EDISON

NeuroVive Pharmaceutical

Initiation of coverage

Mitochondrial medicine specialist

Pharma & biotech

NeuroVive Pharmaceutical is a mitochondrial medicine specialist with a diversified asset portfolio. It employs a two-pronged strategy and has a portfolio of drug candidates for orphan mitochondrial diseases, which it aims to develop internally; more recently, it has also identified in-house assets suitable to tackle larger indications, which NeuroVive aims to out-license in pre-clinical development. The most advanced projects are Phase IIb ready NeuroSTAT for traumatic brain injury and KL1333 in Phase I for various mitochondrial diseases. We value NeuroVive at SEK1.5bn.

Year end	Revenue (SEKm)	PBT* (SEKm)	EPS* (SEK)	DPS (SEK)	P/E (x)	Yield (%)
12/15	2.5	(89.6)	(3.00)	0.0	N/A	N/A
12/16	0.0	(70.7)	(1.72)	0.0	N/A	N/A
12/17e	0.0	(62.0)	(1.39)	0.0	N/A	N/A
12/18e	0.0	(51.4)	(1.12)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

Core portfolio focuses on orphan diseases

NeuroVive's core portfolio, which the company aims to develop internally, targets orphan indications: traumatic brain injury (TBI) with NeuroSTAT, various genetic mitochondrial diseases with KL1333 and NVP015, and mitochondrial myopathy with NVP025. Recent R&D news regarding the positive outcome in a Phase IIa study with NeuroSTAT (novel ciclosporin A formulation) means that the drug candidate is ready for a proof-of-concept study. The second most advanced product KL1333 (NAD+ modulator) was in-licensed from Yungjin Pharm in May 2017 and currently is in Phase I.

Assets for out-licensing may add cash in short term

NeuroVive's experience in mitochondrial diseases led to observations that some of its assets have beneficial effects in larger indications, which in turn led to the formation of a product portfolio for out-licensing before clinical development. This includes NV556 and NVP022 for non-alcoholic steatohepatitis (NASH) and NVP024 for hepatocellular carcinoma (HCC). The most advanced is NV556, undergoing late stage preclinical studies, in which NV556 demonstrated consistent antifibrotic effect in *in vivo* studies. Currently NASH remains one of the few large indications with no approved specific treatment, attracting great interest from a range of players.

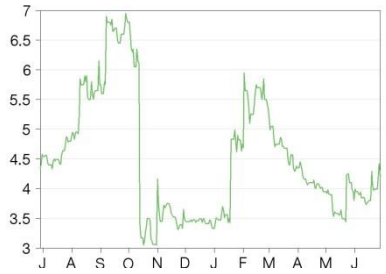
Valuation: rNPV SEK1.5bn or SEK30/share

We value NeuroVive at SEK1.5bn or SEK30/share based on a risk-adjusted NPV model using a 12.5% discount rate, including SEK67.3m net cash at end-Q117. We include five of the company's seven assets. We value the two clinical stage assets, NeuroSTAT and KL1333, at SEK299m and SEK441m respectively, which comprises 50% of the total rNPV. NeuroVive's initiation of the proof-of-concept Phase IIb trial with NeuroSTAT in TBI and initiation of the Phase I study with KL1333 by NeuroVive (Yungjin is already recruiting to its own Phase I) are the near-term R&D events within the next 12-18 months. Meanwhile, potential out-licensing of NV556 could be a substantial trigger for the share price.

29 June 2017

Price	**SEK4.19**
Market cap	**SEK207m**
	SEK8.72/US$
Net cash (SEKm) at end-Q117	67.3
Shares in issue	49.5m
Free float	80%
Code	NVP
Primary exchange	Nasdaq Stockholm
Secondary exchange	OTCQX

Share price performance



%	1m	3m	12m
Abs	2.2	(2.3)	(3.7)
Rel (local)	2.3	(7.2)	(25.2)
52-week high/low	SEK6.95	SEK3.05	

Business description

NeuroVive Pharmaceutical is a Swedish biopharmaceutical company with deep expertise in mitochondrial medicine. It has a diversified portfolio in terms of indications and employs a dual strategy: it develops a core portfolio of assets for orphan diseases and seeks to out-license proprietary products for non-orphan indications. NeuroSTAT (neurotrauma, Phase IIb ready) and KL1333 (genetic mitochondrial diseases) are the most advanced assets.

Next events

Q217 results	17 August 2017
NeuroVive initiation of KL1333 Phase I	H118
Lead candidate drug selection in NVP015 programme	H217

Analyst

Jonas Peciulis +44 (0)20 3077 5728

healthcare@edisongroup.com

Edison profile page

Investment summary

Description: Decades of mitochondrial medicine experience

NeuroVive is a Swedish biopharmaceutical company with deep expertise in mitochondrial medicine. The company traces its roots to when the co-founder and current CSO Eskil Elmér discovered with his colleagues that ciclosporin A has potent neuroprotection properties. Impaired mitochondrial function has been shown to have a profound effect on secondary cell injury. NeuroVive was founded in 2000 (then called NeuroPharma) and has maintained its focus on mitochondrial medicine ever since. As of end-2016, NeuroVive employed 15 full-time and eight part-time employees; however, the company emphasises its wide network of academic partners and R&D organisations, which allows for innovative and flexible studies to advance the R&D programmes. NeuroVive owns 82.5% of Hong Kong-based subsidiary NeuroVive Pharmaceutical Asia and has a 10% equity stake in UK-based, privately owned Isomerase Therapeutics (acquired in 2016), a drug discovery expert within the area of microbial natural products. Isomerase helped NeuroVive to expand its pipeline with novel mechanism of action compounds, including new generation succinate prodrugs and sanglifehrin-based cyclophilin inhibitors. NeuroVive shares were listed on Nasdaq Stockholm in April 2013. In May 2016, NeuroVive raised SEK77m net. The company's shares are also trading on the US OTC Markets Group's OTCQX segment.

Valuation: Mix of preclinical and clinical assets underpin rNPV

We value NeuroVive at SEK1.5bn or SEK30/share based on risk-adjusted NPV model using a 12.5% discount rate, including SEK67.3m net cash at end-Q117. We include five of the company's seven assets, but for the time being exclude NVP025 and NVP022 as so far NeuroVive has disclosed the existence of these assets, but is yet to provide more details about the mechanism of action or *in vivo* proof-of-concept data. NeuroVive's strategy is to develop core products internally and out-license non-core projects, which is reflected by assumed licensing deals in our model.

Financials: Funded to several R&D events

NeuroVive had cash and cash equivalents of SEK67.3m at the end of Q117 compared to SEK93.3m at the beginning of 2017 and was debt free. Total operating expenses in Q117 were SEK21.2m, but the one-off administrative expenses associated with the disposal of a subsidiary were SEK11.0m; we therefore expect quarterly cash burn to decrease in Q217. Our total operating expenses estimate for 2017 is SEK62.3m; as a result we expect a cash positon of SEK13.8m by end-2017. NeuroVive does not provide guidance, but according to our model and based on current R&D plans, the cash reach is into Q118, past several R&D events. Our model implies an additional funding need of SEK416m over the period 2018-20; however, this is the case if NeuroVive runs its R&D plans full speed. The company may scale back the number of parallel studies or increase, depending on the availability of capital. Notably, we do not take into account revenues from any potential licensing-related income in our financial forecasts.

Sensitivities: Typical biotech risks apply

NeuroVive is subject to the usual risks associated with drug development. The company is mainly an early stage drug developer, therefore in the foreseeable future the value creation will depend on successful R&D progress and any potential partnering activities. The biggest near-term development sensitivity is related to the most advanced products – NeuroSTAT and KL1333. Currently NeuroVive is in an arbitration dispute with CicloMulsion regarding the royalty payments as per the original licensing deal, when NeuroVive in-licensed CicloMulsion technology, NeuroVive has discontinued the CicloMulsion product since then and, so far, the outcome in the arbitration case is uncertain.

Outlook: Diversifying portfolio by leveraging mitochondrial medicine expertise

NeuroVive specialises in mitochondrial medicine, with its most advanced assets in traumatic brain injury and genetic mitochondrial diseases. CEO Erik Kinnman was appointed in March 2016 and has since reshaped the company's strategy, employing a dual business model:

- NeuroVive seeks to create value in the long run by advancing assets for orphan indications through to commercialisation. Orphan designation typically allows for a more streamlined R&D process with smaller scale clinical trials. The portfolio includes NeuroSTAT for TBI and three projects for genetic mitochondrial diseases: KL1333 and NVP015 for various genetic mitochondrial diseases; and NVP025 for mitochondrial myopathy.
- NeuroVive seeks to secure short-term income in the form of upfronts and milestone payments by out-licensing assets in the pre-clinical stage. These assets target larger indications and are therefore likely to require significant R&D investments, but also are of interest to larger pharma companies (Exhibit 1). Currently the portfolio includes NV556 and NVP022 for NASH and NVP024 for HCC.

At first glance, NeuroVive appears to have a rather diversified portfolio in terms of indications; however, all the assets are based on improving mitochondrial metabolism and function. This puts NeuroVive among the very few experts in mitochondrial medicine in the industry, in our view. Central to NeuroVive's strategy is maintaining a network of KOLs, academic institutions and research organisations, which help to run innovative design and cost-effective studies.

