tomography (CT) and magnetic resonance imaging (MRI).

TBI is defined as an alteration in brain function or other evidence of brain pathology caused by an external force

Neuroimaging in TBI

MRI is used extensively in medicine and is generally available in every major hospital in the developed world. The principle of MRI builds on using powerful magnets to align the nuclei of the atoms inside the body. With a variable magnetic field, the atoms will resonate, a phenomenon called nuclear magnetic resonance (NMR), where the nuclei of an atom in a magnetic field absorb and re-emit electromagnetic radiation. The produced rotating magnetic fields of every nucleus are detected by a scanner in the MRI system and are used to create an image. In TBI imaging, it has been shown that MRI is more efficient than CT in detecting for instance parenchymal lesions. Furthermore, it has been suggested that advanced MRI could be useful and have prognostic value for several outcome measures for patients with all severities of TBI. The only downside with MRI compared to CT is the timespan. CT scanning is a relatively fast procedure, while MRI is relatively slow in comparison, taking 30 to 45 minutes, and might therefore not be optimal for use in an emergency setting[11].

The only downside with MRI compared to CT is the time frame…

… CT scanning is a relatively fast procedure, while MRI is relatively slow in comparison, taking 30 to 45 minutes

[11] Maas et al. (2017) Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research

Today, CT scanning is the standardised neuroimaging technique used in clinic to make surgical decisions. It is fast and the go-to tool to determine if patients have life-threatening brain injuries when they enter the emergency room. However, it is not sensitive enough to detect all abnormalities associated with TBI. For instance, one study showed that abnormalities could be detected in less than 5% of patients diagnosed with mild TBI[12]. MRI is a valuable complement to CT since it can offer a more detailed view of more subtle injury and is much better than CT in exposing the overall extent of the brain injury.

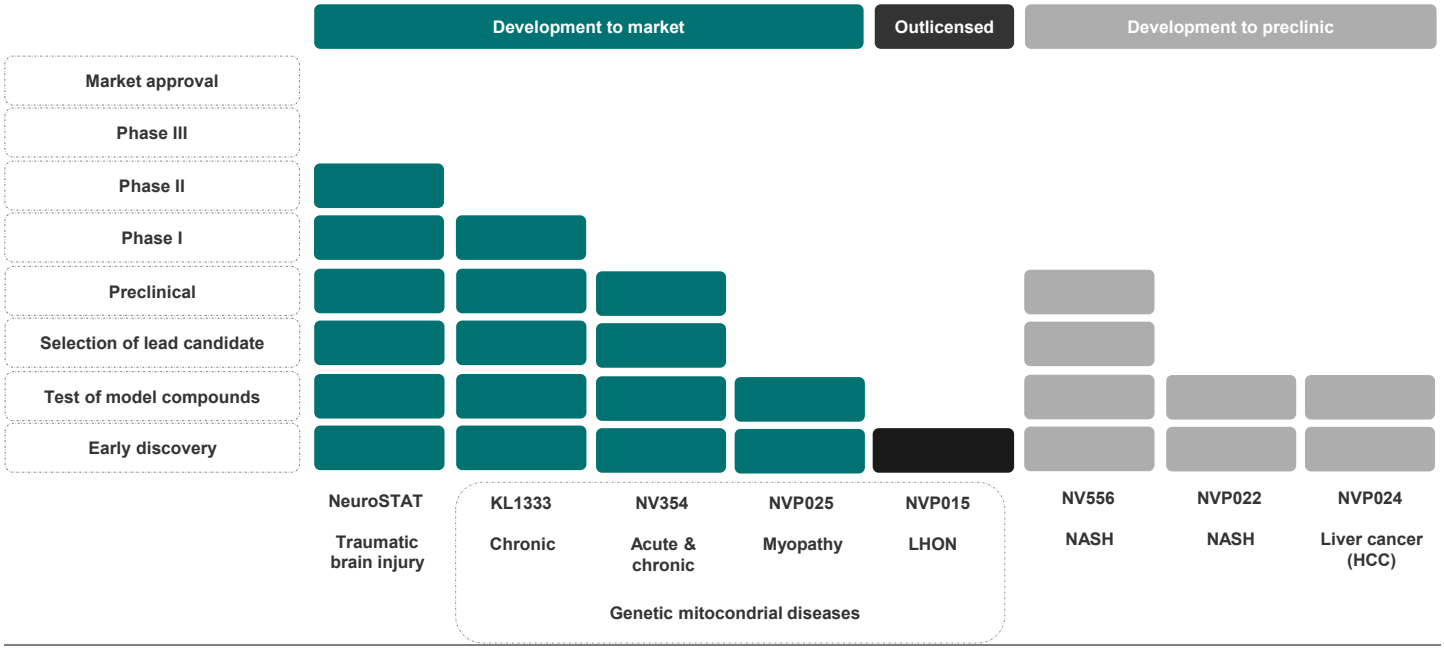
One study showed that abnormalities could be detected in less than 5% of patients diagnosed with mild TBI

Product pipeline

There are currently two drug candidates in clinical development, four in early-stage development and one which has been partially out-licensed to a strategic partner. It is in line with the company's core strategy to launch its drugs on markets, but also to out-license drug candidates to strategic partners. For drug candidates indicated for rare diseases (genetic mitochondrial diseases and TBI), the company aims to develop these all the way to market by itself. As for drug candidates aimed at common diseases (NASH and liver cancer) these are to be developed to a pre-clinical stage and then out-licensed to potential strategic partners.

Currently two drug candidates in clinical development, four in early-stage development and one which has been out-licensed to a strategic partner

Overview of NeuroVive's product pipeline



Source: NeuroVive Pharmaceutical

KL1333

KL1333 is a drug candidate in early-stage clinical development targeting mitochondrial diseases. NeuroVive in-licensed KL1333 from Korean company Yungjin Pharm in May 2017. The deal gives NeuroVive exclusive rights to develop and commercialise KL1333 in all geographies except Korea and Japan. NeuroVive paid USD3m upfront and will pay an additional USD12m in development-related milestone payments and USD42m in milestone payments if KL1333 is granted regulatory approval and reimbursement. In addition, NeuroVive will pay a low double-digit royalty on future potential sales plus additional undisclosed sales and marketing-related milestone payments.

NeuroVive in-licensed KL1333 from Korean company Yungjin Pharm in 2017

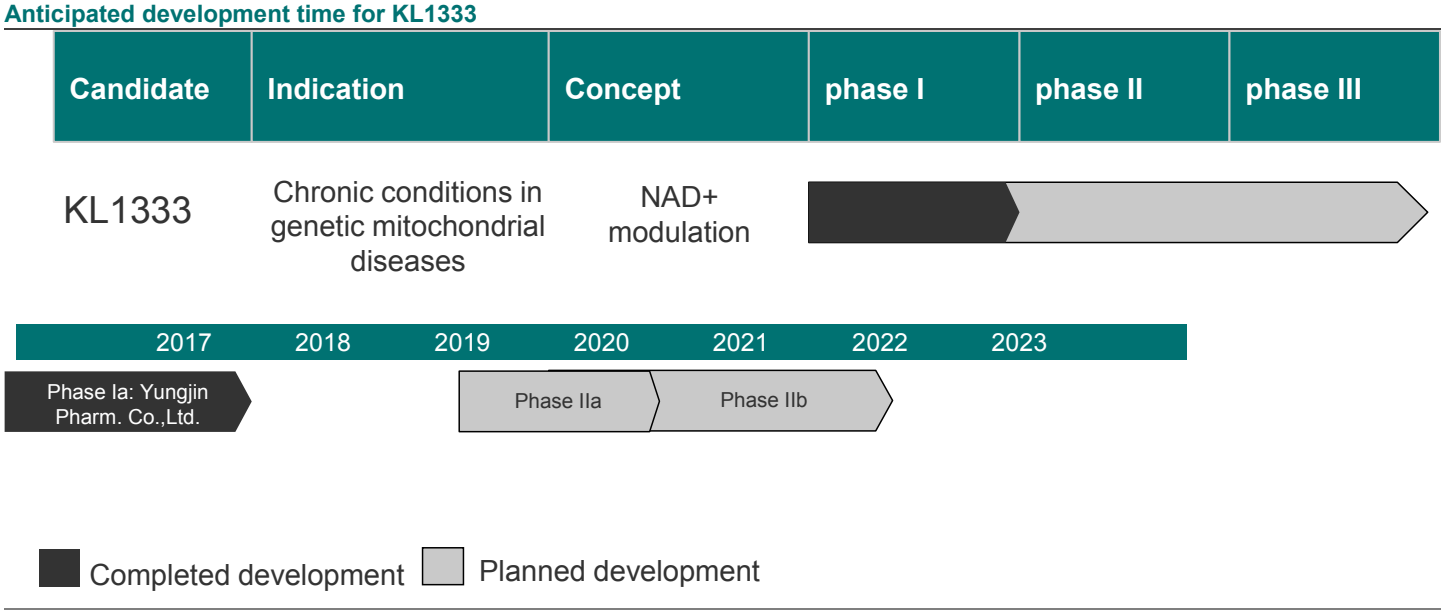
Mechanism of action

It has been demonstrated in an in vitro study on human fibroblast from patients with MELAS, that KL1333 restores ATP generation, increases the anti-oxidant defence and might promote synthesis of new mitochondria. It does so by modulating NAD+, a co-enzyme that plays an essential role in the process of ATP generation in the electron transport chain. The elevated

[12] Mooney JS, Yates A, Sellar L, et al. Emergency head injury imaging: implementing NICE 2007 in a tertiary neurosciences centre and a busy district general hospital. Emerg Med J 2011; 28: 778–82.

NAD+ levels from KL1333 lead to the activation of SIRT1, AMPK and subsequent activation of PGC-1α. PGC-1α is considered a therapeutic target in many mitochondrial diseases since it plays central role in mitochondrial biogenesis, mitochondrial protein expression, and mitochondrial respiratory function[13].

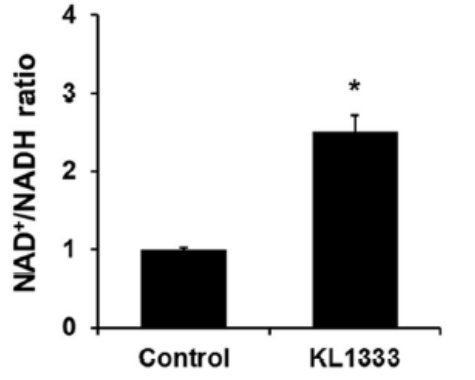
Anticipated development time for KL1333



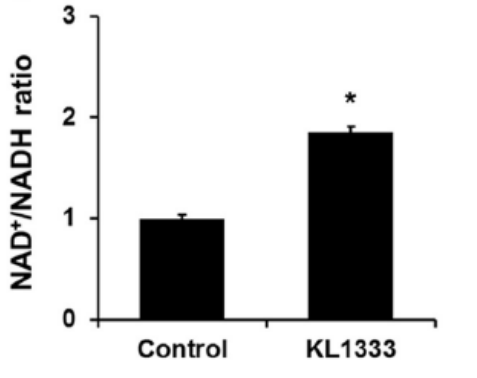
Source: DNB Markets adapted form NeuroVive

- **KL1333 increases the NAD+/NADH ratio.** It was demonstrated in a preclinical study by Seo et al. (2018) that the NAD+/NADH ratio increased after 30 minutes in myoblasts when these were treated with KL1333 of both 1 and 2 micro molar. According to management, the fact that KL1333 successfully modulated the NAD+/NADH ratio in cells is perhaps the most promising result demonstrated in the study by Seo et.al.

NAD+/NADH ratio after 30min after treatment with 1 micro molar KL1333



NAD+/NADH ratio after 30min after treatment with 2 micro molar KL1333

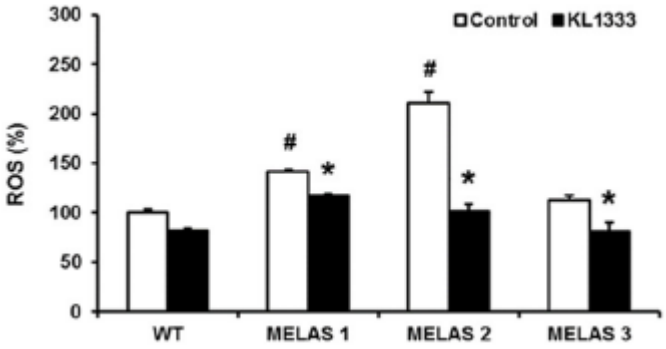


Source: Seo et al. (2018)

- **KL1333 increases the anti-oxidant defence.** In addition to NAD+ modulation, it has been demonstrated that KL1333 reduced the levels of reactive oxygen species (ROS) in cells; ROS is cytotoxic since it promotes oxidative stress. In another figure, the study by Seo et al. (2018), ROS levels decreased in all cells treated with KL1333 compared to its control; this goes for all samples derived from MELAS patients, but also for the healthy cells (WT).

[13] Lehman JJ, et al. (2000). Peroxisome proliferator-activated receptor g coactivator-1 promotes cardiac mitochondrial biogenesis. J Clin Invest.

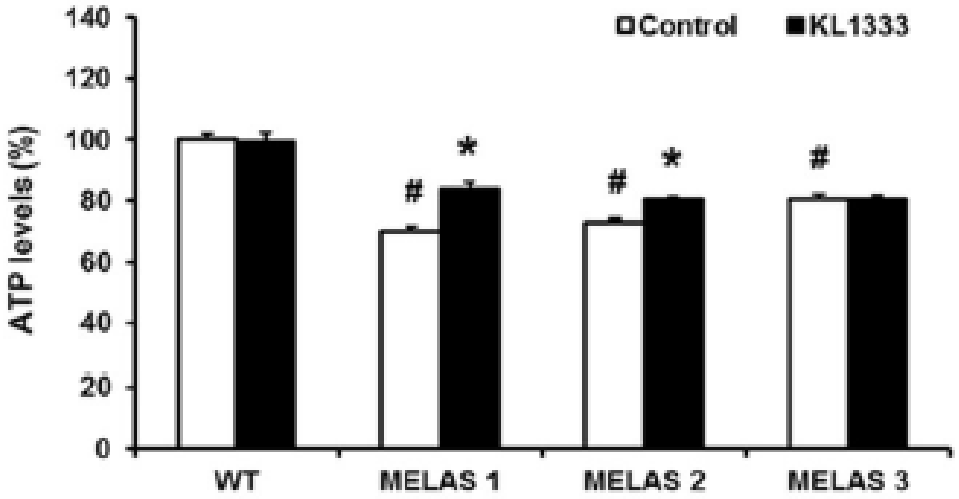
ROS levels in myoblasts derived from MELAS patients



Source: Seo et al. (2018) #P < 0.05: MELAS fibroblast vs. WT control. *P < 0.05: presence versus absence of KL1333.

- **Increased ATP levels.** ATP levels increased in 2 of 3 MELAS samples after treatment with KL1333 for 24 hours, #P < 0.05: MELAS fibroblast versus WT control. *P < 0.05: presence versus absence of KL1333.

Wild type and MELAS samples treated with KL1333 versus control



Source: Seo et al. (2018) #P < 0.05: MELAS fibroblast vs. WT control. *P < 0.05: presence versus absence of KL1333.

Finalised phase I study in healthy volunteers

This was a double-blinded, placebo-controlled, single-dose, phase I study that aimed to investigate the pharmacokinetics and safety/tolerability of KL1333 in 60 healthy subjects. All planned dosing cohorts have been completed according to plan. Results showed that some patients experienced gastrointestinal complications, but overall, KL1333 was tolerated well in by the healthy volunteers. The results of Yungjin's single ascending dose (SAD) study will be referenced for the final design of NeuroVive's upcoming multiple ascending dose (MAD) study in healthy volunteers and patients with genetic mitochondrial disease.

Study in patients with mitochondrial disease

NeuroVive is about to initiate the first in-patient's study with KL1333 in the UK

NeuroVive is about to initiate the first in-patient's study with KL1333 in the UK. On 10 October, the company announced that the British Medicines and Healthcare products Regulatory Agency had approved the study design and NeuroVive is now allowed to start the study. It will include a multiple ascending dose in healthy volunteers as well as in patients with genetic mitochondrial disease. Up to five groups of healthy volunteers with eight individuals in each group are planned to be recruited, followed by one group of eight patients with mitochondrial disease for a second part of the study. The purpose of the study is to investigate the safety and pharmacokinetics of KL1333. NeuroVive will also evaluate biomarkers, but management has made it clear that it does not accept the evaluation of biomarkers to provide any

indications on efficacy. Management anticipates the study to start later in 2018 and results are expected in 2019.

NeuroSTAT

NeuroSTAT is a new formulation based on the active product ingredient cyclosporine and all of its ingredients are registered for human use. The compound is prepared in a ready-to-use solution manufactured according to good manufacturing procedure (GMP) by Fresenius-Kabi. The active product ingredient in NeuroSTAT, cyclosporine, binds and inhibits cyclophilin D.

Mechanism of action

Cyclophilin D plays an essential role in the opening of pores in mitochondria and thereby regulates mitochondrial permeability transition (mPT)[14]. During TBI, neurons experience an overload of CA2+ influx in the mitochondria. The Ca2+ influx causes imbalance in the mPT, which subsequently triggers the release of death ligands, signalling apoptosis, which is programmed cell death. By binding cyclophilin D, NeuroSTAT indirectly inhibits the opening of Ca2+ ion channels and thereby protects mitochondria from Ca2+ overload and could thereby potentially help cells to avoid cell death.

Moderate-to-severe TBI is the target population for NeuroSTAT

In its current clinical development programme, NeuroVive is focused on targeting TBI patients in need of treatment at an Intensive Care Unit (ICU) and are clinically indicated to receive External Ventricular Drainage (EVD) and Intracranial Pressure (ICP) monitoring – they could typically be classified as moderate or severe. Even though the overall prevalence and incidence rates for TBI tell us that the condition is far from rare, only a small portion of patients fulfil these criteria, which is why NeuroSTAT has been granted orphan drug designation by the US Food and Drug Administration (FDA) as well as the European Medicines Agency (EMA).