Exhibit 1: NeuroVive's R&D pipeline, current status and upcoming newsflow

Product	Stage	Indication	Comments and upcoming events
Projects for internal development			
NeuroSTAT ■ novel ciclosporin A formulation ■ -i/v; acute treatment	Phase IIb ready	TBI	In May 2017, reported a positive outcome in the Phase IIa trial with TBI patients and an experimental study. **Currently preparing for proof-of-concept Phase IIb study**. Orphan drug designation in the US with market exclusivity for seven years for moderate to severe TBI. The formulation technology was in-licensed from CicloMulsion.
KL1333 ■ NQO1 and NAD+ modulator ■ oral; chronic treatment	Phase I	Various genetic mitochondrial diseases	In-licensed from Yungjin Pharm (South Korea) in May 2017. Yungjin retained rights to Korea and Japan and received approval to initiate Phase I in healthy volunteers. **NeuroVive is preparing for Phase I, with expected initiation in H118. Yungjin has initiated a Phase I clinical trial in June 2017.** NeuroVive plans to seek orphan disease designation.
NVP015 ■ succinate prodrug ■ i/v; acute treatment during energy crisis	Lead selection	Various genetic mitochondrial diseases	In January 2017, NeuroVive signed a preclinical collaboration agreement with KOLs at the Children's Hospital of Philadelphia (CHOP), where the most promising compounds are being tested in various experimental models with the **goal to select a lead candidate in H217**. NeuroVive plans to seek orphan disease designation.
NVP025 ■ novel sangamide class cyclophilin inhibitor ■ -oral; chronic treatment	Lead identification	Mitochondrial myopathy	In January 2017, NeuroVive signed an agreement with KOLs at Karolinska Institutet in Sweden to study NV556 in preclinical models in mitochondrial myopathy. NV556 is being used as a model compound, but NeuroVive is working on a dedicated asset for this indication, NVP025. The Karolinska Institutet research team previously published results showing that another cyclophilin inhibitor, ciclosporin, prevented muscle fibre weakness in an experimental model of mitochondrial myopathy. **The company expects to select a lead drug candidate in 2018** and plans to seek orphan disease designation.
Projects for out-licensing			
NV556 ■ sangamide class cyclophilin inhibitor ■ oral; chronic treatment	Drug candidate selected	NASH	In April 2017, NeuroVive released *in vivo* proof-of-concept data from a second pre-clinical model confirming that NV556 has antifibrotic effects. Currently NeuroVive is finalising the data package with the goal to **start out-licensing activities in mid-2017.**
NVP022 ■ novel undisclosed compound	Lead identification	NASH	NeuroVive initiated another programme targeting NASH, in which currently the company is testing model compounds. The details of the technology remain undisclosed, but NVP022 has a completely different mode of action to NV556 and can be used as an alternative or complementary therapy for NASH. **The company expects to select a lead drug candidate in 2018.**
NVP024 ■ sangamide class cyclophilin inhibitor ■ oral	Lead identification	HCC	In February 2017, NeuroVive presented *in vitro* and *in vivo* proof-of-concept data showing efficacy in HCC. Currently NeuroVive continues preclinical development and **expects to select a lead drug candidate in the NVP024 programme in 2018, which subsequently should be out-licensed.**

Source: Edison Investment Research. Notes: TBI – traumatic brain injury; NASH – non-alcoholic steatohepatitis; HCC – hepatocellular carcinoma.

What is a mitochondrion?

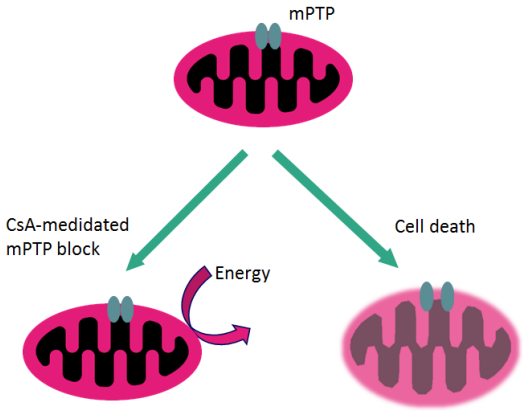
Mitochondrion is a cellular organelle found in large numbers in most cells and is responsible for the majority of energy production needed for cell survival. Strikingly, mitochondria have their own DNA, which codes genes essential for their function. One of the leading evolutionary theories is that mitochondria originated from bacteria, which were engulfed and assimilated by early eukaryotic organisms, which gave birth to advanced life.

"Energy factory", ATP and aerobic vs anaerobic respiration

Normal cell metabolism is powered by the consumption of adenosine triphosphate (ATP), which is the main energy source. Once consumed, ATP is resynthesised from adenosine diphosphate (ADP), which can occur via two main pathways: inside cells via glycolysis and in mitochondria via oxidative phosphorylation. The former is also called anaerobic cellular respiration (oxygen is not needed), and the latter aerobic cellular respiration (oxygen is needed). Aerobic respiration in mitochondria is the main pathway to synthesize ATP, therefore mitochondria can be perceived as the main energy factories in cells. In some cases this pathway cannot ensure the production of needed ATP. Such situations activate the anaerobic pathway, which is much less efficient, ie breaking down one glucose molecule via aerobic pathway produces 38 ATP molecules, while breaking down one glucose molecule via the anaerobic pathway produces only two ATP molecules. By-products of the aerobic pathway are carbon dioxide and water, while by-products of the anaerobic pathway are lactates or lactic acid. Lactate levels can be measured, which demonstrates whether mitochondria are functioning well. For example, during strenuous exercise, the muscles of an untrained individual need to be supplemented with ATP synthesised via the anaerobic pathway, as aerobic pathway is not sufficient. This increases lactic acid and acidity in muscle cells, and causes a disruption of other metabolites, which in turn decreases the efficacy of the anaerobic pathway itself leading to a slowdown of the body, a defence reaction so that extreme exertion would not cause permanent damage to the body.

The so-called "mitochondrial permeability transition phenomenon" has been thought to play a key role in cell death and neurodegeneration. Mitochondrial permeability transition pore (mPTP) is comprised of a complex of mitochondrial proteins located in mitochondrial membranes, which form a mega channel[3] (Exhibit 2). Various disruptive processes, like primary trauma, can lead to the opening of mPTP, which then causes a sudden increase in permeability of mitochondria's membranes, subsequent swelling and bursting, all adding to secondary cellular injury.

Exhibit 2: Schematic representation of mitochondria and mPTP



Source: NeuroVive. Note: CsA – ciclosporin A.

NeuroSTAT for TBI is the most advanced asset

Worldwide, TBI is considered a leading cause of mortality and morbidity in young adults. In the US alone around 1.7 million people sustain TBI each year, of whom c 275k are hospitalised and c 52k die. The US Centers for Disease Control and Prevention estimates that direct and indirect costs associated with TBI are as high as $60bn annually.[1]

TBI pathophysiology

Progression of TBI can be classed into two sequential phases: primary injury resulting from the mechanism of damage (contusions, lacerations, haemorrhages) and secondary injury, which typically is a result of impaired oxygenation of the brain, brain swelling and compression within the skull. The severity of the primary injury determines the prognosis, however, the progress of secondary damage can influence the outcome significantly. It is widely recognised that this secondary injury can be managed; however, despite efforts no new neuroprotective therapies have been approved besides surgery and neuro-intensive care management.[2]

The disruption of brain metabolism after TBI has been extensively studied in preclinical models and researchers have demonstrated that mitochondria are key participants in the pathophysiology of the propagation of the secondary brain injury. Following TBI, mitochondria sustain structural and functional impairments, which leads to metabolic dysfunction and cellular energetic failure. Treatments aimed at restoring mitochondrial function have been shown as a potential neuroprotection strategy, which could complement intensive care treatments of TBI patients. Several mitochondria-targeted therapeutics have been studied over the years and ciclosporin so far is among most promising options.[2]

Typically TBI leads to impaired cerebral blood flow, reduced brain oxygenation, increased lactate production and depletion of brain energy reserve, which in turn leads to opening of mPTP, increase in intracellular Na^+ and Ca^{2+}, mitochondria swelling and rupture, excessive release of neurotransmitters and ultimately the initiation of neuronal cell death.[3] This metabolic crisis is a hallmark of mitochondrial dysfunction after brain trauma, therefore impaired mitochondria metabolism is a primary focus for medical intervention to treat metabolic dysfunction. The goal is to stop the vicious circle that leads to the propagation of the secondary damage. A number of different strategies (ketogenic diet, magnesium, erythropoietin, various translocator protein ligands, Nrf2 activation) were explored with the aim to preserve mitochondrial function and alleviate secondary injury,[2, 4] but no definitive new drugs were established for TBI patients. So far, ciclosporin appears to have accumulated a substantial amount of data supporting its use in this space.[4]

NeuroSTAT vs other ciclosporin formulations

Ciclosporin was one of the earliest immunosuppressant drugs first approved in 1983 for the prevention of organ transplant rejection. Ciclosporin binds to mitochondrial cyclophilin-D, preventing opening of mPTP, and also inhibits interleuking-2 blocking the immune response of natural killer T cells, hence the initial approval for immunosuppression. NeuroVive's founder, Dr Eskil Elmér, who is the current chief scientific officer, was one of the early researchers of ciclosporin's

---

1 Centers for Disease Control and Prevention. *Get the Stats on Traumatic Brain Injury in the United States*. www.cdc.gov/TraumaticBrainInjury accessed on 5 June 2017.

2 Sh. Gajavelli et al. Evidence to support mitochondrial neuroprotection, in severe traumatic brain injury. *Journal of Bioenergetics,* October 2014.

3 R. L. Veech et al. The mitochondrial permeability transition pore provides a key to the diagnosis and treatment of traumatic brain injury. *IUBMB Life.* 2012 February ; 64(2): 203–207.

4 Sh. Yokobori et al. Mitochondrial Neuroprotection in Traumatic Brain Injury: Rationale and Therapeutic Strategies. *CNS & Neurological Disorders - Drug Targets,* 2014, 13.

neuroprotection properties in early 1990s. Later on, ciclosporin's potential ability to alleviate secondary damage after TBI led to multiple preclinical studies and several clinical trials conducted by various research groups. Exhibit 3 lists selected preclinical and two third-party clinical studies.

Ciclosporin was originally developed and brought to market by Sandoz (now part of Novartis) under the brand name Sandimmune as an intravenous formulation. Later an orally administered formulation, Neoral, was launched. In 2016, despite generic competition these brands brought in $515m for Novartis, still in the top 20 products. The intravenous formulation of Sandimmune now constitutes only a small part of Novartis's total sales, but it is still a market leader in this formulation. According to EvaluatePharma, other ciclosporin products, excluding Allergan's Restasis, accounted for sales of just $36m (Restasis is a topical formulation for chronic dry eye, a tear secretion enhancer, $1.5bn in sales in 2016). Ciclosporin, however, is highly hydrophobic and requires a lipophilic solvent for administration, which in Sandimmune's formulation is Cremophor. Cremophor was shown to exert side effects in some cases. Patients receiving Sandimmune have to be monitored for hypersensitivity reactions, which can range from mild to severe anaphylactic reactions (sudden blood pressure drop). In pre-clinical studies intravenous administration of ciclosporin with Cremophor has caused neurotoxicity, cardiotoxicity and nephrotoxicity.[5, 6]

Exhibit 3: Selected third-party preclinical and clinical TBI studies

Study	Model/design	Results
Sullivan et al. 1999	CCI/rodents; ciclosporin administered 15 minutes after the injury. Mitochondrial morphology and function assessed.	Ciclosporin significantly attenuated mitochondrial function: restored mitochondrial membrane potential, reduced intra-mitochondrial calcium levels and reduced reactive oxygen species productions following TBI.
Sullivan et al. 2000	CCI/rodents; as above	Continuous administration of ciclosporin early post injury ameliorated cortical damage with significant reduction in cortical lesion.
Alessandri et al. 2002	Lateral FPI	Improvement in cognitive performance, improved motor deficit.
Kilbaugh et al. 2011	Immature piglets and rodents (paediatric model)	Alleviated mitochondrial dysfunction, preserving bioenergetic state.
Hatton et al. 2008	40 severe TBI patients, prospective, placebo controlled, randomised within eight hours after injury. Four dose ascending cohorts 1.25-5mg/kg/day. Six-month follow up period	No difference in mortality rate. A dose-related improvement in outcome (Glasgow outcome score) in the ciclosporin group at six months was observed. No significant safety issues.
Mazzeo et al. 2008	50 severe TBI patients, prospective, randomised within 12 hours after the injury, placebo controlled. Endpoints: safety, tolerability and pharmacokinetics. Dose: 5mg/kg/day or placebo.	Significantly higher extracellular fluid glucose and pyruvate, which may be evidence of a beneficial effect. Significant increase in cerebral perfusion pressure, which may contribute to neuroprotective effect. Demonstrated ciclosporin penetration into the cerebrospinal fluid after 24 hours of continuous infusion. No significant safety issues, no evidence of immunosuppression.

Source: Yokobori et al, Sh. Gajavelli. Note: CCI – controlled cortical impact; FPI – fluid percussion injury; RNR – rapid non-impact rotational injury.

NeuroSTAT is NeuroVive's innovative, patent protected formulation of ciclosporin without the use of Cremophor or ethanol. The company conducted bioequivalence studies and concluded that the proprietary formulation was bioequivalent, but exhibited fewer adverse reactions than Sandimmune. One anaphylactoid and one anaphylactic reaction (both considered serious) were reported after treatment with Sandimmune.[5] While Sandimmune is a very established drug and physicians have a lot of experience with it, we believe that it will not be used as a substitute for NeuroSTAT. One reason is NeuroSTAT's more favourable safety profile, but it is also well documented that the blood-brain barrier is impaired and more permeable after TBI, which means the excipient Cremophor could be accumulated in higher concentrations in the central nervous system. Neurotoxicity issues reported in preclinical trials may be a deterrent to using Cremophor containing formulations in TBI patients.

[5] J. K. Ehinger et al. Bioequivalence and Tolerability Assessment of a Novel Intravenous Ciclosporin Lipid Emulsion Compared to Branded Ciclosporin in Cremophor EL. *Clin Drug Investig.* 2013 Jan; 33(1): 25–34.

[6] A. J. Windebank. Potential neurotoxicity of the solvent vehicle for ciclosporin. *J Pharmacol Exp Ther.* 1994 Feb;268(2):1051-6.

Safety profile: Short-term usage should minimise side effects

Chronic usage of ciclosporin has been associated with a number of side effects including increased infection rates, nephrotoxicity, hepatotoxicity and neurotoxicity. However, this is an issue mainly for organ transplant patients, who have to take the drug on a regular basis to avoid organ rejection. In the TBI setting, mitochondria are affected very early after the trauma, therefore the treatment should be initiated as soon as possible and maintained for at least two to three days.[4] Several clinical studies, including NeuroVive's, confirmed that no significant side effects emerged after such a short treatment period.

Learning from the past

NeuroVive has had its share of experience with late stage trials failing to meet endpoints. The company in-licensed a formulation patent for CicloMulsion (NeuroSTAT's other code name) in 2004 and advanced the drug candidate in two clinical trials exploring ciclosporin's potential in reperfusion injuries after myocardial infarction (MI) and acute kidney injury (AKI). In October 2016, NeuroVive announced results from an investigator-led Phase II trial, in which CicloMulsion was used to prevent AKI in patients who undergo open heart surgery and are at risk of AKI. The results did not show efficacy, when compared to placebo, and the development was stopped. In August 2015, an investigator-initiated Phase III study explored CicloMulsion's potential to improve outcomes in patients after MI, who are undergoing percutaneous coronary intervention; however, the results did not show significant efficacy either.

In an MI trial, NeuroVive's hypothesis was to limit the so-called reperfusion injury following percutaneous coronary intervention (PCI) treatment. Reperfusion injury is the additional tissue damage due to inflammation and oxidative damage caused when blood supply returns to the tissue after a period of ischemia. Reperfusion injury has been shown in preclinical studies to occur within seconds to a few minutes after restoration of blood flow to the heart. This means that the time window for intervention to treat the reperfusion injury in MI is extremely short and it is a major challenge to develop cell protective therapies for clinical use. In the AKI trial, kidney function impairment was temporary and patients regained normal kidney function during the follow-up period. There was no indication of cell death or persistent kidney injury in the treated patients, which likely meant that there was no opportunity for cell protective treatments, ie no cell death to prevent. In TBI the secondary injury cascade occurs after the trauma and persists for days to weeks, leading to neuronal cell death. Therefore, NeuroSTAT in TBI appears to be a rather different setting when compared to the MI and AKI trials. The injury mechanisms and time windows are very different in different organs; we therefore see no direct read-through from NeuroVive's earlier trials in MI and AKI to NeuroSTAT in TBI patients.

Advancing NeuroSTAT in TBI

So far, NeuroVive has been more successful with NeuroSTAT in TBI, most recently announcing positive findings in the Phase IIa Copenhagen Head Injury Ciclosporin (CHIC) study, which explored NeuroSTAT in severe TBI patients. The trial was conducted at Rigshospitalet in Copenhagen, Denmark, and was complemented by an experimental large animal (piglets) study conducted in collaboration with the University of Pennsylvania, US. The purpose of both studies was to accumulate pharmacokinetic/pharmacodynamic (PK/PD) data, confirm safety and understand what factors are important to design efficacy trials. TBI varies significantly in each case and can be characterised as 'no two similar cases exist'. Therefore defining a target patient population and which measures are the best to evaluate efficacy need careful consideration before going into efficacy trials. So far, NeuroVive has released a limited amount of data, but based on its findings, the company was comfortable stopping the clinical trial earlier than planned in May 2017:

- **The Phase IIa CHIC trial** was an open-label study. It aimed to recruit 20 severe TBI patients and explore PK/PD, safety and exploratory outcomes tests, such as electroencephalography changes. Two dosing regimens were used: 5mg/kg/day and 10mg/kg/day. Preliminary disclosed findings show that dose-dependent concentration levels can be measured in the blood and that NeuroSTAT reaches the CNS (target tissue), meaning that NeuroSTAT passes the blood-brain barrier. The safety profile was confirmed.
- **The experimental pre-clinical study** consisted of three different sub-studies, all of which were randomised. The first two sub-studies confirmed PK/PD and that that NeuroSTAT reaches the CNS in a dose-dependent manner. The third sub-study evaluated several efficacy measures related to mitochondrial function and also MRI scans. The later revealed that the volume of brain injury was reduced by 35% in the NeuroSTAT group when compared to the placebo group five days after TBI. NeuroVive also mentioned that positive changes in brain energy metabolite levels and mitochondrial respiratory function were also observed.

NeuroVive is now preparing for Phase IIb trials, the timing of which is still to be determined. The company mentioned that the next steps are discussion with the regulatory authorities in Europe and the US, finalising the design of the next proof-of-concept Phase IIb study and obtaining an investigational new drug application in the US.

Genetic mitochondrial diseases complete core portfolio

NeuroVive's portfolio for genetic mitochondrial diseases constitutes three projects: KL1333 (Phase I), NVP015 (preclinical: selection of the lead drug candidate) and NVP025 (preclinical: testing model compounds). While KL1333 is the most advanced, it is also the most recent addition after the in-licensing deal with Yungjin Pharm. Both KL1333 and NVP015 target a range of genetic mitochondrial diseases, but have different mechanisms of action, which, notably, are complementary. NVP025 is in the earliest stage and targets mitochondrial myopathy.

Complex diseases, complicated diagnosis, few treatment options

Mitochondrial diseases are a group of conditions with the hallmark symptom of impaired energy production. Varying, often non-specific symptoms and the fact that the syndromes are rare make the diagnosis challenging. Mitochondrial disease is a relatively recent concept first introduced in 1962, when a group of Swedish researchers described a patient case with severe hyper-metabolism and a defect in mitochondrial function.[7] Overall, Approximately 12 in 100,000 people suffer from mitochondrial diseases, which makes this a group of rare conditions.