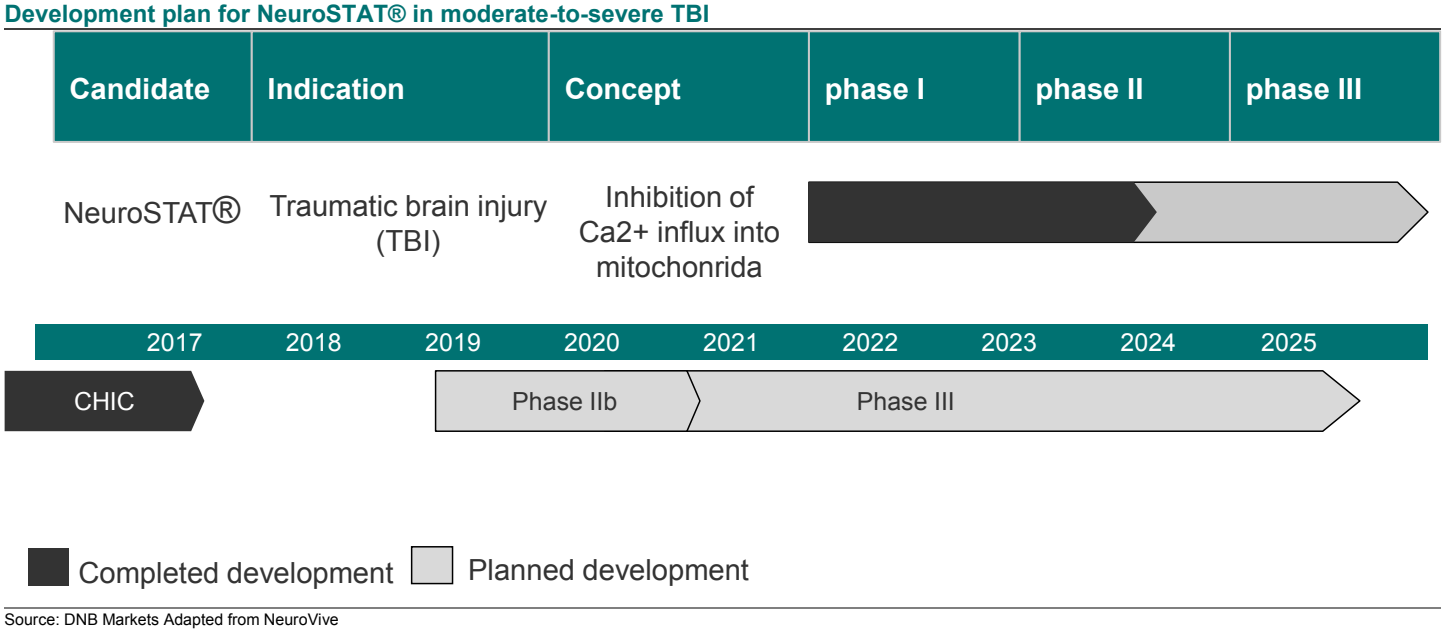
NeuroVive is focused on targeting TBI patients in need of treatment at an Intensive Care Unit (ICU)

NeuroVive's development of NeuroSTAT

In this section, we go through existing data which have been generated from preclinical and clinical studies led by NeuroVive. In summary, complementary pre-clinical studies in animals have shown a significantly reduced volume of brain injury after treatment with NeuroSTAT. Positive changes in brain energy metabolite levels, mitochondrial respiratory function, as well as decreased generation of reactive oxygen species, have also been demonstrated in preclinical studies. The company now intends to initiate a phase IIa study which could be followed by a phase IIb/III study starting in 2021.

Complementary pre-clinical studies in animals have shown a significantly reduced volume of brain injury after treatment with NeuroSTAT

Development plan for NeuroSTAT® in moderate-to-severe TBI



Source: DNB Markets Adapted from NeuroVive

[14]Sabzali J & Kuznetov A. (2013) Mitochondrial permeability transition and cell death: the role of cyclophilin D

Preclinical development showed promising potential in reducing brain damage

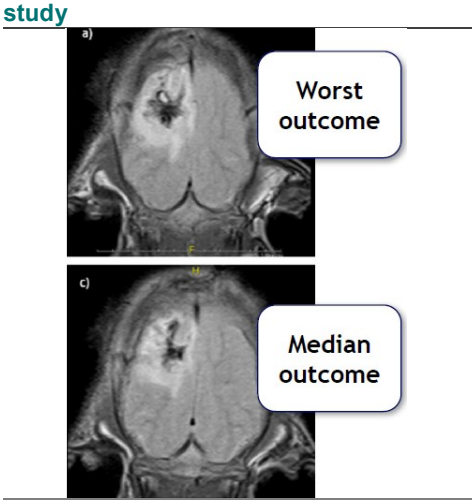
A preclinical study with NeuroSTAT was carried out in collaboration with the University of Pennsylvania. It could be considered a proof-of-efficacy study in large animal species, where mild-to-moderate focal contusional injury was induced in piglets, a three-step investigation which aimed to:

- Evaluate the bioequivalence of NeuroSTAT and Sandimmune. Over 24 hours, NeuroSTAT or Sandimmune was injected (IV) at a dose of 20mg/kg/day formulation of cyclosporine, (N=3/group).
- Pharmacokinetic dose escalation study over 24 hours. In this study, doses of 5, 10 and 40 mg/kg/day of NeuroSTAT were evaluated (N=3/group).
- Randomised blinded placebo controlled study (5 days), with continuous infusion (20 mg/kg/d NeuroSTAT, N=10) or placebo (N=13).

In summary, outcomes based on medical imaging showed a 35% reduction in injured brain volume in pigs treated with NeuroSTAT versus placebo – both the treated and placebo had induced TBI. Furthermore, these studies displayed positive changes in brain energy metabolite levels and mitochondrial respiratory function, as well as decreased generation of reactive oxygen species.

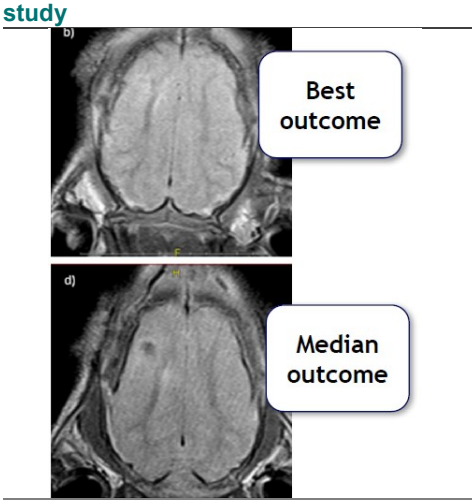
A 35% reduction in injured brain volume in pigs treated with NeuroSTAT versus placebo

Placebo group from the pre-clinical study



Source: NeuroVive Pharmaceutical

NeuroSTAT group from the pre-clinical study



Source: NeuroVive Pharmaceutical

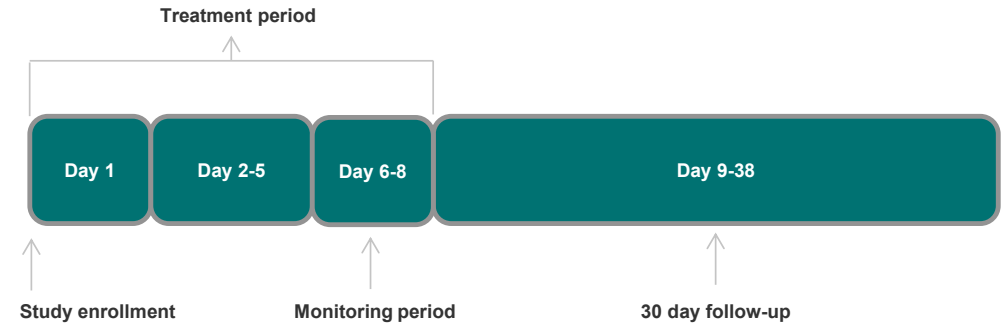
Previous studies have confirmed safety of NeuroSTAT

In the two previous studies CIRCUS and CiPRICS, a total of 548 patients were exposed to a 2.5 mg/kg bolus injection of NeuroSTAT. These studies evaluated NeuroSTAT in other patient populations (myocardial infarction and patients undergoing CABG surgery).

Completed phase II trial showed NeuroSTAT is safe and measurable in TBI patients

The Copenhagen Head Injury Cyclosporine (CHIC) study is a phase IIa trial finalised in 2017. CHIC was an open-label phase IIa trial investigating safety and pharmacokinetics in 20 patients with severe TBI. All patients received an initial NeuroSTAT dose of 2.5mg/kg by bolus infusion; patients were then randomised into two different dose groups where they received additional NeuroSTAT doses of either 5mg/kg per day or 10 mg/kg per day for five days. The primary outcome measures were the pharmacokinetic analysis of cyclosporine in blood and incidence of adverse events. Secondary outcome measures included cyclosporine levels in cerebrospinal fluid and safety biomarkers for nephrotoxicity. Outcomes from the study showed that dose-dependent concentration levels of NeuroSTAT can be measured in the blood for patients with TBI, while it also demonstrated that NeuroSTAT reaches the central nervous system (CNS), which is the intended target for the investigational drug. No unexpected safety signals were detected.

Study design of finalised phase II trial: Copenhagen Head Injury Cyclosporine (CHIC)



Source: DNB Markets

NeuroVive expects to initiate a phase II efficacy study in 2019

The planned study will be a placebo-controlled and randomised phase IIb trial evaluating the efficacy of NeuroSTAT in a homogenous subpopulation of TBI patients. Outcome measurements for efficacy will include both novel biomarkers and imaging. The study aims to recruit 70–80 patients at 17 clinical sites in both the US and Europe who will be followed for six months[15].

The FDA and EMA have provided positive feedback on MRI as an outcome measurement

On 6 September 2018, a press release from NeuroVive stated that the company had received feedback from the FDA on the clinical development plan for NeuroSTAT in TBI. In summary, the most important feedback the company received from the pre-IND meeting was that the FDA supports the proposed design for the planned phase II proof-of-concept study where advanced imaging (MRI) will be used to assess efficacy. Similar feedback has previously been received by the company from the EMA in September 2017.

Other studies on cyclosporine in TBI

The active product ingredient in NeuroSTAT, cyclosporine, has been evaluated in many preclinical and clinical studies of TBI. In our review of relevant publications on cyclosporine in TBI, our general view is that many preclinical studies, especially animal models, have shown impressive efficacy results. In clinical studies, cyclosporine appears to be safe; however, as for efficacy, the few small academic clinical studies to date have not generated equally encouraging results.

As for efficacy, clinical studies have not generated equally encouraging results

Several preclinical studies reported benefits of cyclosporine in animal TBI models

Riess P et al. (2001) showed that daily treatment with cyclosporine after severe brain injury improved motor and sensory function in rats. Animals treated with cyclosporine had significant improvement in motor function after 28 days; motor function was measured through both a composite neuro-score as well as a sensory function test[16]. One experimental TBI model evaluating the effect of cyclosporine on lesion volume by Sullivan et al. (2000) concluded that all animals who received cyclosporine demonstrated a significant reduction in lesion volume, where the highest tested dose seemed to be the most efficacious[17]. In another study by Sullivan et al. (2000), it was suggested that cyclosporine offers neuroprotection with a therapeutic window of up to 24 hours after the event of injury and that the neuroprotective properties of cyclosporine appeared dose-dependent in rats.

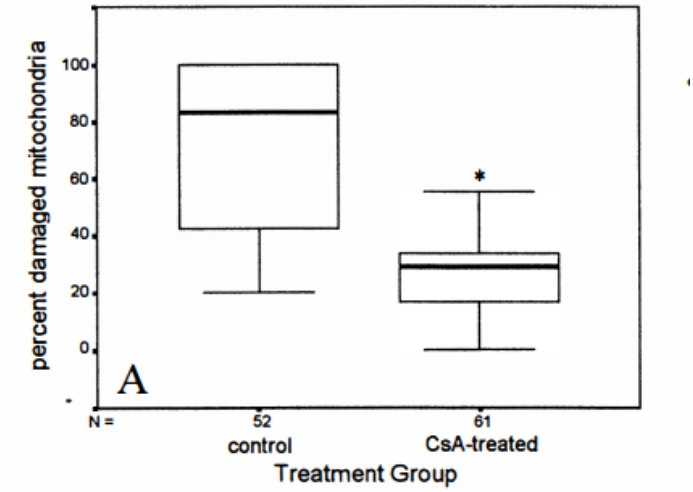
A study focusing on cyclosporine's impact on mitochondria in association with traumatic axonal injury (TAI) and cyclosporine concluded that mitochondrial integrity can be preserved if cyclosporine is administered early after trauma[18]. Also, Albensi et al. (2000) suggest it

[15] Okonkwo DO, Melon DE, Pellicane AJ, Mutlu LK, Rubin DG, Stone JR, et al. Dose-response of cyclosporin A in attenuating traumatic axonal injury in rat. Neuroreport 2003;14:463–466. [PubMed:12634504]
[16] Riess P, Bareyre FM, Saatman KE, Cheney JA, Lifshitz J, Raghupathi R, et al. Effects of chronic, post-injury cyclosporin A administration on motor and sensorimotor function following severe, experimental traumatic brain injury. Restor Neurol Neurosci 2001;18:1–8. [PubMed: 11673665]
[17] Sullivan PG, Thompson M, Scheff SW. Continuous infusion of cyclosporin A postinjury significantly ameliorates cortical damage following traumatic brain injury. Exp Neurol 2000;161:631–637. [PubMed: 10686082]
[18] Büki A, Okonkwo DO, Povlishock JT. Postinjury cyclosporin A administration limits axonal damage and disconnection in traumatic brain injury. J Neurotrauma 1999;16:511–521. [PubMed: 10391367]

stabilises mitochondrial function but that a stabilised mitochondrial function as a result of cyclosporine administration can also help to improve synaptic plasticity, which is crucial for learning and memory improvements after TBI[19]. Furthermore, it has been shown that preservation of mitochondrial function induced by cyclosporine after TBI translates to improvements in motor function and cognitive behaviour[20]. A study by Okonkwo et al. (1999) suggests cyclosporine has a protective effect on mitochondria and concluded that the agent may be of therapeutic use in TBI. In the figure below, results demonstrate that rats that were administered cyclosporine have a lower number of damaged mitochondria versus placebo.

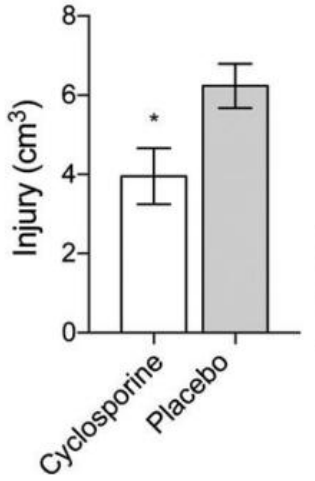
We would like to add that with NeuroSTAT, NeuroVive is testing higher doses and longer duration than any of the academic trials above. It should also be stressed that previous academic trials support that treatment with cyclosporine is safe in TBI, but have not yet provided evidence for efficacy.

The protective effect of cyclosporine on mitochondria in an animal model of TBI



Source: Okonkwo et al. (1999)

Neuroprotective Effects of Cyclosporine in a porcine pre-clinical trial of focal TBI



Source: Karlsson et al. (2018)

Preclinical TBI studies with positive cyclosporine outcome

Model	Species	Outcomes	Reference
Impact acceleration	Rat	Mitochondrial morphology, Axonal injury	Okonkwo DO et al. 1999
Impact acceleration	Rat	Axonal injury, Immuno-histochemistry	Büki A et al. 1999
Impact acceleration	Rat	Cytoskeletal damage & proteolysis	Okonkwo DO et al. 1999
Controlled cortical impact	Mouse	Lesion volume	Scheff SW et al. 1999
Controlled cortical impact	Rat	Mitochondrial morphology + function	Sullivan PG et al. 1999
Controlled cortical impact	Rat	Lesion volume	Sullivan PG, et al. 2000
Lateral FPI + CCI	Rat	Lesion volume	Sullivan PG et al. 2000
Lateral FPI	Rat	Motor + sensorimotor function	Riess P et al. 2001
Impact acceleration	Rat	Axonal injury	Suehiro E et al. 2001
Lateral FPI	Rat	O2 consumption, Motor function, Learning + memory	Alessandri B et al. 2002
Impact acceleration	Rat	Axonal injury	Okonkwo DO et al. 2003
Impact acceleration	Rat	Mitochondrial function, N-acetylaspartate reduction	Signoretti S et al. 2004
Stun gun impact	Sheep	Immuno-histochemistry	Van Den Heuvel C et al. 2004
Diffuse axonal injury	Rat	Morris water maze, Dark avoidance test	Yin et al. 2004
Controlled cortical impact	Rat	Biomarker (C-Tau)	Gabbita SP et al. 2005
Controlled cortical impact	Mouse	Mitochondrial function, Protein nitration + lipid peroxidation	Mbye LH et al. 2008
Controlled cortical impact	Mouse	Calpain-mediated α-spectrin proteolysis, Motor function, Neuroscore	Mbye LH et al. 2009
Midline FPI	Rat	O2 consumption, Electrophysiology	Colley BS et al. 2010
Feeney weight drop model	Rat	Lipid peroxidation, Mitochondrial morphology	Turkoglu OF et al. 2010

[19] Albensi BC, Sullivan PG, Thompson MB, Scheff SW, Mattson MP. Cyclosporin ameliorates traumatic brain-injury induced alterations of hippocampal synaptic plasticity. Exp Neurol 2000;162:385–389.[PubMed: 10739643]
[20] Büki A, Okonkwo DO, Povlishock JT. Postinjury cyclosporin A administration limits axonal damage and disconnection in traumatic brain injury. J Neurotrauma 1999;16:511–521. [PubMed: 10391367]

The protective effect of cyclosporine on mitochondria in an animal model of TBI		Neuroprotective Effects of Cyclosporine in a porcine pre-clinical trial of focal TBI	
Controlled cortical impact	Rat	Lesion volume	Sullivan PG et al. 2011
Controlled cortical impact + RNR	Piglet + Rat	Lesion volume, Mitochondrial function, Microdialysis (lactate/pyruvate), Cerebral blood flow	Kilbaugh TJ et al 2011
Controlled cortical impact + RNR	Piglet	Lesion volume, Mitochondrial function	Margulies et al 2015

Source: DNB Markets

The only preclinical study we looked at that did not show promising outcomes for cyclosporine in TBI was a study conducted by the Operation Brain Trauma Therapy (OBTT); the OBTT is a consortium that aims to bring acute therapies to clinical trials by using multiple preclinical models of TBI. The OBTT assessed animal models such as Morris water maze tasks and lesion volume as well as hemispheric tissue loss. The study concluded that cyclosporine produced limited effects that were beneficial only in the mildest screening model but that beneficial effects could not be demonstrated in the other models. Furthermore, the results left the OBTT with reduced enthusiasm for further investigation of cyclosporine in after TBI injury.

Clinical trials in patients demonstrated less encouraging results

In our analysis, we have also looked at outcomes from clinical studies where cyclosporine has been administered to patients with TBI. Hatton et al. (2008) assessed TBI patients who received cyclosporine within eight hours after trauma; they showed that the mortality rate for patients was not affected by cyclosporine administration, independent of dose, compared to placebo. This was a blinded placebo-controlled and randomised dose-escalation trial evaluating four doses ranging from 0.625mg/kg to 5mg/kg. All doses except the highest dose were administered every 12 hours for 72 hours; the highest dose of 5mg/kg was given first after a 2.5mg/kg loading dose and then 5mg/kg per day over 72 hours. Furthermore, the study concluded that the mortality rate or other adverse events were not significantly different from placebo in TBI patients who received cyclosporine at doses of up to 5mg/kg/day within eight hours after injury.

A 2009 study carried out by Mazzeo A et al.[21] evaluated 50 adult patients with a severe head injury. It was a randomised double-blinded and placebo-controlled study where patients received 5mg/kg of cyclosporine over 24 hours or placebo within 12 hours of injury. In conclusion, Mazzeo A et al. (2009) stated that cyclosporine demonstrated a good safety and tolerability profile in these patients; however, there were no significant differences in neurological outcomes or adverse events between placebo and the dose group at any time point. A more recent study, by Aminmansour et al. (2014), assessed the impact of cyclosporine on cognitive function and consciousness in 100 patients who suffered from DAI after TBI. Outcome measurements included in the study were Glasgow outcome scale-extended (GOS-E) and mini-mental state examination (MMSE) three and six months after injury. In conclusion, Aminmansour et al. suggest that administration of cyclosporine is not effective in improving cognitive function or consciousness in these patients[22].

Studies suggest that administration of cyclosporine is not effective in improving cognitive function or consciousness in adult humans

We would add that NeuroVive is testing at higher doses and longer duration with NeuroSTAT than any of the academic trials above have done with cyclosporine. In conclusion previous academic trials support that treatment with cyclosporine is safe in TBI, but have not yet provided evidence for efficacy.

NeuroVive is testing at higher doses and longer duration with NeuroSTAT than any of the academic trials mentioned here have done with cyclosporine

[21] Mazzeo AT et al. (2009) Safety and tolerability of cyclosporin in severe traumatic brain injury patients: results from a prospective randomised trial. J Neurotrauma. 2009 Dec;26(12)
[22] Hatton J et. al (2008) Dosing and safety of cyclosporine in patients with severe brain injury, J Neurosurg. 2008 Oct; 109(4): 699–707.

Abstract from Mazzeo et al. (2009)

Cyclosporin A (CsA) has recently been proposed for use in the early phase after traumatic brain injury (TBI), for its ability to preserve mitochondrial integrity in experimental brain injury models, and thereby provide improved behavioral outcomes as well as significant histological protection. The aim of this prospective, randomized, double-blind, dual-center, placebo-controlled trial was to evaluate the safety, tolerability, and pharmacokinetics of a single intravenous infusion of CsA in patients with severe TBI. Fifty adult severe TBI patients were enrolled over a 22-month period. Within 12 h of the injury patients received 5 mg/kg of CsA infused over 24 h, or placebo. Blood urea nitrogen (BUN), creatinine, hemoglobin, platelets, white blood cell count (WBC), and a hepatic panel were monitored on admission, and at 12, 24, 36, and 48 h, and on days 4 and 7. Potential adverse events (AEs) were also recorded. Neurological outcome was recorded at 3 and 6 months after injury. This study revealed only transient differences in BUN levels at 24 and 48 h and for WBC counts at 24 h between the CsA and placebo patients. These modest differences were not clinically significant in that they did not negatively impact on patient course. Both BUN and creatinine values, markers of renal function, remained within their normal limits over the entire monitoring period. There were no significant differences in other mean laboratory values, or in the incidence of AEs at any other measured time point. Also, no significant difference was demonstrated for neurological outcome. Based on these results, we report a good safety profile of CsA infusion when given at the chosen dose of 5 mg/kg, infused over 24 h, during the early phase after severe head injury in humans, with the aim of neuroprotection.

Source: Mazzeo AT et al. (2009) *Safety and tolerability of cyclosporin in severe traumatic brain injury patients: results from a prospective randomised trial.* J Neurotrauma. 2009 Dec;26(12)

NVP025

NeuroVive's drug discovery programme aimed at mitochondrial myopathy

Mitochondrial myopathy is a group of muscle diseases associated with mitochondrial disease. It is a large heterogeneous group of disorders resulting from primary dysfunction of the mitochondrial respiratory chain[23]. Many different mutations of mtDNA or nDNA can cause mitochondrial myopathy and the expression of the disease is very much related to heteroplasmy. NVP025 is NeuroVive's drug discovery programme focused on mitochondrial myopathy. In May 2018, results from a mitochondrial myopathy model study with NVP025 were presented. The experimental study which was conducted in animals, demonstrated that survival was 94% in the treated group, compared to 50% in the control group. In addition, muscle function in the treated group was better than in the control group[24]. Management has communicated that a candidate drug will be selected during 2018 and the aim is to initiate clinical development in different types of muscle disorders by 2020.

NVP015

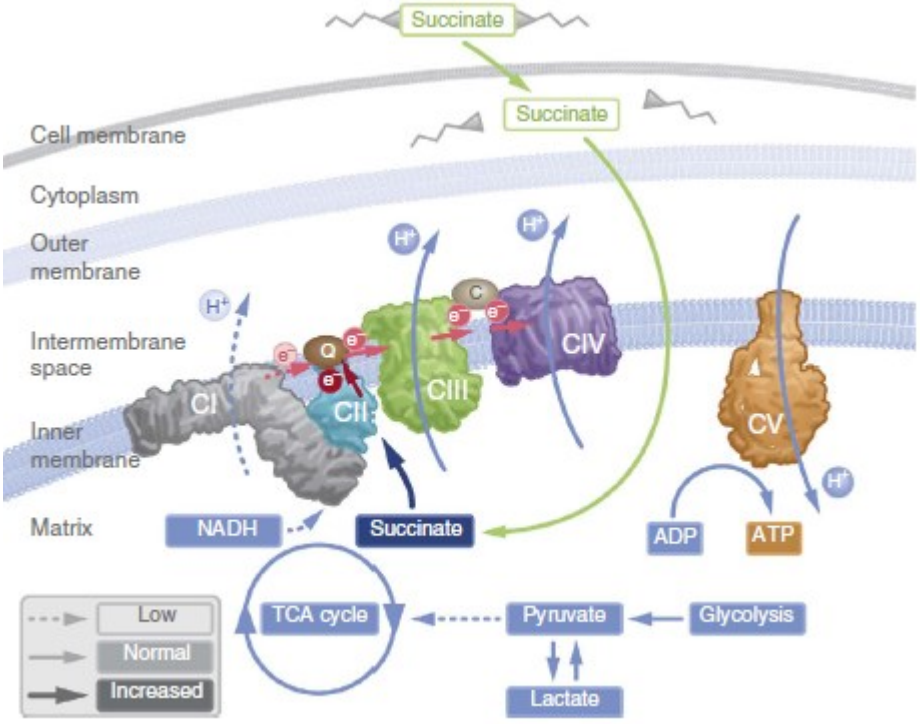
In June 2018, NeuroVive announced that it had out-licensed NVP015 to BridgeBio

NVP015 is a drug discovery programme consisting of >50 different candidates, of which all are succinate prodrugs. Approximately 50% of all patients with mitochondrial disease have dysfunction in the first complex of the electron transport chain; this causes a shift in metabolism towards glycolysis and subsequently accumulation of lactate and limited ATP generation. Succinate in its natural state does not enter into the cells efficiently but when administered through a pro-drug formulation, it could enter the cells. This enables electron transport from complex II and onwards, thereby bypassing of complex I.

In June 2018, NeuroVive announced that it had out-licensed molecules from the NVP015 project suitable for local treatment in the eye to BridgeBio. The licensing agreement is limited to local treatment of Leber hereditary optic neuropathy, with a total deal value of approximately USD60m.

[23] Pfeffer G, Chinnery P (2013) Diagnosis and treatment of mitochondrial myopathies
[24] NeuroVive Pharmaceutical

Prodrug delivery of succinate



Source: Ehringer J et al. (2016) Cell-permeable succinate prodrugs bypass mitochondrial complex I deficiency; nature communications

NV354

NV354 is a lead candidate selected from the NVP015 portfolio. Just like the other assets in NVP015, it is hypothesised that NV354 would provide an extra source of energy to patients with dysfunctional complex I by pro-drug delivery of succinate. The succinate would enable bypassing of complex I in the electron transport chain to generate ATP. NeuroVive intends to develop NV354 toward acute metabolic crises in patients with genetic mitochondrial diseases and it recently communicated that the development programme has been expanded to chronic use in conditions such as Leigh syndrome. The asset has been selected based on tolerability, stability in the cardiovascular system as well as its potential to pass the blood-brain-barrier and other organs. Results from experimental in-vivo proof-of-principle studies were recently presented by the company at Cold Spring Harbor Laboratory (CSHL); the initial results show that NV354 restores tissue succinate levels and reduces lactate levels. NeuroVive intends to develop this asset all the way to market on its own.

NeuroVive currently intends to develop NV354 towards acute metabolic crises in patients with genetic mitochondrial diseases

NV556

NV556 is a cyclophilin inhibitor in pre-clinical development targeting hepatic fibrosis in non-alcoholic steatohepatitis (NASH). NeuroVive has demonstrated efficacy of NV556 in STAM, which is a mouse model resembling NASH. Efficacy has also been demonstrated in methionine and choline-deficient (MCD) mice. NV556 is thought to have a direct anti-fibrotic mode of action by inhibiting cyclophilin B. Inhibiting cyclophilin B in the endoplasmic reticulum could have an anti-fibrotic effect in NASH since the inhibition limits collagen synthesis and stimulates collagenase production. Furthermore, NeuroVive suggests NV556 has a cyto-protective mode of action through mitochondrial stabilisation.

NeuroVive has demonstrated efficacy of NV556 in mice

In the original development plan, NV556 targeted viral diseases, especially hepatitis B, when it was known as NV018. In fact, NV018 was outlicensed to OnCore BioPharma in 2014, which intended to develop the asset targeting hepatitis B. However, OnCore BioPharma was later acquired by Arbutus, which decided to terminate the deal; hence NeuroVive regained all development and commercialisation rights and decided to change the development route towards NASH.

NVP022

NeuroVive is currently testing model compounds of NVP022, another candidate targeting NASH. The mechanism of action aims to partly uncouple OXPHOS, which could potentially allow the body to remove fat stored in the liver. Uncoupling of OXPHOS has been a target in drug development for decades, especially for weight loss purposes. Several compounds, including 2,4-Dinitrophenol, have demonstrated effective uncoupling of OXPHOS, however, the compound is highly toxic, since the uncoupling results in a rise of body temperature that could be deadly. If NeuroVive can demonstrate that NVP022 contributes to a partial uncoupling of OXPHOS while maintaining tolerable safety, we believe this asset could also have significant potential outside of NASH.

The mechanism of action aims to partly uncouple OXPHOS, which could potentially allow the body to remove fat stored in the liver…

… this has been a target in drug development for decades, especially for weight loss purposes

NVP024

NVP024 is a portfolio of early-stage assets targeting hepatic cellular cancer, or liver cancer. Liver cancer is closely related to NASH, and similarly, it is thought that cyclophilins are overexpressed in liver cancer and is a potential driver of the disease. In-vitro studies have shown that non-cancerous cells tolerate NVP024 well while growth of HCC is inhibited with promising potency when exposed to NVP024 at concentrations of 0.1 micro molar. For reference, significantly higher concentrations of >1 micro molar are required to achieve the same inhibitory effect with sorafenib, which is an approved drug indicated for liver cancer.

Competitive landscape

Several competitors are developing assets aimed towards genetic mitochondrial diseases as well as moderate-to-severe TBI. In this section, we will present the drug candidates in clinical development that we believe are potential competitors to KL1333 and NeuroSTAT.

Competing drug candidates for mitochondrial diseases

Stealth BioTherapeutics (elamipretide)

Stealth BioTherapeutics has received fast-track designation and orphan-drug designation from the FDA for the development of elamipretide in primary mitochondrial myopathy. The company initiated a phase III trial in Q4 2017 in a study which aimed to assess approximately 200 patients. The primary endpoint will be a walk test where it will be measured how far patients can walk in six minutes. The total fatigue score on the Primary Mitochondrial Myopathy Symptom Assessment (PMMSA) will also be evaluated[25].

Astellas (MA-0211)

Astellas acquired Mitobridge in early 2018 in a deal worth USD450m. Astellas paid USD225m upfront and USD225m in additional potential R&D-related milestone payments. The two companies had a R&D partnership dating back to 2013, where they co-developed drugs aimed towards several rare conditions including Duchene muscular dystrophy and relevant for NeuroVive, mitochondrial myopathies (associated with KSS and MELAS) and NAD+ modulation[26]. According to clinicaltrials.gov, Astellas finalised a phase I study in healthy individuals with MA-0211, which is its most advanced asset.

Taisho Toyama Pharmaceuticals (taurine)

In 2018 Taisho filed an application to the Japanese authorities for the use of taurine in MELAS. Taurine in 98% powder form could potentially prevent recurrence of stroke-like episodes in MELAS patients.

Santhera Pharmaceuticals (Raxone/Idebenone)

To date, Raxone with the API Idebenone, is currently the only approved drug indicated for any genetic mitochondrial disease. It is currently indicated for LHON by the EMA, but several other clinical trials have been carried out with Idebenone including a phase II MELAS study finalised in 2012. Idebenone is currently not indicated for MELAS, but it has been suggested that MELAS patients can benefit from off-label usage[27].

Khondrion (KH-176)

KHENERGY was a phase II study evaluating KH-176 in individuals with tRNALeu(UUR) m.3243A>G mutation and a number of mitochondrial diseases, including MELAS, maternally inherited diabetes and deafness (MIDD), Leigh's disease and Leber's hereditary optic neuropathy (LHON).

Jupiter Orphan therapeutics (JOT-107)

Jupiter Orphan therapeutics is pursuing MELAS with its preclinical asset JOT-107. The company has communicated that it expects to initiate clinical trials in H2 2019 with an NDA submission targeted for H1 2021[28].

Cambridge University Hospitals NHS Foundation Trust (Nicotinamide Riboside)

A B-vitamin called Nicotinamide Riboside (NR) has been demonstrated to boost the number of mitochondria in mice. As a result, increased generation of ATP and a reduction of disease-related symptoms could also be seen. Clinical studies are now being carried out to investigate if these effects are applicable to humans as well. Cambridge University Hospitals NHS Foundation Trust is leading a study in patients with CPEO; it aims to recruit 15 patients and is estimated to be completed in 2019.

[25] Stealth Biotherapeutics
[26] http://www.biopharminternational.com/astellas-acquires-mitobridge-450-million-deal
[27] http://www.socialstyrelsen.se/ovanligadiagnoser/melas
[28] http://www.jupiterorphan.com/jot107.html

Minova Therapeutics (MNV-BLD)

According to clinicaltrials.gov, the Israeli start-up Minova Therapeutics is running a phase I study in Pearson's syndrome patients. The study is evaluating a personalised cell off-shelf solution, where CD34+ cells are enriched with MNV-BLD.

Competing drug candidates moderate-to-severe TBI

Neuren Pharmaceuticals (Trofinetide)

Intravenous dosage of Trofinetide in moderate-to-severe TBI at trauma has been performed. Trofinetide is currently in phase III development. The results indicate an improvement in cognitive impairment for patients with severe TBI

VasoPharm (VAS203)

The company is recruiting patients to a phase III trial. An inhibitor of nitric oxide synthase, it is intended to reduce inflammation and edema and the associated increase of intracranial pressure. The trial is planned to include 220 patients with different types of TBI.

SanBio (SB623 cell therapy)

Currently in phase II development, this is a stem cell therapy for patients with neurological motor deficit at least a year following focal TBI.