The diseases may appear at any age and consist of a number of syndromes with clinical presentation varying widely. For example, Chi (2017) lists 78 separate mitochondrial disease entities.[7] Children have more acute onset, while adults have more slowly progressing presentations. Cells with high energy requirements, such as neurons, skeletal and cardiac muscles, are most susceptible to impaired energy metabolism; therefore encephalopathy and myopathy are the most common features of the clinical picture. However, other organs may also be affected, such as eyes, kidneys, endocrine glands, liver, bone marrow and gastrointestinal tract[7] (Exhibit 4).

Different consensus diagnostic criteria are available, which means the lack of standardisation further complicates the diagnosis of mitochondrial diseases. Current diagnostic approach includes clinical, biochemical, radiological tests, pathohistological analysis and DNA-based molecular diagnostic testing[7]. When it comes to treatment options, mainly supportive strategies are available

[7] Ch. Chi. Diagnostic Approach in Infants and Children with Mitochondrial Diseases. *Pediatrics and Neonatology* (2015) 56, 7e18.

and only to only to alleviate the symptoms[8]. To our knowledge Raxone (idebenone, Santhera) is the only approved drug for retinopathy in Leber's hereditary optic neuropathy (LHON). In 2016, the drug brought CHF19m in sales from 15 EU countries growing from CHF4m in 2015, when Santhera rolled out the drug. By end 2016 full reimbursement was achieved only in four countries and the company expected more to follow in 2017. According to consensus, Raxone is estimated to bring in CHF473m by 2022 (EvaluatePharma).

Exhibit 4: Selected mitochondrial diseases and symptoms

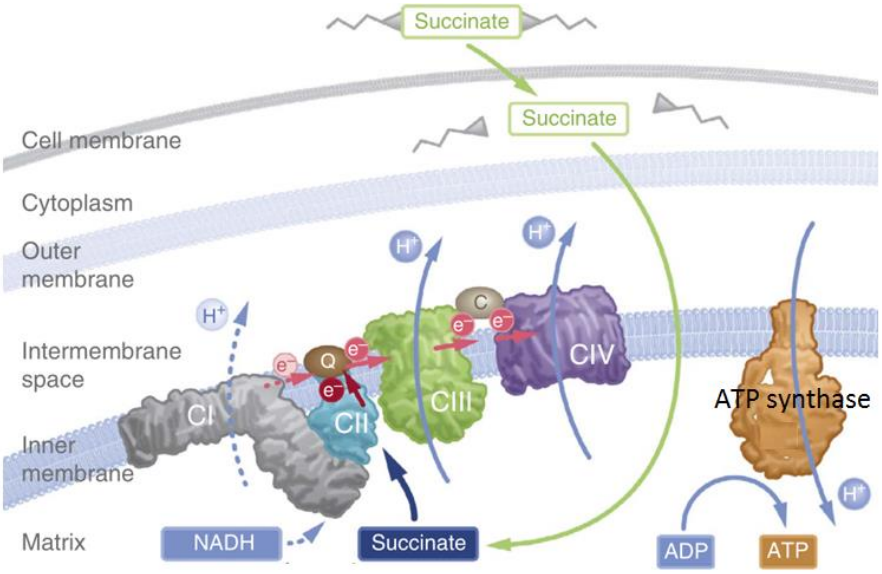
Mitochondrial diseases	Affected organ system	N = 103 (%)
Defined syndromes	Central nervous system	93 (90.3)
■ Leigh syndrome	Ophthalmologic system	37 (35.9)
■ Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)	Failure to thrive	37 (35.9)
■ Alpers' disease	Cardiovascular system	26 (25.2)
■ Lethal infantile mitochondrial disease (LIMM)	Gastrointestinal system	23 (22.3)
■ Pearson's syndrome	Muscular system	22 (21.4)
■ Kearns-Sayre syndrome (KSS)	Hearing system	20 (19.4)
■ Myoclonic epilepsy with ragged-red fibres (MERF)	Hepatic system	19 (18.4)
■ Neuropathy, ataxia, and retinitis pigmentosa (NARP)	Short stature	18 (17.5)
■ Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)	Urologic system	9 (8.7)
■ Chronic progressive external ophthalmoplegia (CPEO)	Endocrinologic system	8 (7.8)
■ Leber's hereditary optic neuropathy (LHON)	Peripheral nervous system	4 (3.9)
■ Barth syndrome	Pancreas	2 (1.9)
Non-categorised syndromes	Hematologic system	1 (1.0)
■ Patients who do not meet specific criteria of recognised syndromes	Psychic	1 (1.0)
	Pulmonary oedema	1 (1.0)

Source: Chi (2015). Note: Right-hand side column summarises frequency rates of organ system symptoms of 103 paediatric patients with various mitochondrial diseases as reported by Chi (2015).

Impaired mitochondrial function results in impaired cellular respiration. Cellular respiration is a complex set of processes with the main end result being energy production for cells. The metabolic pathways can be classified into three main groups: glycolysis (occurs in the cytoplasm), citric acid cycle (also known as Krebs cycle; occurs inside of the mitochondria) and electron transport chain (occurs in the inner membrane of the mitochondria). The latter process is when the majority of energy is produced in a form of ATP. This happens as the electrons transfer their energy to certain proteins (complexes) in the inner membrane, which pump hydrogen ions across the membrane. This flow forms a gradient that allows an enzyme ATP synthase to produce ATP (Exhibit 5). Oxygen is the final electron acceptor (therefore this process is called cellular respiration), which is then combined with hydrogen to produce water.

[8] G. Pfeffer. Treatment for mitochondrial disorders. *Cochrane Database of Systematic Reviews* 2012, Issue 4.

Exhibit 5: Schematic representation of electron transport chain in mitochondria



Source: J. K. Ehinger et al. Notes: CI to CIV – complex I to complex IV, H^+ - hydrogen, e^- - electron flow, Q – coenzyme Q, C – cytochrome, ADP – adenosine diphosphate, ATP – adenosine triphosphate, NADH - nicotinamide adenine dinucleotide.

KL1333: Boosting mitochondrial function

KL1333 is the latest addition to the portfolio. In May 2017, NeuroVive announced that it had in-licensed a Phase I-ready drug candidate, KL1333, from Yungjin Pharm (a diversified South Korean pharmaceutical company). KL1333 targets genetic mitochondrial diseases and is envisioned for chronic oral use in a variety of mitochondrial diseases. Deal terms are summarised in Exhibit 6. Both companies will continue developing the drug, with Yungjin already recruiting to its Phase I trial. The study is a double-blind, placebo-controlled, single-dose, dose-escalation trial and will recruit 60 healthy volunteers. The primary outcome is safety/tolerability, while PK/PD are secondary endpoints.

Exhibit 6: NeuroVive and Yungjin Pharm licensing deal

NeuroVive received	Price
NeuroVive received exclusive global rights to KL1333, excluding South Korea and Japan, where Yungjin Pharm retained all rights. Both companies will develop KL1333 in their respective territories. Yungjin Pharm has received an approval for investigational new drug application in South Korea. The clinical study started recruiting in June 2017.	NeuroVive will pay: ■ an upfront of $1m upon finalising the deal, ■ $1m one year after the signing, ■ $1m after the completion of a successful Phase I trial by Yungjin, ■ development milestones of $12m in total, ■ $42m upon marketing authorisation and reimbursement approval, ■ sales-related milestone payments, and ■ tiered, single to low double-digit royalties on net sales.

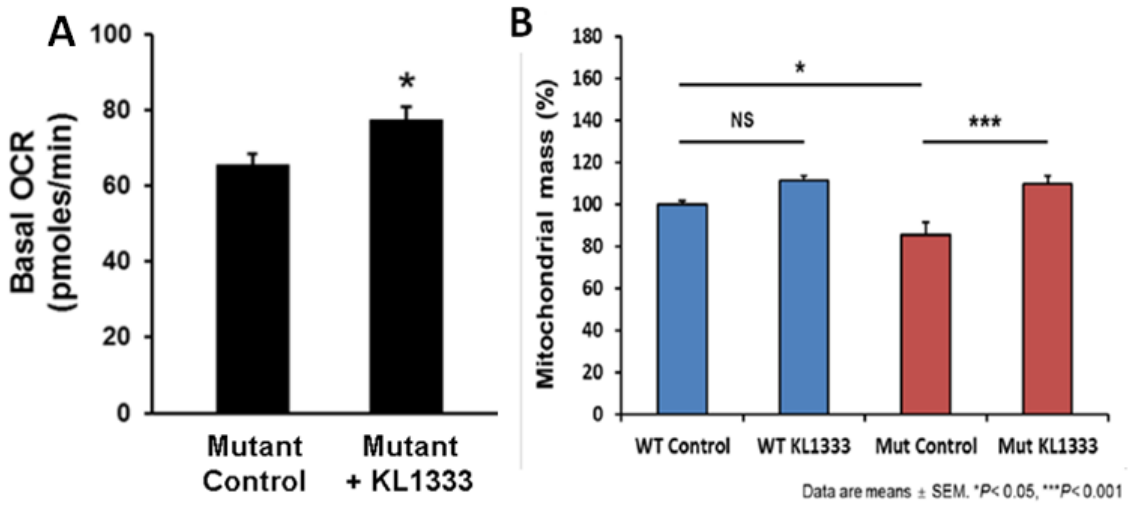
Source: NeuroVive Pharmaceutical

KL1333 was originally developed by KT&G Life Sciences, which was acquired by Yungjin in January 2017. KL1333 is a novel NAD+ modulator, which interacts with NAD(P)H:quinone oxidoreductase 1 (NQO1) as a substrate and regulates the levels of nicotinamide adenine dinucleotide (NAD+), which is a coenzyme necessary for many cellular metabolism processes. In preclinical studies, KL1333 was shown to exert long-lasting positive effects on energy metabolism:

- increased mitochondrial energy production (Exhibit 7A) without production of lactates (ie allows to avoid anaerobic respiration),
- directly transferred energy from the cell's cytoplasm to the last parts of the mitochondrial electron transport chain bypassing the most common sites of dysfunctions,

- increased NAD+ enhances the cells' production of new mitochondria (mitochondrial biogenesis; Exhibit 7B), and
- prevented the formation of free radicals and improved antioxidant defence mechanisms in mitochondria by increasing glutathione levels.

Exhibit 7: KL1333 in wild type and MELAS patient-derived fibroblasts



Source: Seo et al, UMDF Mitochondrial Medicine Meeting 2016. Notes: OCR – oxygen consumption rate (mitochondrial activity); WT – "wild type" or "normal" fibroblasts, mutant – MELAS fibroblasts.

In June 2017, Yungjin announced the start of its Phase I trial in healthy volunteers. Currently NeuroVive is also preparing for its own Phase I study, with an expected initiation in H118. The trial design or which mitochondrial disease indications will be targeted is not yet specified. NeuroVive also plans to seek orphan disease designation.

NPV015: Targeting complex I deficiency

Mitochondrial complex I deficiency is the most prevalent defect in the respiratory chain in paediatric mitochondrial diseases (around 50%) and clinically presents as a group of syndromes, which can be caused by changes in either nuclear or mitochondrial genome.[9] It is often a serious or even fatal syndrome. Complex I is the entry point to the electron transport chain for energy carriers (NADH). In case of complex I defect, the whole cellular respiratory process becomes disrupted. However, complex II also derives electrons from a substrate succinate (Exhibit 5). NeuroVive hypothesised that supplementation of succinate could replenish the electron transport chain with electrons, in such a way bypassing the complex I defect.

Succinate cannot easily pass through the cell's membrane and therefore biological availability is limited if supplemented externally. NeuroVive's NPV015 is a programme that explores several succinate prodrugs that can pass through a cell's membrane and are subsequently metabolised to succinate, which in turn can be used by complex II. The company aims to select the lead candidate in H217.

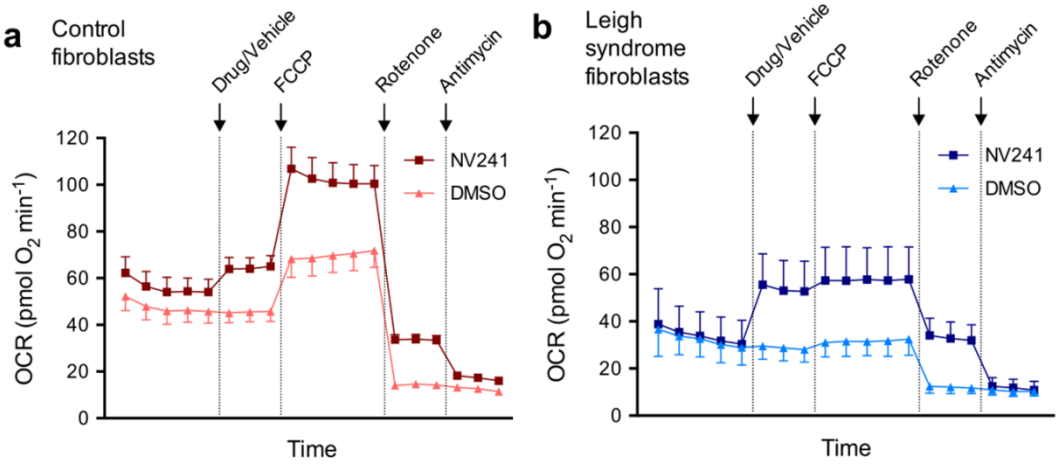
In the discovery programme, NeuroVive and its partners designed more than 50 different prodrugs (a prodrug turns into a drug once metabolised) of succinate and evaluated their ability to pass through the cell membrane and aid mitochondrial respiration with defective complex I. The accumulated data was published in *Nature Communications* in August 2016 (J K Ehinger et al.), one of the top science journals worldwide. In preclinical *in vitro* proof-of-concept studies, the researchers evaluated the top three lead compounds, which all showed similar results using healthy

[9] J. K. Ehinger et al. Cell-permeable succinate prodrugs bypass mitochondrial complex I deficiency. *Nat. Commun. 7:12317, 2016.*

human fibroblasts (most common connective tissue cell) and in fibroblasts from patients with Leigh syndrome. Exhibit 8 shows oxygen consumption rate (OCR) in healthy fibroblasts and Leigh syndrome fibroblasts and the dynamics under various conditions:

- Basal OCR was decreased in the Leigh syndrome patient cells compared to control (Exhibit 8a versus 8b). Maximum respiration (achieved with the addition of FCCP, see notes in the chart) rate was decreased similarly.
- After the addition of NeuroVive's succinate prodrug, the OCR in Leigh syndrome patient fibroblasts increased to similar or higher levels of the untreated control cells.
- After inhibiting complex I with rotenone, the remaining respiratory activity was comparable between the cells and responded to succinate prodrug treatment. In the case of Leigh syndrome patient, the OCR rebounded to basal OCR.

Exhibit 8: *In vitro* succinate prodrug treatment of Leigh syndrome patient fibroblasts



Source: JK Ehinger et al. Notes: FCCP – protonophore carbonyl cyanide, a so called uncoupling agent that disrupts ATP synthesis, which results in an increased activity of electron transport chain or maximum respiration. Rotenone – inhibits complex I, ie mimics complex I diseases. Antimycin – complex III inhibitor. DMSO – vehicle used on fibroblast.

In vivo studies are the next step. However, JK Ehinger et al. noted in the article that the tested compounds lacked sufficient blood plasma stability. NeuroVive's top priority was to solve this issue and, according to the latest update, NeuroVive and Isomerase have developed a new series of succinate prodrugs with improved stability in the bloodstream. In January 2017, NeuroVive signed a preclinical collaboration agreement with a KOL at the Children's Hospital of Philadelphia (CHOP), where the most promising compounds are being tested in various experimental models with the goal to select a lead candidate in H217.

NVP025 for mitochondrial myopathy

Mitochondrial myopathies are a subgroup of neuromuscular diseases with hallmark symptoms being muscle weakness, exercise intolerance, fatigue and heart problems, often accompanied by neurological symptoms such as dementia, movement diseases, stroke-like episodes, deafness and blindness. NVP025 is an early programme with the goal to develop a compound that prevents the weakening of muscle fibres associated with these diseases. The NVP025 mechanism of action is different to that of succinate prodrugs or KL1333. As a model compound for initial proof-of-concept studies, NeuroVive is using NV556, a sanglifehrin-based cyclophilin inhibitor originating from NeuroVive's sangamide class of compounds. In January 2017, NeuroVive signed an agreement with Karolinska Institutet to study NV556 in preclinical models in mitochondrial myopathy. The Karolinska Institutet research team previously published results showing that another cyclophilin inhibitor, ciclosporin, prevented muscle fibre weakness in an experimental model of mitochondrial myopathy. The company expects to select a lead drug candidate in 2018 and plans to seek orphan disease designation.

Evolution of mitochondrial technology towards fibrosis and cancer – out-licensing portfolio

More recently NeuroVive has expanded its focus beyond the core portfolio and reported promising preclinical data in NASH and liver cancer (HCC). In line with the company's dual business model, these programmes constitute a portfolio for out-licensing in pre-clinical stage and currently include NV556 and NVP022 for NASH, and NVP024 for HCC.

NASH and NAFLD – a large, untapped market

Non-alcoholic steatohepatitis (NASH) is an advanced form of non-alcoholic fatty liver disease (NAFLD), defined as the presence of hepatic steatosis (fatty degeneration) with inflammation and liver cell injury. NASH can lead to fibrosis, liver cirrhosis and liver failure. According to the British Liver Trust, NAFLD is considered to be the most common liver problem in the Western world with around 20-30% of the population affected, of whom the vast majority are undiagnosed. Most of the affected people have mild liver changes (simple steatosis), but around 10-30% will develop NASH, the most severe form of NAFLD. Around 15% of NASH patients will go on to develop liver cirrhosis. NAFLD is mainly diagnosed when an unrelated test reveals evidence of a fatty liver, but all other conditions are excluded. This and the fact that many cases are asymptomatic mean that NAFLD tends to be underdiagnosed. NASH is an even more complicated condition, since the diagnosis requires liver biopsy, although often patients experience no symptoms. Currently there are no approved specific therapies for NASH, while the treatment is based on correcting underlying conditions, such as obesity or diabetes.

Exhibit 9: NASH background

What is NASH?	NAFLD is the most common form of liver disease in the Western world and represents a spectrum ranging from bland steatosis to NASH. Patients with bland steatosis typically follow a more benign course, whereas with NASH, the fat that accumulates in the liver causes inflammation and scarring, and has the potential to progress to cirrhosis and liver cancer.
Prevalence	NAFLD: 20-30% of the population, NASH: 3-5%. Found in all ethnic and age groups but peaks in fourth decade in men and sixth decade in women.
Symptoms	Usually asymptomatic and diagnosis of exclusion after evaluation for liver enzyme elevation or incidental abdominal imaging. Occasionally, fatigue, right upper abdominal pain and weight loss.
Diagnosis of NASH	Liver function tests. Imaging: ultrasound, CT scan, magnetic resonance imaging. Liver biopsy and histopathology remains the gold standard. No validated biomarker yet. Liver fibrosis staging: 0...4 – from no fibrosis (0) to cirrhosis (4).
Treatment	No drugs specifically licensed for NASH; mainly symptomatic treatment (only vitamin E and pioglitazone have shown beneficial effects in NASH).

Source: Edison Investment Research

About 3-5% of all Americans (c 15m people) suffer from NASH and there are currently no registered treatments. The global market is estimated to exceed $15bn by 2025[10], while Global Data projects the market value at $25bn by 2026. The sheer magnitude of the market and lack of approved therapeutics for NAFLD/NASH underpins the surging interest in this field from biotechs to large pharma companies over recent years. EvaluatePharma lists 98 projects in clinical R&D stage. Moreover, recent deals have reached overall values of up to $1.7bn (Exhibit 10), which is indicative of the interest of pharmaceutical companies in this field. Probably the most prominent asset in this area is obeticholic acid (OCA), a compound developed by Intercept and currently in Phase III development. Although NeuroVive's asset is in a much earlier stage, given the large patient population, we believe there will be plenty of room for a number of players. In addition, a winner will not necessarily be the first to the market, but the drug that demonstrates the best outcome. Also, given NASH's chronic nature, it is likely that treatment combinations will be explored.