Academic sponsor (Tranexamic acid)

Antifibrinolytic therapy is being evaluated in moderate-to-severe TBI to avoid intracranial bleeding. It is a phase III trial that aims to enrol 13,000 patients. The primary outcome is death in hospital within 28 days of injury among patients randomised within three hours of injury

Orphan drug market

Most genetic diseases are rare, but not all rare diseases are genetic

Nearly all genetic diseases are rare, e.g. genetic mitochondrial diseases, but not all rare diseases are genetic, e.g. TBI patients treated in critical care. Today, there is no disease-modifying drug available on markets indicated for TBI. Furthermore, there is only one approved drug (Raxone) indicated for one genetic mitochondrial disease (LHON). Since there is basically no market for the indications which NeuroVive is focusing on, we will instead describe the overall market for orphan drugs.

Classification of orphan diseases

Legislation in place to support development of drugs for rare diseases

There are rules to determine what diseases can be classified as 'rare', helping to support companies in the development of drugs for them.

- **The US.** Legislators found that certain rare diseases received significantly less attention from the pharmaceutical industry, so few new drugs for them were developed. The medical need for these patient groups remained high but there was no real incentive for the industry to develop drugs for them. The industry 'abandoned' the diseases, which were seen as 'orphaned', hence the expression.
  - In 1983, the Orphan Drug Act was passed to encourage pharmaceutical companies to develop drugs for rare disorders. The incentives for a company include market exclusivity for seven years (regardless of patent protection) and tax benefits for the costs of carrying out clinical trials.
  - In 2002, the Rare Disease Act became law, aiming to support the creation of a central entity, the Office of Rare Diseases, to recommend a national research agenda, co-ordinate research projects, and provide education for researchers in rare diseases. The 1983 Act in no way provided for a centralised approach to research into rare diseases.
- **The EU.** Rules governing rare diseases came significantly later than in the US. The rules are from 2000 (Regulation (EC) No 141/2000), according to which a drug developed for a rare disease is a so-called 'orphan medicinal product'. The EU rules are in some respects slightly broader than the US rules, as they also cover the development of drugs for tropical diseases not found in the EU. The rules give the new orphan medicinal product market exclusivity for 10 years after approval (but no tax incentives).

Orphan disease definitions

Different countries have different definitions of a 'rare' disease

As might be expected, there is no clear, common, global definition for how rare a disease must be to be classed as 'rare'. There are, however, definitions in various markets where rare disease acts are in place. In some markets the definitions are based solely on the prevalence of the disease in question, while elsewhere other factors (e.g. severity of the disease or availability of treatment options) are included in the definition.

- **In the US**, the Rare Disease Act of 2002 states that a rare disease is "any disease or condition that affects less than 200,000 people in the USA". This equates to fewer than 7.5 in 10,000 people.
- **In Japan,** a rare disease is one that affects fewer than 50,000 patients in Japan, or 4 in 10,000 people.
- **In the EU,** a rare disease is "life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them". The term 'low prevalence' was later defined as affecting around 5 in 10,000 people.

It is interesting to note that diseases that are rare (statistically speaking) but not life-threatening or chronically debilitating are not included in the rules.

Below, we have summarised the most important countries where specific orphan drugs rules are in place. Apart from market exclusivity in most markets, companies might get other support, e.g. tax reductions for the costs of carrying out clinical trials and expedited review timelines at filing and support to formulate a clinical trial protocol, etc.

Summary of orphan drug acts globally

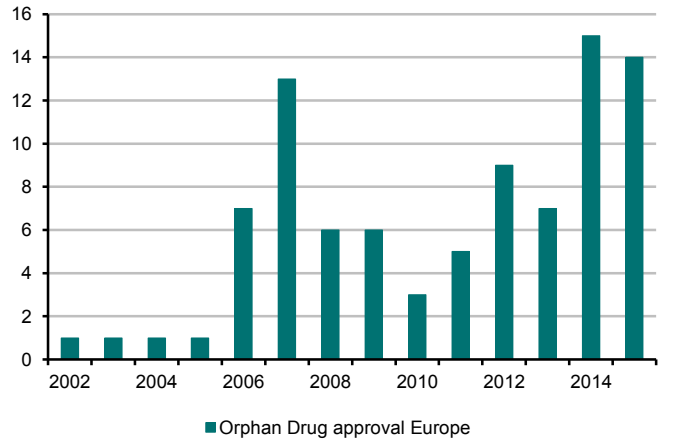
	Official legislation	Maximum prevalence	Number of patients absolute	Market exclusivity (years)
US	1983	7.5 : 10,000	<200,000	7
Japan	1993	4 : 10,000	<50,000	10
EU	2000	5 : 10,000	<200,000	10
Australia	1997	1.1 : 10,000	<2,000	5
Singapore	1991	n.a.	n.a.	n.m.

Source: Orpha.net

Orphan drugs on the market

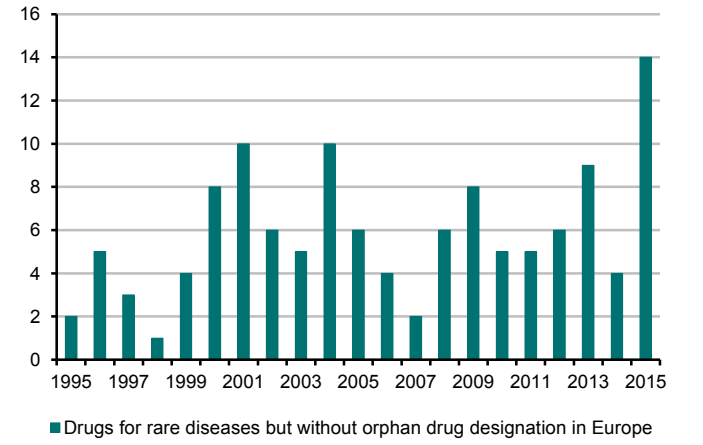
When we look at the number of orphan drugs approved, we see that there are fewer available drugs classified as orphan in the European market than the US market. The main reason for this is that the US orphan drug regulations have been in place much longer than in the EU, but also that some drugs aimed at rare diseases for one reason or another have been registered in European markets without orphan drug designation. Below we show the number of drugs approved in the European market with orphan drug designation, and the number of drugs approved without this designation but that still have a focus on rare diseases.

Drugs approved in the EU with orphan drug designation



Source: Orpha.net

Drugs approved for rare diseases without orphan drug designation in the EU



Source: Orpha.net

The pattern in the US is relatively similar to that in Europe in terms of approved orphan drugs. In general over the past few years, the proportion of orphan drugs has been around 35–40% of the total number of drugs approved.

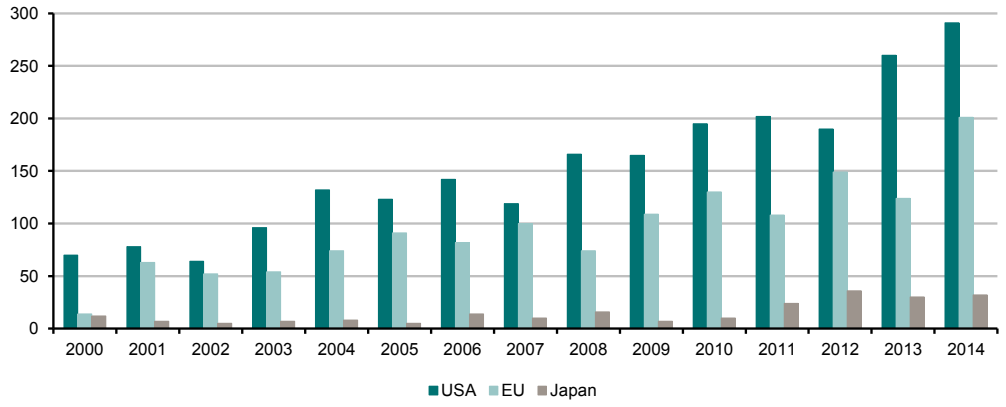
Orphan drugs as a proportion of all NME (new molecular entities) approved in the US

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
All orphans	19	24	16	14	20	14	26	26	32	49	42
NME orphans	10	8	8	9	15	6	14	15	9	17	21
All NMEs	28	29	26	31	34	26	35	43	27	41	45
NME orphan share	36%	28%	31%	29%	44%	23%	40%	35%	33%	41%	47%

Source: FDA

Besides actual approvals, it is worth looking at the number of orphan designations, i.e. drugs under approval/development where the regulatory authorities acknowledge that they are approvable as an orphan drug. The number of orphan drug designations has increased in all markets as the pharmaceutical industry has become keener to develop drugs for this segment. In the figure below, we show the number of orphan designations in the three markets with established orphan drug legislation.

Orphan drug designation accepted per year in three areas with orphan legislation



Source: FDA, EMA and MHLW

Attractiveness of orphan drug market

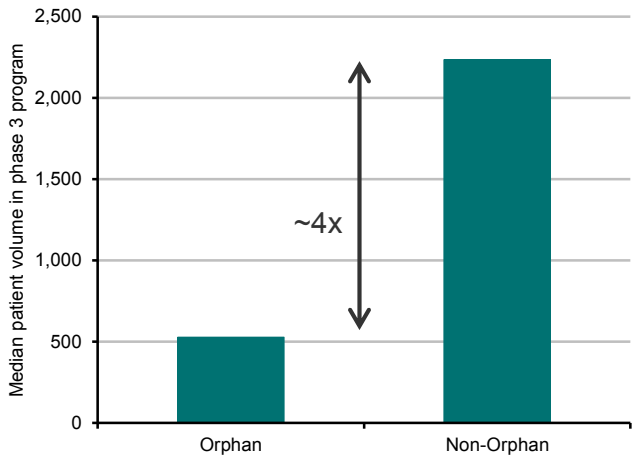
There are, as we see it, several reasons the orphan drug segment of the pharmaceutical market is attractive to companies such as NeuroVive. Besides the financial benefits of doing development in this segment, there are other more indirect benefits for companies from the way the trials are carried out.

Several reasons the orphan drug segment is attractive to companies

Below, we show the median trial size of the phase III trials for orphan drugs compared to non-orphan drugs; and, as might be expected given that the diseases are rare, the median size trial is around 4x larger for non-orphan drugs. This reflects that patient recruitment for trials is more difficult when a disease is rare. On the cost side, we also see the median cost for phase III trials is smaller for orphan drugs, but not to the same extent as the trials contain fewer patients.

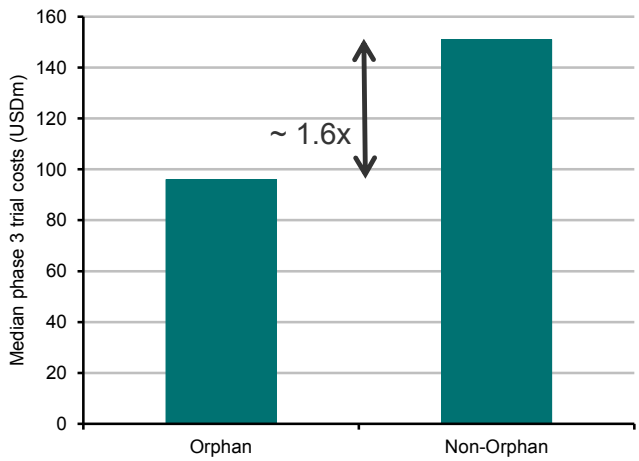
One explanation might be that in order to recruit enough patients, trials need to contain relatively many trial sites (as the number of patients per site will be low in rare diseases) and a large proportion of the costs relate to the infrastructure of the trial rather than to the direct costs per patient. For example, having a trial in 45 sites that each recruit two patients or 20 patients implies the same infrastructure cost for the trial but a significantly smaller trial group (90 orphan patients versus 900 non-orphan patients).

Smaller median phase III trial size in orphan drugs



Source: Evaluate Pharma

Cheaper phase III programmes on average

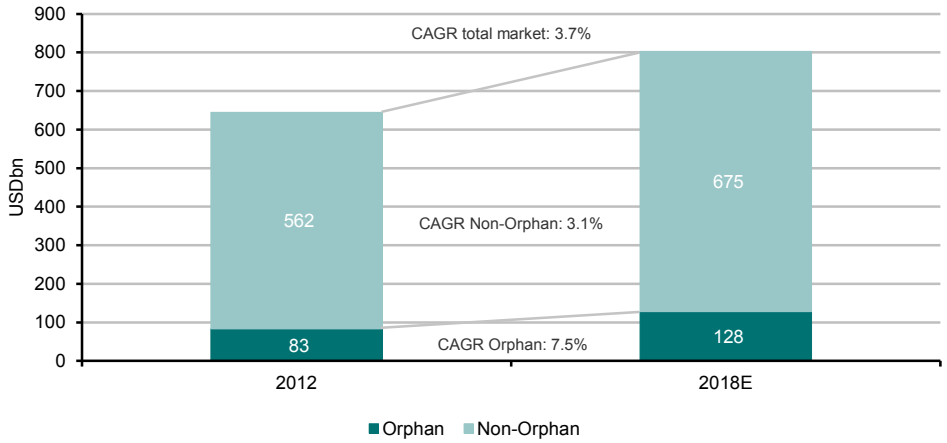


Source: Evaluate Pharma

However, clinical trial programmes are in many cases smaller and less costly to conduct for orphan drugs and this is another attraction for pharmaceutical companies. On top of this, the ability to charge high revenues per patient for the finished drug is higher, the smaller the addressable patient population for the drug.

Looking at the total market for pharmaceuticals, the orphan drug segment is expected by Evaluate Pharma to have one of the fastest growth rates in the market, with a CAGR of c7.5% for 2012–2018e. This is about twice as fast as the overall pharmaceutical market.

Total pharmaceutical market – orphan drugs the fastest growing segment



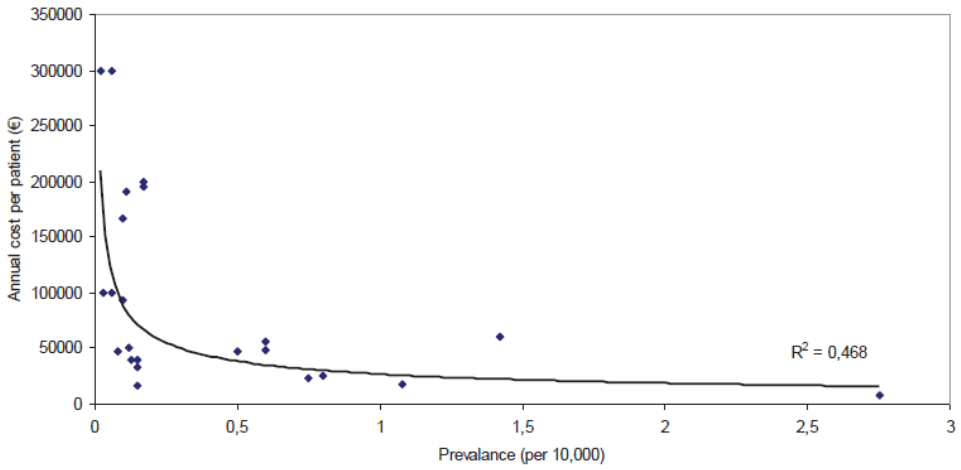
Source: Evaluate Pharma

Pricing

Another feature that makes the orphan drug space attractive is the high price points that companies can get for the drugs. In general, one can say that the rarer the disease the higher the price of the drug. However, the relationship in other markets might not be as steep as in the Belgian example below, where has been a gradual rise in orphan drug prices over the past few years and nearly all of the most expensive drugs (treatment cost per patient per year) are orphan. This is, however, not that surprising given the rarity of some of the diseases.

Relatively high price points for orphan drugs

Relationship between drug price and prevalence (Belgium)



Source: Orphanet Journal of Rare Diseases 2011, 6:42

Below, we list some of the more expensive orphan drugs on the market – as shown, the rarer the disease, the higher the price even though the relationship is less clear than in Belgium. Drug prices are more regulated in Europe in general than in the US; hence, ultra-expensive treatments (>USD300,000 per patient per year) are less common than in the US.

Prices and prevalence of some orphan drugs in the US

Drug	Indication	US prevalence	Administration	Price/patient/year (USD)
Sutent	Advanced renal cell carcinoma	90,000	Oral	48,000
Tarceva	NSCLC	148,800	Oral	56,000–84,000
Zavesca	Gaucher disease type-1	4,000	Oral	128,000
Fabrazyme	Fabry disease	2,564	Infusion	239,000
Elaprase	Hunter syndrome	1,500	Infusion	300,000–500,000
Naglazyme	Mucopolysaccharidosis VI	1,200	Infusion	441,000
Cerezyme	Gaucher disease type-1	4,000	Infusion	442,000–600,000
Soliris	Paroxymal nocturnal hemogobinuria	1,050	Infusion	486,000–508,000

Source: InVentive Advance Insight

Access to orphan drugs in Europe varies from market to market, so in the Belgian example above there might be more or fewer of the orphan drugs available to patients. The rare disease patient organisation in Europe, EURORDIS, carried out an investigation a few years ago on the correlation of the price of a drug and the prevalence, and found that the correlation was relatively strong but not proportional. The relationship was 100 times lower the prevalence, 10 times higher the individual drug costs.

Needless to say, the orphan drug market is attractive from a pricing point of view, especially if the alternative treatments available for patients are limited, or if existing treatments have a sub-optimal effect or side-effect profile.

Probability of success

One of the most important parameters when evaluating an early-stage biotech company is to assess the Likelihood of Approval (LOA) i.e. the probability that the current development project will reach the market. As NeuroVive is focusing on several indications where currently no disease-modifying drugs exist, there is limited available data on probabilities of success that would be relevant to NeuroVive's disease from which to get a feeling for the probability of success for the drug candidates NeuroSTAT and KL1333. We can, however, look at the general LOA and phase successes for the overall industry. With that as a base, we can make adjustments that seem reasonable for each drug candidate individually.

Assessing LOA is key when evaluating early-stage biotech companies

Latest data covers large set of companies and drugs

There was a large study in Nature Biotechnology in January 2014, where researchers looked at 835 companies, 7,300 indications, and more than 4,400 drugs in various phases. The companies were a mix of large pharma, mid-sized pharma, and emerging biotech.

Base-line characteristics of companies in the Hay article

	Companies		Indications		Drugs	
Company size	Number	%	Number	%	Number	%
Large pharma/biotech (>USD5bn in sales)	33	4%	3,573	48%	2,075	47%
Small -to mid-sized pharma/biotech (USD0.1bn–5bn in sales)	90	11%	1,099	15%	724	16%
Emerging biotech (<USD0.1bn in sales)	712	85%	2,700	37%	1,652	37%
Total	835	100%	7,372	100%	4,451	100%

Source: Hay M. et al. *Nature biotechnology* 32.1 (2014): 40-51

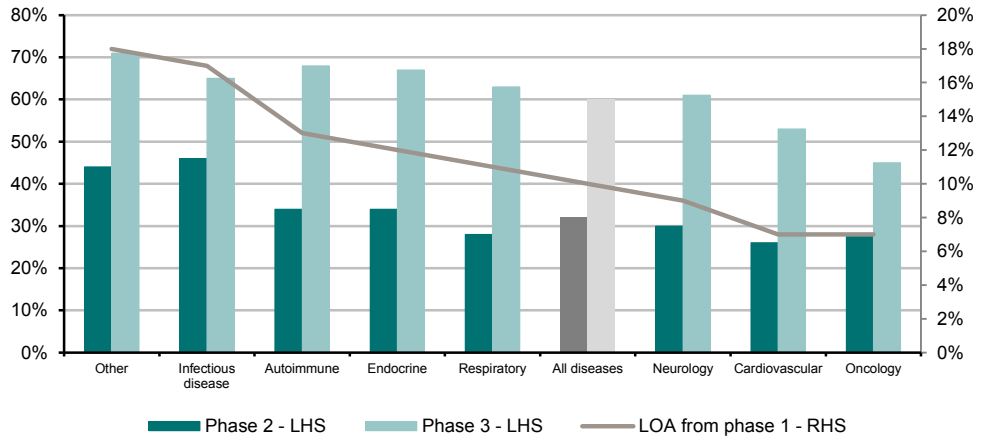
The large population of drugs and companies also allowed the authors to split success rates by broad indication and by more narrowly defined diseases in some cases. As in other studies, the authors looked at two types of success: 'phase success' and 'likelihood of approval'. The first metric gives the probability of a development project moving from its current development phase to the next stage, while the LOA gives a probability of the project moving all the way to an approved drug from its current position in the development process.

The breadth of Hay et al.'s 2014 study enables splitting success rates by broad indication and by more narrowly defined diseases in some cases

Based on data in the Hay's study, we show the likelihood of phase success (that a substance moves from current phase to the next phase) in phase II and phase III as well as the likelihood of approval (LOA) from phase I. LOA is the probability that the asset moves all the way from phase I to the market. As the study included more than 4,400 unique compounds at various stages of development and for a multitude of indications, it was possible to display phase successes and overall likelihood for approval down to individual indications in certain cases.

Below we display the data for selected large therapy areas.

Phase success and LOA for selected therapy areas

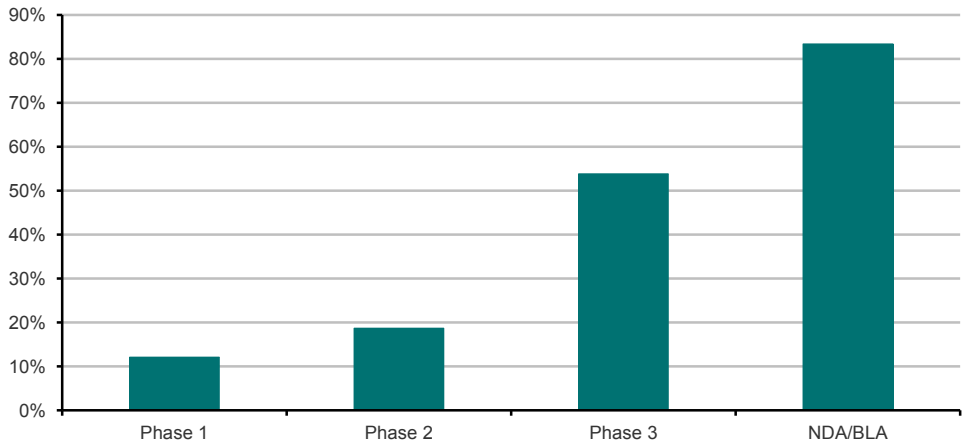


Source: Hay M. et al. *Nature biotechnology* 32.1 (2014): 40-51
Note: LHS=Left Hand Scale and RHS= Right Hand Scale

What is somewhat special about the NeuroVive case is that the company is focusing on disease-modifying drugs in TBI and generic mitochondrial diseases, and so far the overall success rate for such drugs is basically zero for TBI and most genetic mitochondrial diseases, with the exception of Leber's hereditary optic neuropathy (LHON), for which there is currently one approved drug (Raxone) in some European countries. Hence, the numbers for neurology in the table are not fully representative of the type of drugs the company is developing.

NeuroVive is focusing on disease-modifying drugs in TBI and generic mitochondrial diseases, and so far the overall success rate for such drugs is basically zero

LOA – In non-oncology disease groups

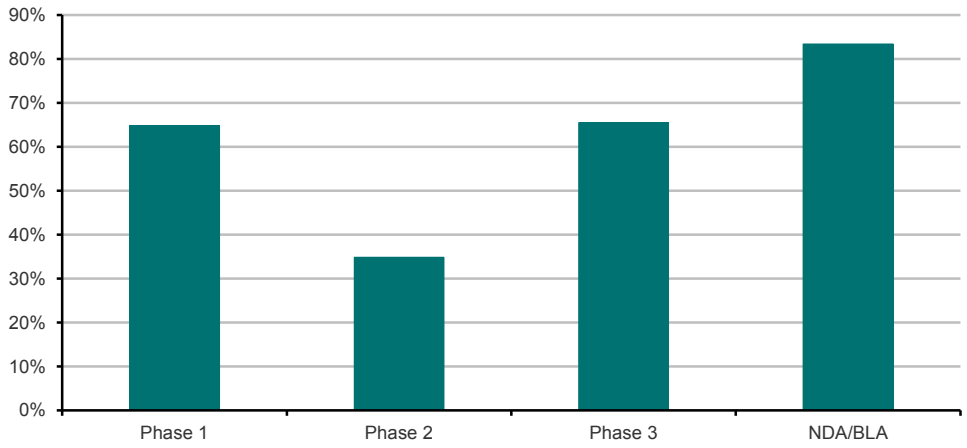


Source: Hey et al. Nature Biotechnology 32, 40-51 (2014)

As shown above, the LOA from phase I in non-oncology products is 12.1%, which is nearly twice that of oncology products alone that have an LOA of only 6.7%.

Below we show the phase success in the non-oncology indications, outlined in the study.

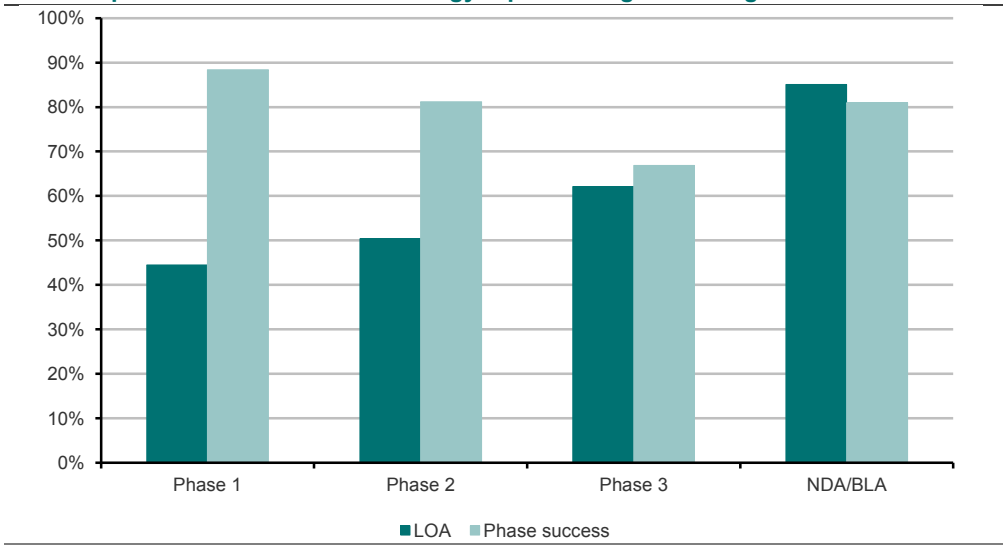
Phase success – In non-oncology disease groups



Source: Hey et al. Nature Biotechnology 32, 40-51 (2014)

As expected, the phase success is lowest in phase II and highest in the approval phase. This is not very surprising as phase II is the first time (in general) a drug is tested in a slightly larger scale for the disease it is aimed for and is in general the first time the drug is tested for efficacy. When it comes to the point that matters the most – phase III, where the outcome data is confirmed in large trials – the phase success is higher than in phase II but lower than in phase I. This is in line with what should be expected as projects not indicating good enough efficacies are weeded out in phase II. The high phase success in phase I is likely due to the relatively cheap trials carried out initially and hence the still relatively limited financial commitment moving from phase I to phase II implied in many cases.

LOA and phase success of non-oncology orphan designated drugs



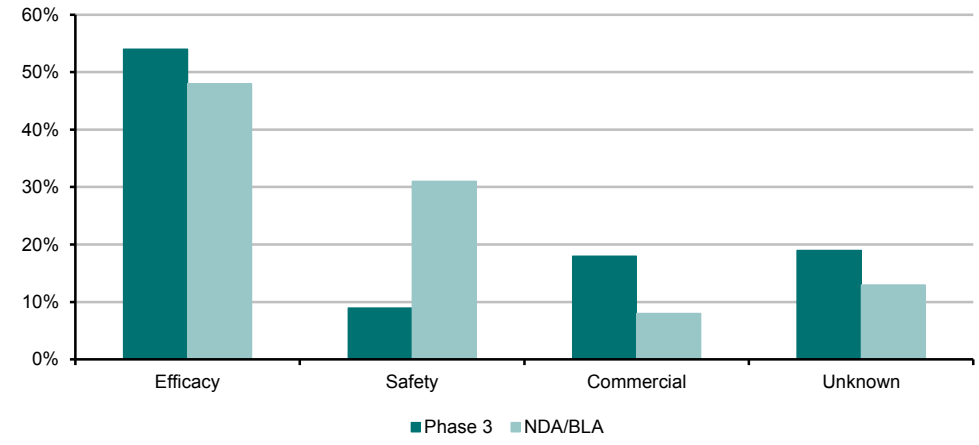
Source: Hey et al. Nature Biotechnology 32, 40-51 (2014)

As shown above, both the phase success and LOA are significantly higher for orphan drugs, especially in the early development stage (phase I and II). However, these figures are subject to some bias. Orphan designations can be granted any time during the clinical development, and most often during phase II. Therefore positive bias is introduced in the early phase data, from drug designated orphan status later in development. Although we believe drugs with an orphan designation have a higher LOA (albeit likely not the same extent in early development as shown above), the reasons for this could include: the need for smaller clinical cohorts, better defined disease groups, and getting included in an expedited regulatory programme and therefore receiving close guidance from the FDA.

Both phase success and LOA are significantly higher for orphan drugs, especially in the early development stage (phase I and II)…

… though these figures are subject to some bias

Causes of failure in drug development



Source: Hey et al. Nature Biotechnology 32, 40-51 (2014)

Approval process of New Molecular Entities

US regulatory approval process

In the US it is the Food and Drug Administration (FDA) that regulates medicinal products and is responsible for approving and monitoring the safety of drugs. The FDA's Center for Drug Evaluation and Research (CDER) is responsible for evaluating new drugs before approval, by assessing if the risks outweigh the benefits of the drug. The FDA's Center for Biologics Evaluation and Research (CBER) has a similar task, but evaluates biologics rather than chemical drugs.

Before clinical trials can begin, the developers/sponsors must submit an Investigational New Drug (IND) application to CDER or CBER, which must include animal and toxicity data, manufacturing information, clinical study plans, data from prior human trials, information about the investigator. The FDA has 30 days to review an IND, and to decide whether to allow the sponsor to move into the clinical stage of drug development.

Once the sponsor has finished clinical trials, a New Drug Approval (NDA) is submitted to the FDA for reviewing. An NDA intends to demonstrate that the drug is safe and effective for its intended use, and must include all data collected on the drug; from pre-clinical to the pivotal trial. Once the FDA receives an NDA, the review team can choose to refuse to file the NDA, i.e. not review it, if it is not complete. However, if the application is complete, the review team has 6–10 months to decide whether or not to approve the drug.

Expedited programmes for serious conditions

Due to long development and review times, the FDA has initiated four programmes: one pathway and three designations, to expedite the development and review of drugs targeting serious illnesses where there is a great need for better treatments.

Due to long development and review times, the FDA has initiated four programmes to speed up the process

Expedited development and review programmes initiated by the FDA

Programme	Year started	Characteristics of qualifying products	Does it formally change evidentiary standard?	Phase during which it exerts most direct effect
Orphan drug	1983	Treats disease occurring in <200,000 people/year in the US	No	Drug development
Fast-track	1988	Treats life threatening or severely debilitating diseases	Yes; can approve after single phase II study	Drug development and FDA review
Priority review	1992	Seems to offer therapeutic advance over available therapy	No	FDA review
Accelerated approval	1992	Treats serious or life threatening disease	Yes; can approve on basis of surrogate endpoint reasonably likely to predict patient benefit	Drug development and FDA review
Breakthrough therapy	2012	Treats serious disease where preliminary clinical evidence suggests substantial improvement over existing therapies on one or more clinically important endpoints	No	Drug development and FDA review

Source: Kesselheim A. et al. BMJ: British Medical Journal 351 (2015)

- **Orphan drug designation** is not formally one of these programmes, as it does not change the statutory approval standard. However, studies show that orphan drugs are often approved based on clinical trials that would be insufficient for non-orphan drugs; also, many orphan drugs approved by the FDA are done so under priority review.
- **Fast-track** designation is given to drugs that intend to treat a serious condition, and some non-clinical and clinical data must be available, demonstrating the drug's potential to meet the unmet need. Fast-track provides most notable benefits prior to the NDA meeting with the FDA, as a drug developed under fast track allows for frequent interaction with the FDA review team to discuss matters such as study design, required data to support approval, use of biomarkers, etc., as well as rolling submission of the NDA. Drugs under fast-track may also be eligible for priority review.
- **Breakthrough therapy** designation is the newest expedited programme, established in 2012. Unlike fast-track, drugs eligible for breakthrough therapy have to show some preliminary clinical evidence (based on a clinically significant endpoint) for substantial improvement in the condition, i.e. non-clinical data is not sufficient. The implications of

receiving a breakthrough designation can be a significantly shorter development programme in the disease being studied; however, the trial programme must still generate sufficient data to show that the drug is safe and effective. However, it is usually not the clinical development programme that is the approval bottleneck for breakthrough therapies; it is rather the chemistry, manufacturing and control (CMC) development that lags behind, which delays the approval of these drugs. Furthermore, a breakthrough therapy designation provides the sponsor with the possibility of receiving extensive guidance from the FDA on trial design that can significantly reduce the trial time and patients needed for completion of the trial. Breakthrough therapy products may also be eligible for priority review.

- **Accelerated approval** is a pathway rather than a designation, and can be provided to treatments that intend to treat a serious condition with a surrogate endpoint that reasonably likely predicts a clinical benefit of the drug. Accelerated approval based on a surrogate endpoint enables faster approval, as a clinical endpoint takes longer to record.
- **Priority review** can be given to a drug treating a serious condition that offers significant improvement over current treatment regarding safety or efficacy. Priority review guarantees a shorter FDA review; the FDA aims to review the NDA within six months instead of 10 months normally. A priority review is applied for in conjunction with the NDA filing. Note that to take part in the other expedited programmes, the sponsor also has to actively apply for the designation, i.e. it is not automatically handed out by the FDA. However, these programmes can be applied for and granted before the NDA filing, unlike a priority review.
- **Priority review vouchers (PRV)** became law in 2007 and aim to encourage the development of treatment for a selection of neglected tropical or rare paediatric diseases, as PRVs are handed out to sponsors that successfully develop drugs for neglected tropical diseases. The PRVs can then be used for priority review of another drug or sold to another manufacturer; in 2015 a voucher was sold for USD350m. In 2012 some rare paediatric diseases were added to the voucher programme.

Expedited reviews in 2015

In 2015 60% (27/45) of the NMEs approved in the US were handled under some kind of expedited review, most of which were handled under priority review in combination with one or more of the other expedited programmes (FDA).

In 2015 60% (27/45) of the NMEs approved in the US were handled under some kind of expedited review

The EMA also has a pathway for accelerated approval; however, it is significantly less used than the FDA's programmes. In 2015, only 13% (5/39) of the NMEs recommended for approval by the EMA were handled under accelerated approval.