[10] S. Cassidy and B. A. Syed. Nonalcoholic steatohepatitis (NASH) drugs market. *Nature Reviews / Drug Discovery*. Vol 15, November 2016.

Exhibit 10: Selected NASH competitors

Product	Company	Status	Comments
Ocaliva	Intercept	Phase III	2,000-patient REGENERATE Phase III study; it will complete interim cohort enrolment in H117. Phase II CONTROL trial readout in 2017.
Elafibranor	Genfit	Phase III	2,000-patient RESOLVE-IT Phase III trial. Complete enrolment in H117. Readout in H218.
IVA337	Inventiva	Phase IIb	225-patient study. Two doses, randomised, placebo-controlled. Primary completion date June 2018.
Cenicriviroc	Tobira (Allergan)	Phase II	Currently in a Phase II study. Due to start a Phase III trial in 2,000 patients in April 2017. Acquired by Allergan for $1.7bn overall value.
Emricasan	Conatus	Phase II	Recruiting patients in two Phase II trials. Data in 2018. Option granted to Novartis for $50m upfront.
Selonsertib	Gilead	Phase II	Data in combination with mAb simtuzumab presented at The Liver Meeting in November 2016 showed regression of fibrosis and improvements in other measures of liver disease.
GS-9674	Gilead	Phase II	Phase I data presented at The Liver Meeting in November 2016. Safety profile and biological activity established. Acquired from Phenex Pharmaceuticals; total deal value $470m.
GS-0976	Gilead	Phase II	Programme acquired from Nimbus Therapeutics. $1.2bn total deal value ($600m paid to date).

Source: Edison Investment Research

NV556 – a novel drug candidate for a large indication with no approved therapeutics

NV556 is a novel cyclophilin inhibitor originating from NeuroVive's sangamide class compounds, which are derivatives of sanglifehrin A. Sanglifehrin A, like ciclosporin A, inhibits cyclophilin but binds to a different site from ciclosporin A. Currently NV556 is in advanced preclinical development and has been optimised for potency, no or minimal off-target inhibition and pharmacokinetics suitable for once-daily dosing[11]. In *in vivo* toxicology studies the compound was well tolerated for 15 weeks.

Originally this programme targeted viral diseases, especially hepatitis B infection and the discovery process was described by Hansson et al. In September 2014, NeuroVive out-licensed NV556 (then NVP018) to OnCore BioPharma (now Arbutus), which aimed to develop the drug candidate for the treatment of chronic Hepatitis B infection. The deal was valued at $150m plus undisclosed royalties. Arbutus subsequently terminated the licence citing its preclinical research did not support further development and the company's willingness to focus its resources on higher priority candidates. In addition to returned rights, NeuroVive also received compound and materials manufactured by Arbutus and valued at around $1.5m.

Using its expertise in cyclophilin inhibition, NeuroVive chose to advance NV556 in NASH, which is an even larger market than hepatitis B infection. According to findings by NeuroVive and other researchers, cyclophilin inhibition in NASH can be beneficial in three ways:

- **Preservation of liver cell mitochondrial integrity** by inhibiting mitochondrial cyclophilin D.
- **Anti-inflammatory effect** in liver fibrosis via CD147 due to cyclophilin A inhibition.
- **Direct antifibrotic effect** on collagen folding and export due to cyclophilin B inhibition.

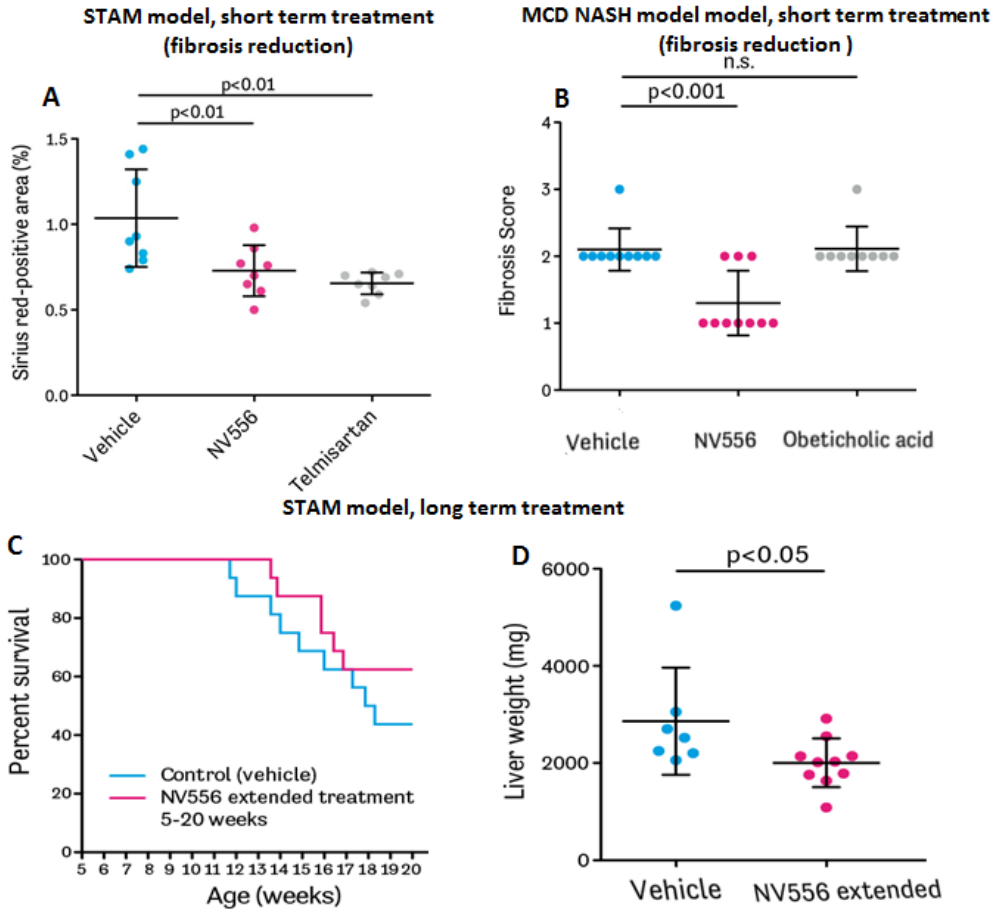
NeuroVive conducted *in vivo* studies with two well-defined mouse models: STAM and methionine and choline deficient (MCD) mice. The conclusions were:

- Treatment with oral NV556 was well tolerated.
- Oral NV556 reduced fibrosis during the NASH phase in both mouse models (Exhibit 11A and 11B).
- In the STAM model metabolic or inflammatory markers were not affected by NV556 after seven weeks of treatment; however, after prolonged treatment period of 15 weeks NV556 significantly attenuated the liver weight increase caused by the tumour burden and trended to prolong overall survival (Exhibit 11C and 11D).

[11] Hansson et al. Bioengineering and Semisynthesis of an Optimized Cyclophilin Inhibitor for Treatment of Chronic Viral Infection. *Chemistry & Biology* 22, 285–292, February 19, 2015.

- In the MCD model, NV556 decreased liver fibrosis and liver enzymes AST and ALT (reflecting reduction in liver cell injury), while other biomarkers were not affected after seven weeks of treatment.

Exhibit 11: NV556 in STAM and MCD mouse models – short term (7 weeks) and long term (15 weeks)



Source: A. Gronberg et al. Anti-fibrotic effect of NV556, a sanglifehrin-based cyclophilin inhibitor, in a preclinical model of non-alcoholic steatohepatitis. Poster presentation, EASL April 2017. Notes: telmisartan – positive control.

In preclinical models, NV556 appears to target specifically fibrosis and prevent liver tumour development, while metabolic and inflammatory biomarkers were not affected in the STAM model, but liver enzymes improved in the MCD model. Liver fibrosis is the primary pathological change that eventually leads to the disruption of liver function. For example, currently the lead drug candidate for NASH in clinical development, obeticholic acid, is in Phase III run by Intercept Pharmaceuticals. Two co-primary endpoints rely on fibrosis: (1) "the proportion of obeticholic acid treated patients relative to placebo achieving at least one stage of liver fibrosis improvement with no worsening of NASH", and (2) "The proportion of Obeticholic Acid treated patients relative to placebo achieving NASH resolution with no worsening of liver fibrosis." Interestingly, NV556 showed fibrosis reduction in the MCD model (Exhibit 11B), while obeticholic acid did not show such an effect. Currently NeuroVive is finalising the data package with the goal to start out-licensing activities in mid-2017.

NVP022 – runner up in NASH

NeuroVive initiated another programme targeting NASH, in which the company is testing model compounds. While the details of the technology remain undisclosed, NVP022 has a completely different mode of action than NV556 and can be used as an alternative or complementary therapy for NASH. In line with NeuroVive's core expertise, NVP022 also targets mitochondrial metabolic pathways in NASH.