Expedited reviews – less frequent in Europe

EMA and FDA (CDER) 2015 activities

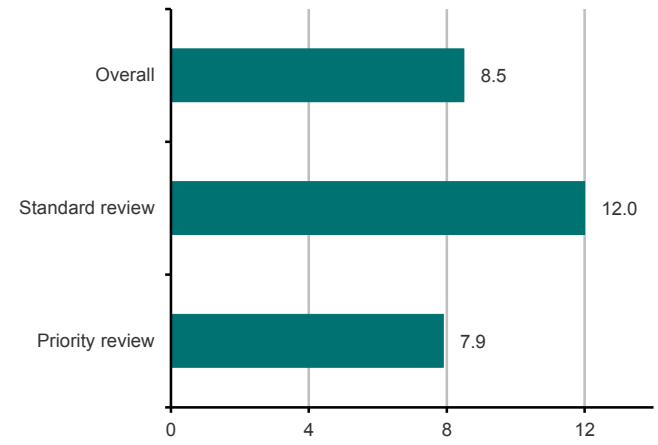
Regulator	EMA	FDA
New drugs	39	45
Expedited review	5 (13%)	27 (60%)

Source: Adapted from: http://www.raps.org/Regulatory-Focus/News/2016/01/12/23890/EMA-Carries-2014-Momentum-Recommends-39-New-Drugs-and-Sets-Orphan-Record/

In the US, expedited review programmes have become increasingly popular, and the number of drugs receiving some kind of expedited review has risen by 2.4% p.a. since 1987[29], which could be explained by the increasing number of orphan drugs in development. However, there could also be other explanations, e.g. the FDA is less strict in handing out designations, but this is just our speculation.

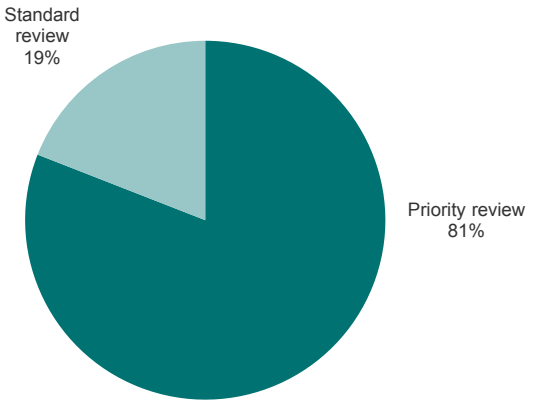
[29] Kesselheim A. et al. BMJ: British Medical Journal 351 (2015)

FDA review time reduced by priority review designation (2015)



Source: FDA

Majority of orphan drugs receive priority review (2015)



Source: FDA

The time saved by receiving priority review by the FDA is significant, and in 2015 the median time for a standard review was 12 months, while for drugs under priority review it was only 7.9 months, thereby providing drugs market access four months earlier if reviewed with priority. Furthermore, a majority of the drugs designated priority review were orphan drugs, and the majority of orphan drugs approved in 2015 were handled under priority review (17 out of the 21 orphan drugs approved were given priority review designation).

However, it is worth mentioning again that orphan designation does not guarantee priority review by the FDA, as the drug still has to meet the criteria for priority review (which are not synonymous with orphan designation). It is common that orphan drugs developed target serious conditions where there are no alternative treatments, or only poor treatment choices, and are thus eligible for priority review. In addition, the data points to a correlation between an orphan designation and priority review, indicating a faster review time for orphan drugs.

Note that orphan designation does not guarantee priority review by the FDA

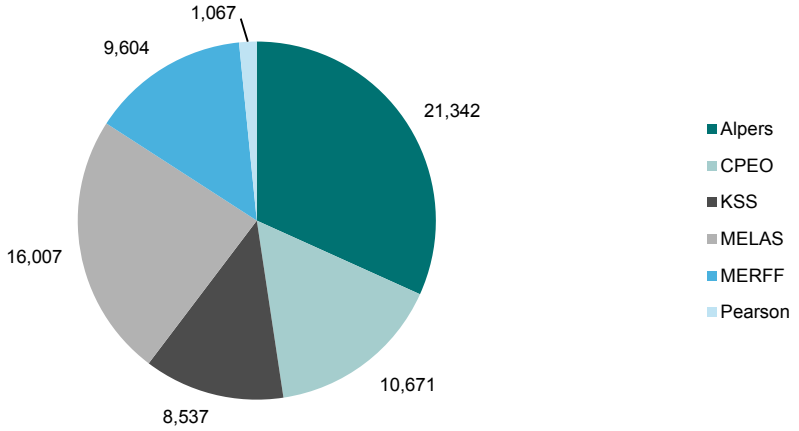
Market models

KL1333

For most genetic mitochondrial diseases, there is limited data on the actual number of affected individuals. Some countries are better than others in collecting data from for instance patient records definite number on affected individuals exist. In our assumptions for prevalence, we have based these on rates stated by The National Board of Health and Welfare, a government agency in Sweden under the Ministry of Health and Social Affairs. We have also used estimates stated by Orphanet, which was originally established by the French National Institute for Health and Medical Research but since 1997 has been supported by the European Commission. Furthermore, we have in our analysis used prevalence rates and applied these to the overall population in US (325.7m)[30] and EU (741.4m)[31] to translate this into the number of potential patients in the US and EU for NeuroVive's target populations (see pie chart and table below).

For most genetic mitochondrial diseases, there is limited data on the actual number of affected individuals

Combined target populations for KL1333 in US and EU



Source: DNB Markets estimates

Prevalence and estimated number of affected individuals per geography

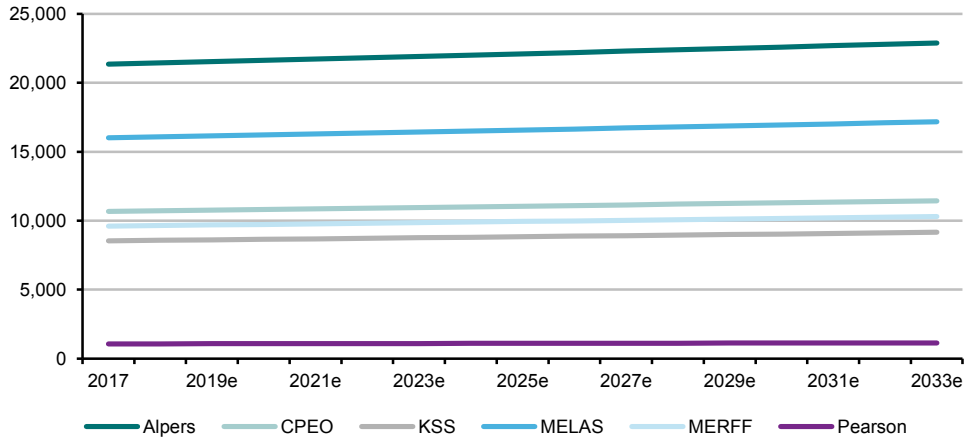
KL1333 target indications	Prevalence /100,000	Affected US	Affected EU
Alpers	2.00	6,514	14,828
CPEO	1.00	3,257	7,414
KSS	0.80	2,606	5,931
MELAS	1.50	4,886	11,121
MERFF	0.90	2,931	6,673
Pearson	0.10	326	741

Source: Socialstyrelsen, Orpha.net

The incidence rate of rare genetic diseases is not expected to grow dramatically short- or long-term; hence the flattish lines illustrated in the graph below. In our market model, we have calculated that the incidence of these diseases will grow at a similar rate as the overall population i.e. an annual increase of 0.85% in the US and 0.25% in the EU.

[30] United States Census Bureau, World Bank
[31] Statista (2016)

Combined target populations for KL1333 over time



Source: Socialstyrelsen, Orpha.net

Pricing

We have assumed a flat price per patient per year for KL1333 in all target indications, but we assume the US price per patient per year will be twice that of the EU price. In our price analysis, we have looked at several currently available orphan drugs indicated for diseases where patients have limited treatment options. For instance, Orfadin indicated for hereditary tyrosinemia type 1 (HT-1) is an example an orphan drug which was the very first disease-modifying drug indicated for HT-1, which is a very severe disease affecting children who have no other treatment options. Before Orfadin was available, the survival rate for HT-1 was 29% after two years for children who developed symptoms before two months of age. After the introduction of Orfadin, the survival rate for the same group rose to 93%[32].

In our view it is likely that a higher price could be charged in the US

In Canada, the cost of Orfadin per person per year is approximately USD51,500 and we therefore believe a price of USD50,000 would be reasonable to assume for KL1333 across all target indications in Europe. However, we believe is very likely that a higher price could be charged in the US. We know that many orphan drugs are priced at least twice the rates in for instance Europe and Canada. This relates to the Federal government's limited ability to negotiate prices with pharmaceutical companies, owing to laws passed in 2003 when prescription drugs were included in Medicare. Successful lobbying from the pharmaceutical industry prohibits the US government from using its purchasing power to negotiate prices.

Peak penetration

In our market model for KL1333, we assume 80% of patients would be eligible for treatment. There are many reasons why patients might not receive treatment, such as a lack of access to healthcare, old age and unwillingness; hence we assume 20% of our overall estimated prevalence for all target indications would not receive treatment. Looking at a geographical markets, we believe it is likely that KL1333 could be granted market approval for Pearson's syndrome and MELAS after finalisation of pivotal trials. However, we believe KL1333 could have potential beyond these two indications; particularly in other genetic mitochondrial diseases such as Alper's syndrome, CPEO, KSS and MERFF. Therefore, we have in our valuation assumed that KL1333 will be used off-label in these indications, primarily in the EU where physicians can prescribe drugs off-label without patients having to receive clearance from insurance companies, which is often the case in the US.

[32] Simoncelli M, (2015) Cost-Consequence Analysis of Nitisinone for Treatment of Tyrosinemia Type I, The Canadian Journal of Hospital Pharmacy

NeuroSTAT

In 2018, it is estimated that approximately 2.5 million TBI patients will have been diagnosed, treated and released from emergency centres in the US during the year. The vast majority of these will have suffered mild TBI and approximately 15% will have long-lasting problems. Only a minority of patients will suffer from moderate-to-severe TBI and become hospitalised. According to Centers for Disease Control and Prevention, 282,000 patients will have been hospitalised due to TBI in the US in 2018[33]; this is NeuroVive's target group. In Europe, data on hospitalisation in much less homogenous; instead we have looked at the incidence rates reported from a few studies in the UK, France, Germany and Finland[34]. Based on these, the average incidence rate for moderate-to-severe TBI is 42.05 per 100,000 individuals. We then apply this rate to the overall population in the EU5 (France, Germany, Italy, Spain, United Kingdom), which gives us 131,300 patients.

Average incidence rate for moderate-to-severe TBI is 42.05 per 100,000 individuals…

…We then apply this rate to the overall population in the EU5, which gives us 131,300 patients

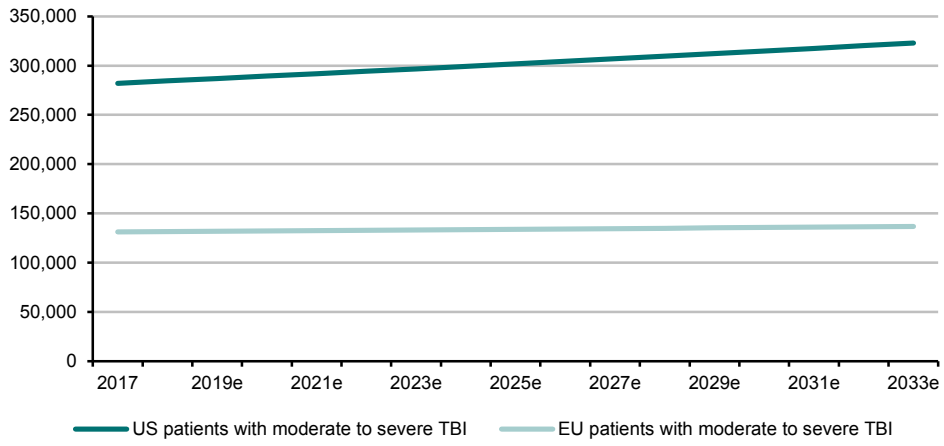
Epidemiology of moderate-to-severe TBI in Europe

Study	Population	Incidence moderate-to-severe TBI per 100,000
Hawley and colleagues (2003)	United Kingdom	42
Javouhey and colleagues (2006)	France	61.2
Puljula and colleagues (2013)	Finland	35
Rickels and colleagues (2010)	Germany	30
Average	**Pooled**	**42.05**

Source: Hawley et al.(2003), Javouhey et al.(2006), Puljula et al. (2013), Rickels et al. (2010)

As seen in the graph below, we expect the TBI population in the US to grow slightly faster than in the EU5. We base this assumption on the fact that the overall population growth is greater in the US compared to in Europe; c0.85% in US and c0.25% in Europe.

Target population for NeuroSTAT over time



Source: DNB Markets

Pricing

As in the case of KL1333, we have assumed a flat price of USD50,000 in the EU5 and USD100,000 in the US per patient for NeuroSTAT. Is our price analysis, we have looked at several currently available orphan drugs indicated for diseases where patients have limited treatment options. Furthermore, if NeuroSTAT is granted regulatory approval in moderate-to-severe TBI, we think it very likely that generic cyclosporine will be used to some extent and that this could potentially affect the pricing for NeuroSTAT. NeuroSTAT is intended to be administered as a one-time treatment with dosing over c5 days, and USD50,000–100,000 might appear expensive for one treatment; however, it should be stressed that TBI patients suffer from life-long complications and a significant unmet medical need exists in this patient population.

[33] Centers for Disease
[34] Hawley et al.(2003), Javouhey et al.(2006), Puljula et al. (2013), Rickels et al. (2010)

Peak penetration

We assume 80% of moderate-to-severe TBI patients will be eligible for treatment with NeuroSTAT. We assume a peak penetration of 35% in both the US and the EU5 with a linear ramp-up over 5 years. As previously mentioned, it is likely that generic cyclosporine could be used in hospitals instead of NeuroSTAT and this would impact the market uptake negatively in all geographies.

Forecasts

Key assumptions

As the company is still in a development phase, actual earnings (losses) for the coming years (as shown in its quarterly and annual reports) give little guidance of future performance. On the front page and at the end of this report, we show our forecasts until 2020. However, as we estimate KL1333 could be approved in 2022, the only information these forecasts give is on losses and capital consumption.

Classic peer group valuations are less useful as the company will, on our forecasts, be loss-making until 2024 in our bull case and until 2026 in our bear case; hence, multiples give no guidance. We have probability-adjusted our DCF valuation based on the probability that NeuroSTAT and KL1333 will reach markets.

We have probability-adjusted our DCF valuation based on the probability that NeuroSTAT and KL1333 will reach markets

- **Likelihood of approval**
  - **NeuroSTAT.** We have assigned an LOA for NeuroSTAT of 10%. In doing so, we looked at attrition rates for similar projects in clinical development (see section 'Probability of success'), for instance, In phase II Neurology clinical trials, the average probability of success is c30% and the overall LOA from phase II to launch is c9%. We have also evaluated previous clinical trials of cyclosporine in TBI patients, and key reasons why some of these projects have failed historically (primarily due to lack of efficacy). Many previous trials evaluating cyclosporine in TBI have failed to demonstrate efficacy over placebo, we therefore believe NeruoSTAT should have a slightly lower LOA than suggested by Hay (2015) for Neurology projects in phase II.

Low LOAs

  - **KL1333.** We have assigned an LOA ranging between 10–15% for MELAS and 5% for the indications Alper's syndrome, CPEO, Pearson's syndrome, KSS and MERFF. We believe MELAS and Pearson's syndrome are the two indications where KL1333 has the highest probability of reaching approval, hence we have set an LOA of 10% in our bear case and 15% in our bull case. KL1333 has demonstrated efficacy in preclinical studies where fibroblasts have been derived from MELAS patients; this has not been done for other diseases and thus we believe MELAS represents an edge for the company. There are currently no drugs approved for Alper's disease, CPEO, PEO, KSS, MELAS, MERFF or Pearson's syndrome. These are diseases which we believe KL1333 could target, primarily through off-label use; however, there is no historical data in these indications and no approved therapies to date, thus we have assumed a fairly low LOA of 5%.

- **Pricing**
  - **NeuroSTAT.** We assume an annual treatment price in the US of USD150,000 and USD80,000 in Europe. A significant unmet medical need exists for these patients; hence we believe a fairly high price could be charged. Our price assumptions would of course be revised if more clinical data becomes available from future studies.

High prices

  - **KL1333.** In both our bull and bear case, we assume a flat treatment price of KL1333 for all indications we believe it could target. However, we have set the estimated price in the EU at half the price in the US (USD50,000 versus USD100,000 for one year of treatment). The European price is in the same range as the price of Raxone in European markets.
- **R&D.** Until 2023 we expect R&D to account for the vast majority of NeuroVive's operating costs. We believe the majority will be attributed to the clinical development of KL1333.
- **WACC.** We have used a WACC of 10% to discount the potential profits back to an NPV. We use the same WACC for all small biotech companies, and mainly adjust for the difference in risk profile in the LOA variable.
- **Currency.** We have converted all revenues (mainly in USD) back to SEK at an SEK/USD rate of 8.9. Our operating cost forecasts are in SEK.

Valuation

We initiate coverage of NeuroVive with a fair value range of SEK3–SEK9/share. We have included only NeuroSTAT and KL1333 in our valuation of NeuroVive since these are currently the company's only two assets in clinical development. However, the company has many other assets including NV354, NVP025, NV556, NVP022, and NVP024 and some of these, especially NV354, seem promising to us. If in the future NeuroVive can advance or out license any of these projects, there could be additional upside potential beyond our fair value range.

Valuation of NeuroSTAT

NeuroVive is about to move forward with NeuroSTAT and initiate a phase IIb study. However, the company's current focus is on KL1333, and a phase IIb study with NeuroSTAT will be initiated only if soft funding can be granted from e.g. Horizon 2020. Management has said that a phase IIb study in TBI would take 1–2 years and estimates a total cost of the study at USD4m. However, it should be stressed that these are just estimates and costs could vary depending on where the study has recruitment sites, since the cost of care for TBI patients varies significantly between countries.