NVP024 for HCC

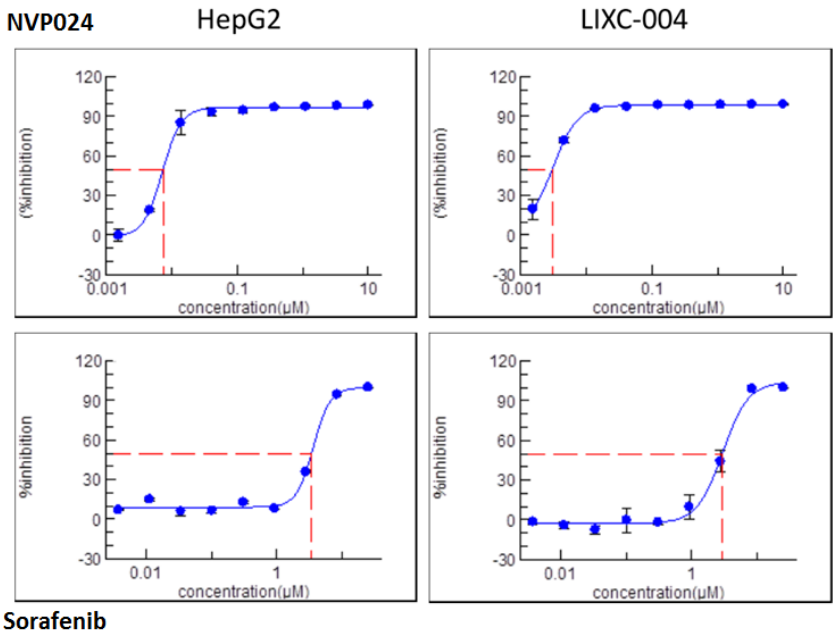
The addition of the HCC indication to NeuroVive's portfolio was an evolution of the company's research in NASH in addition to the well-known feature that cyclophilins are overexpressed in HCC. HCC is closely related to liver cirrhosis caused by an underlying chronic liver disease such as NASH, hepatitis C or B, or alcohol abuse. HCC is now the third leading cause of cancer deaths worldwide with over 500,000 people affected by the disease currently (Medscape). Overall HCC is a difficult condition to treat, with surgical intervention and transplantation yielding best results. HCC is minimally responsive to classical systemic chemotherapy, therefore represents a high unmet need for new treatment options. Sorafenib (Nexavar, Bayer) was the first targeted therapy to demonstrate significant improvement in survival, but not time to symptomatic progression. Sorafenib is also indicated for renal cell carcinoma and thyroid cancer (Medscape). 2016 HCC sales were $789m (EvaluatePharma). More recently, regorafenib (Stivarga, Bayer) has also been approved for HCC, but only for patients failing the treatment with sorafenib.

NVP024 is an early preclinical programme, in which NeuroVive is testing novel model compounds. The mechanism of action is also based on sanglifehrin A and cyclophilin inhibition, but the company is using its second generation compounds. NeuroVive conducted *in vivo* studies, which showed:

- NVP024 is not toxic to normal cells and well tolerated *in vivo*.
- NVP024 showed potency up to 500 times higher than sorafenib (Exhibit 12; IC_{50} data not shown).
- Both oral and intraperitoneal first generation cyclophilin inhibitor demonstrated *in vivo* anticancer activity xenograft model (Exhibit 13).
- NVP024 (second generation) was up to 100 times more active on HCC cell line growth inhibition than first generation NeuroVive's cyclophilin inhibitor.

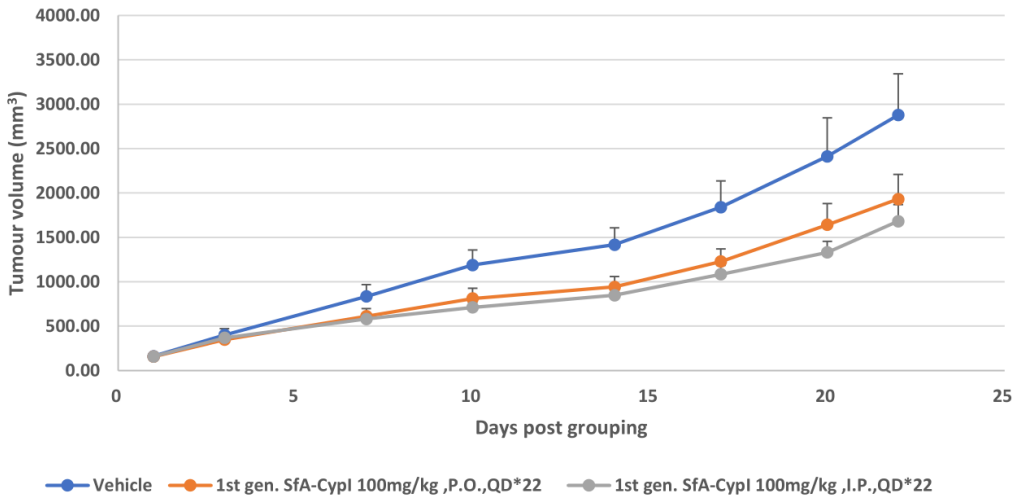
Currently NeuroVive continues preclinical development and expects to select a lead drug candidate in the NVP024 programme in 2018.

Exhibit 12: NVP024 was up to 500 times more potent than sorafenib inhibiting HCC cell lines



Source: M. Tavecchio et al. Preclinical analysis of sanglifehrin-based cyclophilin inhibitors showing potential for treatment of hepatocellular carcinoma. Poster presentation, EASL HCC Summit, February 2017. Notes: HepG2 and LIXC-004 - HCC cell lines.

Exhibit 13: NVP024 predecessor's *in vivo* efficacy; Huh-7 xenograft HCC mouse model



Source: M. Tavecchio et al. Notes: SfA-CypI – NeuroVive's 1st generation of cyclophilin inhibitors derived from sanglifehrin A; P.O. – pre oral; I.P. – intraperitoneal administration.

Sensitivities

NeuroVive is subject to the usual risks associated with drug development, including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks and financing risks. NeuroVive is mainly an early stage drug developer, therefore in the foreseeable future the value creation will depend on successful R&D progress and any potential partnering activities. The biggest near-term development sensitivity is related to the most advanced products – NeuroSTAT and KL1333, which are both expected to be developed in house. The company employs a dual strategy and has a portfolio of assets for out-licensing. Typically, the timing of licensing deals is difficult to forecast. Currently NeuroVive is also in an arbitration dispute with CicloMulsion regarding the royalty payments as per the original licensing deal, when NeuroVive in-licensed CicloMulsion technology, which was used in post-operative acute kidney injury and myocardial infarction studies. NeuroVive has discontinued the development of CicloMulsion. The outcome from the arbitration case is uncertain.

Valuation

We value NeuroVive based on risk-adjusted NPV analysis using a 12.5% discount rate, including $67.3m net cash at end Q117. This corresponds to a value of SEK1.5bn or SEK30/share. Exhibits 14 and 15 provide assumptions and our valuation of assets in specific indications. Only NeuroSTAT and KL1333 are clinical stage projects, while the remaining assets are still in preclinical development. Nevertheless, NeuroVive is an early stage developer, therefore we include both clinical and preclinical stage assets and base our valuation on five of the company's seven assets. We exclude NVP025 (mitochondrial myopathy) and NVP022 (NASH) as NeuroVive is yet to provide more details about the mechanism of action and *in vivo* proof-of-concept data. Exhibit 15 summarises our detailed bottom-up assumptions for NeuroVive's valuation. For the R&D projects we have used standard industry assumptions. Probabilities to reach the market and timelines were selected according to the stage of the project. NeuroVive's strategy is to develop core products internally and out-license non-core projects, which is reflected by assumed licensing deals in our model. For the calculation of target patient groups, we use the US population plus the top five European countries, Benelux, the Nordics and Austria with Switzerland.

For the clinical-stage products, NeuroSTAT and KL1333, we calculate the addressable target populations of 410k (15% of the total TBI cases of c 2.7 million in selected geographies) and 90k (prevalence is calculated at 12.5/100,00[12]) patients respectively in the US and Europe. Assuming 20% market penetration for NeuroSTAT and 10% for KL1333, we arrived at treated populations of 82k and 9k at peak. An assumed 20% penetration for NeuroSTAT is rather conservative, as currently there are no specific neuroprotective therapies approved for TBI patients. Likewise, KL1333 has the potential for substantially higher market penetration than we assume, especially if KL1333 demonstrates a ubiquitous mitochondrial function boosting effect in various mitochondrial diseases. However, KL1333 is in Phase I and the exact patient populations have not been defined yet. Pricing, R&D costs and launch dates are further summarised in Exhibit 14.