10 year P&L (SEKm) estimates for NeuroSTAT when we assume a 50% peak penetration

	2018e	2019e	2020e	2021e	2022e	2023e	2024e	2025e	2026e	2027e	2028e
Total revenues	0	0	0	0	0	0	0	0	67	135	204
COGS	0	0	0	0	0	0	0	0	-7	-13	-20
R&D Costs	0	-15	-20	-30	-30	-50	-60	-80	0	0	0
EBIT	0	-15	-20	-30	-30	-50	-60	-80	60	121	183

Source: DNB Markets

- Gross margin – 90%
- LOA – 10%
- Price per patient per treatment year – USD150,000 (the US) and USD80,000 (EU5)
- WACC – 10%
- Overall peak penetration – 50%

EBIT valuation sensitivity against WACC and LOA

		LOA				
		5%	10%	15%	20%	25%
WACC	8%	-	121	503	1,038	1,726
	9%	-	96	436	911	1,523
	10%	-	75	377	800	1,344
	11%	-	57	326	703	1,188
	12%	-	41	282	618	1,051

Source: DNB Markets estimates

EBIT valuation sensitivity against peak penetration and LOA

		LOA				
		5%	10%	15%	20%	25%
Peak penetration	10%	-	-	-	27	135
	20%	-	-	51	220	438
	30%	-	-	160	414	740
	40%	-	27	268	607	1,042
	50%	-	75	377	800	1,344

Source: DNB Markets estimates

Valuation of KL1333

Based on our sum-of-the-parts analysis, KL1333 is NeuroVive's most valuable asset and is also the drug candidate that the company could potentially launch first – we estimate 2022. In our analysis, we have looked a bull and a bear-case scenario. In the bull-case scenario, we assume a higher LOA for KL1333 in Pearson's syndrome and MELAS and also higher market

KL1333 is NeuroVive's most valuable asset and is also the candidate that it could potentially launch first

penetration in the same two indications; more details of the differences in our bull and bear-case scenarios are specified in the bullets in the next section.

Market strategies: Pearson's syndrome or multiple indications

The company has suggested that one potential go-to-market path that would enable a launch in 2022 is to conduct a registration study in patients with Pearson's syndrome. We view this as the most attractive launch plan since it would de-risk the development significantly compared to if it were to launch a multi-indication trial. Pearson's syndrome is a condition with significant unmet medical need and is one of the most severe genetic mitochondrial diseases. According to the literature, Pearson's is estimated to be most rare of the genetic mitochondrial diseases we touch upon in this report. Since there are so few patients with this disease, we assume only a small number of patients would be needed in a potential phase II or registration study and costs could be kept fairly low throughout clinical development, compared to larger studies with more patients which are generally much more costly. A multi-indication trial would be costly since more patients would have to be recruited and this would also prolong the development plan. Furthermore, it is unclear if regulators would approve a study design with pooled indications; we have previously seen trials where patients have been recruited based on mutation status instead of diagnosis of disease; but in NeuroVive's case, it would be impossible to carry out a multi-indication trial with all target diseases (Alper's disease, CPEO, PEO, KSS, MELAS, MERFF or Pearson's syndrome).

Higher LOA for MELAS

We would argue that LOA for KL1333 should be higher for MELAS compared to other target indications. Preclinical studies with KL1333 in fibroblasts derived from MELAS patients indicate that KL1333 improves mitochondrial biogenesis and function, and therefore could be a promising therapeutic agent for the treatment of MELAS. Such studies have not been carried out in other target indications, hence we have assumed an LOA of 10% in MELAS in our base case and 15% in our bull case. For other target indications (Alper's syndrome, CPEO, KSS and MERFF), we have assumed an LOA of 5% independent of scenario.

Costs related to the partnership with Yungjin Pharm

We have assumed a low-double-digit royalty rate to Yungjin Pharm of 12% on all future sales. As for the total milestone payments of USD64m; we assume USD22m is related to development milestones and the remaining USD42m will be attributed to reimbursement decisions and sales/marketing. We assume NeuroVive will have to pay USD11m upon completion of phase III in Pearson's syndrome in 2022 and USD21m in market and reimbursement milestones in 2023. We have assumed the same pattern for MELAS, where we assume 11m will be paid upon completion of phase III in 2024 and USD21m in market and reimbursement milestones the following year.

Bull case

Bull case fair company value estimate – SEK834m

- Fair company value estimate – SEK834m
- Gross margin – 90%
- LOA – **15% in MELAS,** 5% in Alper's syndrome, CPEO, Pearson's syndrome, KSS and MERFF
- Peak penetration – **50% in both the US and EU for MELAS,** 15% in the US and 35% in the EU for Alper's syndrome, CPEO, Pearson's syndrome, KSS and MERFF
- Price per patient per treatment year – USD100,000 (the US) and USD50,000 (EU5)
- Royalty paid – 12%
- A total of USD64m of sign-on and sales-related milestones
- WACC – 10%
- Tax rate – 22%
- Terminal year – 2034

KL1333 bull case: 10-year P&L (SEKm) estimates

	2018e	2019e	2020e	2021e	2022e	2023e	2024e	2025e	2026e	2027e	2028e
Total revenues	0	0	0	0	170	342	515	690	776	780	784
COGS	0	0	0	0	-17	-34	-51	-69	-78	-78	-78
Royalty to Yungjin Pharm.	0	0	0	0	-26	-51	-77	-103	-116	-117	-118
Milestones to Yungjin Pharm.					-98	-187	-98	-187			
R&D costs (SEKm)	-30	-45	-60	-75	-90	-75	-90	-120	-20	-20	-20
EBIT	-30	-45	-60	-75	-60	-6	198	211	375	565	568

Source: DNB Markets estimates

Bear case

Bear case fair company value estimate – SEK290m

- Fair company value estimate – SEK290m
- Gross margin – 90%
- LOA – **10% in MELAS**, 5% in Alper's syndrome, CPEO, Pearson's syndrome, KSS and MERFF.
- Peak penetration – **35% in both the US and EU for MELAS**, 15% in the US and 35% in the EU for Alper's syndrome, CPEO, Pearson's syndrome, KSS and MERFF
- Price per patient per treatment year – USD100,000 (the US) and USD50,000 (EU5)
- Royalty paid – 12%
- A total of USD64m of sign-on and sales-related milestones
- WACC – 10%
- Tax rate – 22%
- Terminal year 2034

KL1333 bear case: 10-year P&L (SEKm) estimates

	2018e	2019e	2020e	2021e	2022e	2023e	2024e	2025e	2026e	2027e	2028e
Total revenues	0	0	0	0	109	219	330	442	555	557	560
COGS	0	0	0	0	-11	-22	-33	-44	-55	-56	-56
Royalty to Yungjin Pharm.	0	0	0	0	-16	-33	-49	-66	-83	-84	-84
Milestones to Yungjin Pharm.					-98	-187	-98	-187			
R&D costs (SEKm)	-30	-45	-60	-75	-90	-75	-90	-120	-20	-20	-20
EBIT	-30	-45	-60	-75	-106	-98	59	24	209	398	400

Source: DNB Markets estimates

Combined valuation

In this section, we present our combined valuation of NeuroVive. In both our bull and bear cases, we assume KL1333 will be launched in 2022 and NeuroSTAT in 2026. Our adjustments to LOA and peak penetration for KL1333 as presented in our valuation of KL1333 translate to higher total revenues in our bull case. As for cost estimates, these are estimated to be identical to both cases until 2022, where COGS and royalties paid to Yungjin Pharm. will be higher in the bull case until terminal year due to our applied COGS rate of 10% of total revenues and an estimated 12% royalty of total sales paid to Yungjin Pharm. As for milestone payments, personnel costs and post-approval R&D activities, we believe these will remain the same independent of scenario, since we assume they would not be affected by LOA or total revenues. In both our bull and bear cases, we assume flat yearly other operating expenses of SEK11m, and we expect depreciation to grow from SEK2m to SEK6m by 2022.

DCF valuation bull case scenario (SEKm)

		2018e	2019e	2020e	2021e	2022e	2023e	2024e	2025e	2026e	2027e	2028e	2029e	2030e	2031e	2032e	2033e
Total revenues		0	0	0	0	170	342	515	690	842	914	987	1,061	1,136	1,143	1,149	1,156
COGS		0	0	0	0	-17	-34	-51	-69	-84	-91	-99	-106	-114	-114	-115	-116
Royalty to Yungjin Pharm.		0	0	0	0	-26	-51	-77	-103	-116	-117	-118	-118	-119	-119	-120	-121
Milestones to Yungjin Pharm.		0	0	0	0	-98	-187	-98	-187	-187	0	0	0	0	0	0	0
KL1333 R&D costs		-30	-45	-60	-75	-90	-75	-90	-120	-20	-20	-20	-20	-20	-20	-20	-20
NeuroSTAT R&D Costs		0	-15	-20	-30	-30	-50	-60	-80	0	0	0	0	0	0	0	0
R&D SUM		-30	-60	-80	-105	-120	-125	-150	-200	-20	-20	-20	-20	-20	-20	-20	-20
Personnel costs		-15	-20	-50	-55	-60	-60	-60	-60	-60	-60	-60	-60	-60	-60	-60	-60
Depreciations		-2	-3	-6	-6	-6	-6	-6	-6	-6	-6	-6	-6	-6	-6	-6	-6
Other operating expenses		-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11
EBIT		-58	-94	-147	-177	-167	-133	61	54	358	609	674	740	807	812	818	823
Net financials		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pre-tax profit		-58	-94	-147	-177	-167	-133	61	54	358	609	674	740	807	812	818	823
Tax		0	0	0	0	0	0	-14	-12	-79	-134	-148	-163	-177	-179	-180	-181
Net profit		-58	-94	-147	-177	-167	-133	48	42	279	475	526	577	629	633	638	642
Time factor		0.75	1.75	2.75	3.75	4.75	5.75	6.75	7.75	8.75	9.75	10.75	11.75	12.75	13.75	14.75	15.75
PV factor		0.93	0.85	0.77	0.70	0.64	0.58	0.53	0.48	0.43	0.39	0.36	0.33	0.30	0.27	0.25	0.22
PV		-54	-80	-113	-124	-106	-77	25	20	121	188	189	188	187	171	156	143
rNPV	**834**																

Source: DNB Markets estimates

DCF valuation bear case scenario (SEKm)

		2018e	2019e	2020e	2021e	2022e	2023e	2024e	2025e	2026e	2027e	2028e	2029e	2030e	2031e	2032e	2033e
Total revenues		0	0	0	0	109	219	330	442	621	692	763	836	909	914	919	925
COGS		0	0	0	0	-11	-22	-33	-44	-62	-69	-76	-84	-91	-91	-92	-92
Royalty to Yungjin Pharm.		0	0	0	0	-16	-33	-49	-66	-83	-84	-84	-84	-85	-85	-85	-86
Milestones to Yungjin Pharm.		0	0	0	0	-98	-187	-98	-187	-187	0	0	0	0	0	0	0
KL1333 R&D costs		-30	-45	-60	-75	-90	-75	-90	-120	-20	-20	-20	-20	-20	-20	-20	-20
NeuroSTAT R&D Costs		0	-15	-20	-30	-30	-50	-60	-80	0	0	0	0	0	0	0	0
R&D SUM		-30	-60	-80	-105	-120	-125	-150	-200	-20	-20	-20	-20	-20	-20	-20	-20
Personnel costs		-15	-20	-50	-55	-60	-60	-60	-60	-60	-60	-60	-60	-60	-60	-60	-60
Depreciations		-2	-3	-6	-6	-6	-6	-6	-6	-6	-6	-6	-6	-6	-6	-6	-6
Other operating expenses		-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11	-11
EBIT		-58	-94	-147	-177	-213	-225	-78	-133	192	442	506	571	637	641	645	649
Net financials		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pre-tax profit		-58	-94	-147	-177	-213	-225	-78	-133	192	442	506	571	637	641	645	649
Tax		0	0	0	0	0	0	17	29	-42	-97	-111	-126	-140	-141	-142	-143
Net profit		-58	-94	-147	-177	-213	-225	-60	-103	150	345	395	445	497	500	503	507
Time factor		0.75	1.75	2.75	3.75	4.75	5.75	6.75	7.75	8.75	9.75	10.75	11.75	12.75	13.75	14.75	15.75
PV factor		0.93	0.85	0.77	0.70	0.64	0.58	0.53	0.48	0.43	0.39	0.36	0.33	0.30	0.27	0.25	0.22
PV		-54	-80	-113	-124	-136	-130	-32	-49	65	136	142	145	147	135	123	113
rNPV	**290**																

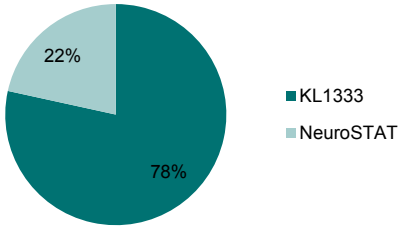
Source: DNB Markets estimates

Company value sensitivity against LOA and peak penetration for KL1333 in MELAS in US and Europe

		LOA				
		5%	10%	15%	20%	25%
Peak penetration	15%	-	70	259	448	636
	20%	-	125	341	557	773
	25%	-	180	423	667	910
	30%	-	235	506	776	1047
	35%	-	290	588	886	1184
	40%	19	344	670	996	1321
	45%	46	399	752	1105	1458
	50%	73	454	834	1215	1595
	55%	101	509	917	1325	1732
	60%	128	564	999	1434	1869

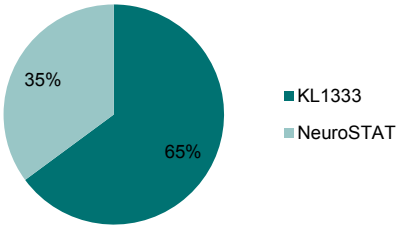
Source: DNB Markets estimates

Value split by drug candidate bull case



Source: DNB Markets estimates

Value split by drug candidate bear case



Source: DNB Markets estimates

We initiate coverage with a fair value range of SEK3–SEK9/share

Source: DNB Markets estimates

Risks

In this section, we highlight some of the risks to be evaluated when considering investing in NeuroVive. We believe the risks can be divided into several areas; in our view the most important concerns are the clinical development of the pipeline, financials, and market-related risks. The list below should not be seen as complete and exhaustive.

Clinical development

Limited clinical data

There is limited publicly available data on patient outcomes for the safety and efficacy of the company's products. For six of the company's eight drug candidates, there is no clinical data available at all on the planned indications. For NeuroSTAT, there is limited efficacy data (based on biomarkers) from the clinical trial CHIC; however, this study did not apply the same outcome measurements to be used in a potential phase IIb trial where MRI is to be applied.

For six of the company's eight drug candidates, there is no clinical data available at all on planned indications

Development of drugs takes time

Several of the company's assets are in an early-development phase, and even though orphan indications can be speeded through clinical development faster than for other indications, it will take until at least 2022 before NeuroVive could have a product on the market. It should be stressed that while a launch in 2022 is estimated, it is more common than uncommon that the launch gets delayed for such projects, since a myriad of both regulatory and development hurdles first have to be passed.

It is more common than uncommon that launch gets delayed for such projects, due to myriad regulatory and development hurdles

Unexpected side effects in future development

The company's main asset, NeuroSTAT, has shown a beneficial safety profile in TBI patients and in other indications. KL1333 has appeared to be safe in the first clinical trial carried out in healthy volunteers. However, larger studies could reveal unwanted side effects or severe adverse events that would delay or lead to a termination of clinical projects.

Risks related to financials

No revenues from product sales historically or in the near future

The company has no products on the market and we do not expect it to have any products in the market in the next few years.

Could need additional financing in the coming years

As the company is still in the development phase for all of its assets, it will likely need additional financing to complete clinical trials and/or build a sales organisation (in the event the development phase is successful, we would expect a product to be launched). There is no guarantee that this type of financing would be available if needed and/or at terms that are acceptable to shareholders.

Will likely need additional financing to complete clinical trials and/or build a potential sales organisation

Risks related to the market

Limited IP protection – dependent on other means of protection

All use patents for NeuroSTAT have expired and the company currently holds only one formulation patent (WO2012/042023). Limited patent protection means that NeuroVive will have to rely on orphan drug exclusivity in the US as well as market and data exclusivity. Data exclusivity is c10–11 years in Europe and c8 years in Japan. There is a risk it will not obtain orphan drug exclusivity Japan, which would limit the market potential for NeuroSTAT.

General risk factors for share price performance

High risk of clinical failures and development setbacks

As with all research-based companies, there is a high risk that one or more development projects will face problems of one form or another. In the case of NeuroVive, we have previously seen such a scenario twice before, with CicloMulsion. If this happens again, the impact on the share price could be severe, as we have seen in the past.

Sentiment towards biotech companies is volatile

As companies such as NeuroVive have a high risk profile, such investments tend to be affected by the overall sentiment for risk appetite. Hence, if the general stock market for one

reason or another prefers more stable and predictable companies, shares such as NeuroVive might go out of favour and hence see weak performance for a period.

Lack of news could dampen interest in the shares

Given the nature of the industry, we expect there to be periods when the company does not release news on clinical development, which could affect the share price. Additionally, any news on competing products could have a negative impact on the NeuroVive share price.

Appendix

Management and board

Management

- **Erik Kinnman – CEO.** Erik Kinnman, born 1958, is a seasoned life science executive with broad experience and understanding from the industry across a variety of businesses and functions. He has held a number of senior leadership positions in biopharmaceutical companies such as AstraZeneca and Sobi. His expertise and experience includes clinical development, business strategy, business development, and investor relations. Mr. Kinnman also has experience from the financial sector. In addition, he holds an Executive MBA from the Stockholm School of Economics and has comprehensive scientific qualifications from the Karolinska Institutet, which has rendered him a Ph.D. and an Associate Professor. Moreover, Erik Kinnman is an M.D., board certified in Neurology and Pain Management. Employed since 2016. No. of shares: 82,248. Warrants serie 2018:1: 8 812.
- **Catharina Jz Johansson – CFO & Vice President Investor Relations.** Catharina Jz Johansson, born 1967, possesses experience from work on medtech growth enterprises with multinational operations. Catharina Johansson holds a M.Sc. in Business and Economics. Her previous experience includes serving as interim CFO for medical device company Cellavision, which is listed on Nasdaq Stockholm, and Accounting Manager for Bong and Alfa Laval Europe. Employed since 2013. No. of shares: 17,500 Warrants serie 2018:1: 1 875.
- **Eskil Elmér – CSO & Vice President Discovery.** Eskil Elmér, born 1970, is associate professor of experimental neurology at Lund University (Sweden) and group leader of the Mitochondrial Medicine lab at the department of Clinical Neurophysiology. Dr. Elmér is patentee and co-founder of both Maas Biolab, LLC and NeuroVive Pharmaceutical AB, and CSO of NeuroVive, with overall charge of the company's pre-clinical research. In addition, Eskil Elmér is a practising physician in the department of clinical neurophysiology at Skåne University Hospital in Lund, Sweden. Employed since 2000. No. of shares: 574,478 privately owned (including family) and 17.09% of Maas Biolab, LLC, which owns 4.2% of NeuroVive. Warrants serie 2018:1: 20 769.
- **Magnus Hansson – CMO & Vice President Preclinical and Clinical Development.** Magnus Hansson, born 1976, has extensive experience in the area of mitochondrial medicine. He has previously been serving as a Senior Scientist in NeuroVive since 2008 and as a consultant physician and associate professor in medical imaging and physiology at Skåne University Hospital, Sweden. Dr. Hansson has overall charge of the company's pre-clinical and clinical development programmes. He holds a PhD in experimental brain research from Lund University, Sweden, and has authored more than 30 scientific publications and 10 patent applications. Employed since 2008. No. of shares: 205 774 (including family). Warrants serie 2018:1: 22 046.
- **Mark Farmery – Vice President Business Development.** Mark Farmery, born 1969, is a senior executive with more than 15 years' experience in biopharma business development from Karolinska Institutet Innovations AB, AstraZeneca and Karo Bio AB. He has also managed research teams and led specific projects in the fields of Alzheimer's disease modification and protein modification and misfolding at Karolinska Institutet and the Universities of Gothenburg and Manchester. Dr. Farmery received his BSc in Biomedical Sciences (Microbiology) from the University of Bradford and his PhD in Biochemistry and Molecular Microbiology from the University of Leeds. Employed since 2017. No. of shares: 0. Warrants serie 2018: 0.

Board

- **David Laskow-Pooley – Chairman** since 2017. Born 1954. Education: BSc Pharmacy (1st), Pharmaceutical/Chemical engineering specialty and QP, Sunderland School of Pharmacy. Other assignments: Director of the board of TapImmune Inc, US, LREsystem Ltd, England and Pharmafor Ltd, England. No. of shares in NeuroVive: 15,276. Warrants serie 2018:1: 3 819. Other: Non-affiliated to the company, management or to major owners.

- **David Bejker – Director** since 2017. Born 1975. Education: M.Sc. (Econ.), Stockholm School of Economics. Other assignments: CEO of Affibody Medical AB. No. of shares in NeuroVive: 15,276. Warrants serie 2018:1: 3 819. Other: Non-affiliated to the company, management or to major owners.
- **Jan Törnell – Director** since 2017. Born 1960. Education: MD and PhD in physiology, University of Gothenburg. Other assignments: Editor-in-Chief for Drug Discovery Today – Disease Models and adjunct Professor at the Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg. Jan is also chairman of the Board at LIDDS AB, Glactone Pharma AB and Glactone Pharma Development AB and Director of the Board at Stayble AB and Diaprost AB, CEO at Oncorena AB and Innoext AB and partner of P.U.L.S. AB. No. of shares in NeuroVive: 15,276. Warrants serie 2018:1: 3 819. Other: Non-affiliated to the company, management or to major owners.
- **Denise Goode – Director** since 2018. Born 1958. Education: Institute of Chartered Accountants in England and Wales Chartered Accountant. B.Sc. Zoology from the University of Manchester (UK). Other ongoing assignments: Director of QED Life Sciences Limited. Director of AnaMar AB. No. of shares in NeuroVive: 0. Warrants serie 2018: 0. Other: Non-affiliated to the company, management, or to major owners.

Shareholders

NeuroVive Pharmaceutical has more than 8,700 shareholders.

Top 15 shareholders per September 2018

	Shareholder	Number of shares		Nationality
1	Avanza Pension	13,000,000	14.66%	Sverige
2	Maas BioLab LLC	3,874,432	4.23%	USA
3	Nordnet Pensionsförsäkring	3,472,702	3.79%	Sverige
4	Baulos International SA	3,106,664	3.39%	Belgien
5	Rothesay Ltd	2,200,000	2.40%	Bahamas
6	Handelsbanken Liv Försäkring AB	2,002,711	2.19%	Sverige
7	Tobias Ekman	1,200,000	1.31%	Sverige
8	Eskil Elmér	464,411	0.89%	Sverige
9	Livförsäkringsbolaget Skandia	803,556	0.88%	Sverige
10	Gunvald Berger	691,200	0.75%	Sverige
11	Swedbank Försäkring	678,836	0.74%	Sverige
12	Minwei Zhou	574,167	0.63%	Sverige
13	Stefan Larsson	489,000	0.53%	Sverige
14	Anders Tangen	487,248	0.53%	Sverige
15	Jörgen Dalén	461,100	0.50%	Sverige

Source: Holdings.se

Annual P&L

(SEKm)	2011	2012	2013	2014	2015	2016	2017	2018e	2019e	2020e
Revenues	**6**	**1**	**7**	**8**	**3**	**0**	**0**	**0**	**0**	**0**
Cost of sales	0	0	0	0	0	0	0	0	0	0
Gross profit	**6**	**1**	**7**	**8**	**3**	**0**	**0**	**0**	**0**	**0**
Operating expenses	-15	-18	-29	-53	-93	-71	-70	-56	-91	-141
EBITDA	**-10**	**-16**	**-22**	**-45**	**-91**	**-72**	**-71**	**-58**	**-94**	**-147**
Depreciation	0	0	0	0	-1	-1	-2	-2	-3	-6
EBITA	**-10**	**-17**	**-22**	**-46**	**-93**	**-73**	**-73**	**-60**	**-97**	**-153**
Amortisation			0	0	0	0	0	0	0	0
EBIT	**-10**	**-17**	**-22**	**-46**	**-93**	**-73**	**-73**	**-60**	**-97**	**-153**
Net interest	0	0	0	0	0	0	0	0	0	0
Net financial items	0	0	0	0	0	0	0	0	0	0
PBT	**-10**	**-17**	**-22**	**-46**	**-93**	**-73**	**-73**	**-60**	**-97**	**-153**
Taxes	0	0	0	0	0	0	0	0	0	0
Effective tax rate (%)	0	0	0	0	0	0	0	0	0	0
Net profit	**-10**	**-17**	**-22**	**-46**	**-93**	**-73**	**-73**	**-60**	**-97**	**-153**
Adjustments to net profit	0	0	0	0	-1	2	0	0	0	0
Net profit adj	-10	-17	-22	-46	-93	-71	-73	-60	-97	-153
Per share data (SEK)										
EPS		-0.85	-1.17	-1.53	-3.01	-1.67	-1.33	0.00	-4.42	-3.15
EPS adj								**-3.15**	**-4.42**	**-3.15**
Growth and margins (%)										
Revenue growth	57.1	-76.3	422.1	20.2	-63.7	-96.1	133.1	nm	nm	nm
EPS adj growth	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm
Gross margin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	nm	nm	nm
EBITDA margin	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm
EBITDA adj margin	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm
Depreciation/revenues	-2.7	-9.6	-2.1	-5.3	-39.7	-950.0	-580.0	nm	nm	nm
EBIT margin	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm
EBIT adj margin	-179.2	-1252.0	-324.4	-548.4	-3064.4	nm	nm	nm	nm	nm
PBT margin	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm
Net profit margin	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm

Source: Company (historical figures), DNB Markets (estimates)

Adjustments to annual P&L

(SEKm)	2011	2012	2013	2014	2015	2016	2017	2018e	2019e	2020e
EBITDA	**-10**	**-16**	**-22**	**-45**	**-91**	**-72**	**-71**	**-58**	**-94**	**-147**
Other EBITDA adjustments							0	0	0	0
EBITDA adj	-10	-16	-22	-45	-91	-72	-71	-58	-94	-147
EBITA	**-10**	**-17**	**-22**	**-46**	**-93**	**-73**	**-73**	**-60**	**-97**	**-153**
Other EBITA adjustments							0	0	0	0
EBITA adj	-10	-17	-22	-46	-93	-73	-73	-60	-97	-153
EBIT	**-10**	**-17**	**-22**	**-46**	**-93**	**-73**	**-73**	**-60**	**-97**	**-153**
Other EBIT adjustments			0	0	0	0	0	0	0	0
EBIT adj	-10	-17	-22	-46	-93	-73	-73	-60	-97	-153
Net profit	**-10**	**-17**	**-22**	**-46**	**-93**	**-73**	**-73**	**-60**	**-97**	**-153**
Other EBIT adjustments			0	0	0	0	0	0	0	0
Tax adjustments			0	0	0	0	0	0	0	0
Other adjustments	0	0	0	0	-1	2	0			
Net profit adj	-10	-17	-22	-46	-93	-71	-73	-60	-97	-153
Per share data (SEK)										
EPS		-0.85	-1.17	-1.53	-3.01	-1.67	-1.33	0.00	-4.42	-3.15
Recommended adjustment								-3.15	0.00	0.00
EPS adj								-3.15	-4.42	-3.15

Source: Company (historical figures), DNB Markets (estimates)

Cash flow

(SEKm)	2011	2012	2013	2014	2015	2016	2017	2018e	2019e	2020e
Net profit	-10	-17	-22	-46	-93	-73	-73	-60	-97	-153
Depreciation and amortisation			0	0	1	1	2	2	3	6
Other non-cash adjustments	-1	1	1	0	29	28	11	11	0	0
Cash flow from operations (CFO)	**-10**	**-16**	**-21**	**-45**	**-61**	**-43**	**-59**	**-47**	**-94**	**-147**
Cash flow from investing (CFI)	**-7**	**-10**	**-80**	**-201**	**-23**	**-25**	**-15**	**0**	**0**	**0**
Free cash flow (FCF)	**-17**	**-26**	**-101**	**-246**	**-85**	**-68**	**-74**	**-47**	**-94**	**-147**
Cash flow from financing (CFF)	**0**	**46**	**34**	**77**	**120**	**77**	**9**	**64**	**94**	**147**
Total cash flow (CFO+CFI+CFF)	**-15**	**24**	**3**	**10**	**47**	**-3**	**-64**	**17**	**0**	**0**
FCFF calculation										
Free cash flow	-17	-26	-101	-246	-85	-68	-74	-47	-94	-147
Less: net interest	0	0	0	0	0	0	0	0	0	0
Growth (%)										
CFO	-117.9	-53.7	-32.8	-112.5	-37.6	30.5	-37.5	19.3	-99.7	-55.9
CFI	-18.2	-43.3	-719.3	-152.8	88.4	-6.8	39.0	100.0	nm	nm
FCF	-63.2	-49.6	-294.3	-144.4	65.5	20.2	-9.2	36.0	-99.7	-55.9
CFF	-98.9	11198.0	-27.5	128.0	56.1	-35.3	-88.3	610.6	47.2	55.9
FCFF	nm	nm	nm	nm	nm	nm	nm	nm	nm	nm

Source: Company (historical figures), DNB Markets (estimates)

Balance sheet

(SEKm)	2011	2012	2013	2014	2015	2016	2017	2018e	2019e	2020e
Assets	**34**	**72**	**89**	**131**	**175**	**181**	**120**	**98**	**128**	**148**
Other receivables	0	1	1	1	2	2	2	0	0	0
Cash and cash equivalents	13	37	40	50	97	93	29	46	46	46
Current assets	**13**	**38**	**42**	**51**	**100**	**96**	**33**	**46**	**46**	**46**
Property, plant and equipment	0	1	0	0	0	0	0	0	0	0
Other intangible assets	21	33	47	80	75	71	74	52	82	102
Non-current financial assets	0	0	0	0	0	13	13	0	0	0
Non-current assets	**21**	**33**	**48**	**80**	**75**	**85**	**88**	**53**	**83**	**103**
Total assets	**34**	**72**	**89**	**131**	**175**	**181**	**120**	**98**	**128**	**148**
Equity and liabilities	**34**	**72**	**89**	**131**	**175**	**181**	**120**	**98**	**128**	**148**
Total equity to the parent	33	64	75	103	141	155	101	97	127	147
Minority interests	0	-1	-1	5	14	13	5			
Total equity	**33**	**63**	**75**	**108**	**155**	**168**	**106**	**97**	**127**	**147**
Short-term debt	2	8	15	23	20	12	14	1	1	1
Total current liabilities	**2**	**8**	**15**	**23**	**20**	**12**	**14**	**1**	**1**	**1**
Total non-current liabilities	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Total liabilities	**2**	**8**	**15**	**23**	**20**	**12**	**14**	**1**	**1**	**1**
Total equity and liabilities	**34**	**72**	**89**	**131**	**175**	**181**	**120**	**98**	**128**	**148**
Key metrics										
Net interest bearing debt	14	46	55	-26	-77	-81	-15	-45	-45	-45

Source: Company (historical figures), DNB Markets (estimates)

Valuation ratios

(SEKm)	2011	2012	2013	2014	2015	2016	2017	2018e	2019e	2020e
Enterprise value										
Share price (SEK)			13.65	39.93	7.52	2.98	2.67	3.72	3.72	3.72
Number of shares (m)	19.16	19.16	21.66	27.79	29.09	49.46	52.33	0.00	0.00	0.00
Market capitalisation			296	1,110	219	147	140	0	0	0
Net interest bearing debt	14	46	55	-26	-77	-81	-15	-45	-45	-45
Adjustments to NIBD	0	0	0	0	0	0	0	0	0	0
Net interest bearing debt adj	14	46	55	-26	-77	-81	-15	-45	-45	-45
EV			350	1,083	142	67	125	-45	-45	-45
EV adj			350	1,083	142	67	125	-45	-45	-45
Valuation										
EPS		-0.85	-1.17	-1.53	-3.01	-1.67	-1.33	0.00	-4.42	-3.15
EPS adj								**-3.15**	**-4.42**	**-3.15**
P/E			-11.7	-26.1	-2.5	-1.8	-2.0		-0.8	-1.2
P/E adj								-1.2	-0.8	-1.2
Average ROE	-27.2%	-34.8%	-32.7%	-50.1%	-70.6%	-45.3%	-53.0%	-59.0%	-86.5%	-111.2%
EV/SALES			50.51	130.02	47.00	563.95	453.84			
EV/SALES adj			50.51	130.02	47.00	563.95	453.84			
EV/EBITDA			-15.7	-23.9	-1.6	-0.9	-1.8	0.8	0.5	0.3
EV/EBITDA adj			-15.7	-23.9	-1.6	-0.9	-1.8	0.8	0.5	0.3
EV/EBIT			-15.6	-23.7	-1.5	-0.9	-1.7	0.7	0.5	0.3
EV/EBIT adj			-15.6	-23.7	-1.5	-0.9	-1.7	0.7	0.5	0.3
EV/NOPLAT			-15.6	-23.7	-1.5	-0.9	-1.7	0.7	0.5	0.3
EV/OpFCF (taxed)			-15.7	-23.9	-1.6	-0.9	-1.8	0.8	0.5	0.3

Source: Company (historical figures), DNB Markets (estimates)

Key accounting ratios

	2011	2012	2013	2014	2015	2016	2017	2018e	2019e	2020e
Profitability (%)										
ROA	-26.2	-31.4	-28.0	-41.5	-60.5	-41.2	-48.3	-54.8	-85.8	-110.4
Return on invested capital (%)										
Net PPE/revenues	2.6	50.1	6.6	4.1	10.4	232.2	58.9			
Working capital/revenues	7.1	55.3	15.8	13.5	78.3	1398.3	570.2			
Cash flow ratios (%)										
FCF/revenues	-304.9	-1920.7	-1450.8	-2949.8	-2802.8	-57352.5	-26872.4			
FCF/market capitalisation			-34.0	-22.2	-38.8	-45.9	-53.0			
CFO/revenues	-183.7	-1188.9	-302.4	-534.6	-2027.5	-36136.4	-21316.4			
CFO/market capitalisation			-7.1	-4.0	-28.0	-28.9	-42.0			
CFO/current liabilities	-620.1	-186.6	-144.3	-190.2	-304.3	-343.5	-411.1	-4729.3	-9444.0	-14723.6
Cash conversion ratio	170.2	153.4	447.2	537.9	91.5	92.4	101.7	78.9	97.0	96.3
OpFCF margin	-176.4	-1242.4	-322.3	-543.1	-3024.7	-61110.2	-25850.2			
Leverage and solvency (x)										
Net debt/EBITDA	-1.46	-2.77	-2.44	0.58	0.84	1.12	0.21	0.77	0.48	0.31

Source: Company (historical figures), DNB Markets (estimates)

Important Information

Company: NeuroVive Pharmaceutical
Coverage by Analyst: Patrik Ling
Date: 25/10/2018

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This report was submitted to the company in a redacted form prior to publication for factual verification. As a result of comments received from the company, changes were made to the report, but no amendments were made to the conclusions therein.

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Share positions in the company:	Analyst*	Employees**	DNB***	Update
Number of shares	0	0	0	26/10/2018

*The analyst or any close associates. **Share positions include people involved in the production of credit and equity research, including people that could reasonably be expected to have access to it before distribution.
***Share positions as part of DNB Group. Holdings as part of DNB Markets investment services activity are not included.

Recommendation distribution and corporate clients for the last 12 months

	Buy	Hold	Sell	No_rec	Total
Number	133	69	25	7	234
% of total	57%	29%	11%	3%	
DNB Markets client	22%	10%	2%	1%	82

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