Exhibit 14: Assumptions for R&D and commercial projects

Product, stage, indication	Out-licensing assumptions	Comments
NeuroSTAT Proprietary formulation of ciclosporin A ■ Ph IIb ready ■ TBI	Develops standalone 10% COGS 30% S&M activities 10% royalty rate to CicloMulsion	■ Target population: c 410k: moderate to severe patient population chosen (15% of the total TBI cases of c 2.7m in selected geographies*). Assumed 20% market penetration conservative, as there are no approved neuroprotective therapies. ■ Pricing**: $6,000 per treatment course on average: $1,000 bolus injection, $1,000 a day for five days. ■ R&D costs: $5m for proof-of-concept Phase IIb; $30m for Phase III. ■ Launch: 2024; peak sales reached in 6 years. ■ Rights: Last patent expires or exclusivity until 2035. Licensed from CicloMulsion, assumed 5% royalty rate. Orphan drug designation secures market exclusivity for 7 years in the US and 10 years in EU.
KL1333 NQO1 and NAD+ modulator ■ Phase I ready ■ Genetic mitochondrial diseases	Develops standalone 5% COGS 30% S&M 10% royalty rate to Yungjin	■ Target population: c 90k: total genetic mitochondrial disease prevalence is calculated at 12.5/100,000. Assume 10% market penetration as KL1333 is still in Phase I and exact patient populations have not been defined yet. Market penetration could be substantially larger if KL1333 demonstrates ubiquitous effect in various mitochondrial diseases. ■ Pricing**: $80,000 per patient, per year. Chronic oral use. EvaluatePharma 2017 report calculates that average price per patient for an orphan drug was $140k, while median was $84m. We use sales closer to the median, but the range is wide and higher pricing could be secured depending on cost effectiveness. ■ R&D costs: $2m for Phase I, $5m for proof-of-concept Phase IIb; $13m for Phase III (includes adult and paediatric populations). ■ Launch: 2023; peak sales reached in 6 years. ■ Rights: In-licensed from Yungjin Pharm in May 2017, exclusive global rights to KL1333 excl. South Korea and Japan. Last patent expires or exclusivity until 2034. Could secure orphan drug designation (7 years in the US and 10 years in EU).
NVP015 Succinate prodrug ■ Lead candidate selection ■ Complex I diseases	Develops standalone 5% COGS 30% S&M	■ Target population: c 45k: total genetic mitochondrial disease prevalence is calculated at 12.5/100,000; of those, 50% are estimated to have complex I defect. Assume 30% market penetration. ■ Pricing**: $80,000 per acute episode treatment (see KL1333 pricing). Estimated around 1 episode on average per patient per year. ■ R&D costs: $1m finish pre-clinical development, $2m Phase I, $5m for proof-of-concept Phase IIb; $13m for Phase III (includes adult and paediatric populations). ■ Launch: 2023; peak sales reached in 6 years. ■ Rights: Last patent expires or exclusivity until 2034. Could secure orphan drug designation (7 years in the US and 10 years in EU).
NV556 Cyclophilin inhibitor ■ Advanced preclinical development ■ NASH	Licensing deal assumed in 2018, pre-clinical stage Total deal value $300m (average of two preclinical stage deals in 2012 and 2016); upfront assumed $10m.	■ Target population: c 4m; stage 2 and 3 NASH. Assume 10% market penetration. ■ Pricing**: $4,000/patient/year. ■ R&D costs: $0.5m to assumed out-licensing in 2018. ■ Launch: 2026, peak sales reached in 6 years. ■ Rights: Currently wholly owned. Last patent expires or exclusivity until 2032.
NVP024 Cyclophilin inhibitor ■ Testing model compounds ■ Liver cancer (HCC)	Licensing deal assumed in 2019, pre-clinical stage; Total deal value $40m (average of two preclinical stage deals in 2006 and 2010); upfront assumed 10% or $4m.	■ Target population: c 51k: new cases that are not eligible for curative therapy (around 30%) such as surgery. Assumed 30% penetration as still highly unmet need with few options. ■ Pricing*: $30k, within the range of sorafenib and regorafenib. ■ R&D costs: $1m for remaining preclinical studies. ■ Launch: 2029, peak sales reached in 6 years. ■ Rights: Currently wholly owned. Last patent expires or exclusivity until 2032

Source: Edison Investment Research, NeuroVive. Note: *US prevalence calculated using M. Faul et al., prevalence in selected countries in Europe calculated using W. Peeters et al. **Pricing in US; 20% discount applied in Europe. Licensing deal source EvaluatePharma.

[12] G. S. Gorman et al. Prevalence of Nuclear and Mitochondrial DNA Mutations Related to Adult Mitochondrial Disease. *Ann Neurol* 2015;77:753–759.

Exhibit 15: Sum-of-the parts NeuroVive valuation

Product	Launch	Peak sales*	NPV	NPV/share	Probability	rNPV	rNPV/share
		$m	$m	$		$m	$
NeuroSTAT	2024	454	286.6	5.8	15%	34.2	0.7
KL1333	2023	574	553.1	11.2	10%	50.4	1.0
NVP015	2023	875	910.0	18.4	5%	38.5	0.8
NV556	2026	1,716	173.1	3.5	8%	33.4	0.7
NVP024	2029	702	29.6	0.6	3%	5.4	0.1
Net cash			7.7	0.2	100%	7.7	0.2
Valuation			**1,960.1**	**39.6**		**169.5**	**3.4**
			SEKm	**SEK**		**SEKm**	**SEK**
NeuroSTAT			2,507.9	50.7	15%	299.4	6.1
KL1333			4,840.0	97.8	10%	440.8	8.9
NVP015			7,962.5	160.9	5%	336.8	6.8
NV556			1,514.6	30.6	8%	292.0	5.9
NVP024			258.8	5.2	3%	47.0	1.0
Net cash			67.3	1.4	100%	67.3	1.4
Valuation			**17,151.1**	**346.6**		**1,483.4**	**30.0**

Source: Edison Investment Research. Note: WACC = 12.5% for product valuations. Peak sales reached six years after launch.

Exhibit 16: Peak sales sensitivities to pricing and market penetration

NeuroSTAT	Penetration		
Pricing*	5%	20%	50%
5,000	95	378	946
6,000	113	**454**	1,135
7,000	132	530	1,324

NVP015	Penetration		
Pricing*	10%	30%	50%
40,000	146	438	730
80,000	292	**875**	1,459
140,000	511	1,532	2,553

NVP024	Penetration		
Pricing*	10%	30%	50%
20,000	156	468	780
30,000	234	**702**	1,170
40,000	312	936	1,560

KL1333	Penetration		
Pricing*	5%	10%	15%
40,000	144	287	431
80,000	287	**574**	861
140,000	502	1,005	1,507

NV556	Penetration		
Pricing*	5%	10%	15%
2,000	429	858	1,287
4,000	858	**1,716**	2,574
6,000	1,287	2,574	3,861

Source: Edison Investment Research. Pricing in USD.

Financials

The company reported immaterial revenues and an operating loss of SEK21.2m in Q117 compared to SEK10.9m in Q116. External expenses were SEK6.7m in Q117 versus SEK7.4m in Q116 and personnel expenses came in at SEK3.4m (SEK3.3m in Q116). SEK2.6m (included in external expenses) was spent on preclinical development, at a similar level to a year ago. NeuroVive expenses only preclinical R&D costs, while costs related to clinical development are capitalised (SEK1.5m in Q1 versus SEK18.1m in 2016). During Q117 NeuroVive disposed of a Taiwan-based subsidiary, shares were sold to remaining investors for SEK5m, and reacquired the Hong Kong-based subsidiary (which holds the Asian licence rights for NeuroSTAT) together with its partner Foundation Asia Pacific (respective ownership of 82.5% and 17.5%).

NeuroVive had cash and cash equivalents of SEK67.3m at the end of Q117 compared to SEK93.3m at the beginning of 2017 and was debt free. The administrative expenses associated with the disposal of the subsidiary were SEK11.0m (virtually all other expenditure in Q117); we therefore expect quarterly cash burn to decrease further in 2017. Our total operating expenses estimate for 2017 is SEK62.3m, and as a result we expect a cash positon of SEK13.8m by end-2017. NeuroVive does not provide guidance, but according to our model and based on current R&D plans the cash reach is into Q118, past several R&D events. Our estimated need for additional funds in 2018 is around SEK85.7m, which we include as illustrative long-term debt in our financial forecasts, although the company may seek to raise this sooner. Our model implies an additional funding need of SEK416m over the period 2018-20; however, this is the case if NeuroVive runs its R&D plans full speed. The company may scale back the number of parallel studies or increase, depending on the availability of capital. Notably, we do not take into account revenues from any potential licensing-related income in our financial forecasts. In June 2017, NeuroVive received a SEK1m research grant from Swedish innovation agency Vinnova, for developing a new treatment for genetic mitochondrial diseases.

In line with the Yungjin Pharm deal, we include $1m in Q217 and $1m in Q218 in capital expenditure in our cash flow projections with a resulting decrease in cash and increase in long-term intangible assets. The third payment of $1m due upon successful outcome of Yungjin's Phase I is still not certain, therefore we do not include it in capex yet. NeuroVive has a long-term asset valued at SEK13.1m in the balance sheet, which is a 10% equity stake in Isomerase Therapeutics.

Exhibit 17: Financial summary

SEK'000s	2014	2015	2016	2017e	2018e
December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	7,152	2,502	14	0	0
Cost of Sales	0	0	0	0	0
Gross Profit	7,152	2,502	14	0	0
Research and development	(13,738)	(12,200)	(12,000)	(13,000)	(12,000)
EBITDA	(44,372)	(89,066)	(69,868)	(62,135)	(51,268)
Operating Profit (before amort. and except.)	(44,813)	(90,266)	(70,989)	(62,276)	(51,426)
Intangible Amortisation	0	0	0	0	0
Exceptionals	(441)	(1,200)	(1,121)	0	0
Other	(1)	0	0	0	0
Operating Profit	(45,255)	(91,466)	(72,110)	(62,276)	(51,426)
Net Interest	580	665	265	314	0
Profit Before Tax (norm)	(44,233)	(89,601)	(70,724)	(61,962)	(51,426)
Profit Before Tax (reported)	(44,675)	(90,801)	(71,845)	(61,962)	(51,426)
Tax	0	0	0	0	0
Profit After Tax (norm)	(44,234)	(89,601)	(70,724)	(61,962)	(51,426)
Profit After Tax (reported)	(44,675)	(90,801)	(71,845)	(61,962)	(51,426)
Average Number of Shares Outstanding (m)	27.3	30.1	42.0	49.5	49.5
EPS - normalised (SEK)	(1.70)	(3.00)	(1.72)	(1.39)	(1.12)
EPS - normalised and fully diluted (SEK)	(1.70)	(3.00)	(1.72)	(1.39)	(1.12)
EPS - (reported) (SEK)	(1.72)	(3.04)	(1.75)	(1.39)	(1.12)
Dividend per share (SEK)	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed Assets	79,945	75,369	84,645	95,573	143,731
Intangible Assets	79,601	74,904	71,151	82,032	130,157
Tangible Assets	344	316	274	321	354
Investments	0	149	13,220	13,220	13,220
Current Assets	51,323	99,558	94,901	14,846	1,000
Stocks	0	0	0	0	0
Debtors	502	528	0	0	0
Cash	49,698	96,662	93,251	13,846	0
Other	1,123	2,368	1,650	1,000	1,000
Current Liabilities	(23,427)	(20,148)	(12,413)	(13,000)	(13,000)
Creditors	(23,427)	(20,148)	(12,413)	(13,000)	(13,000)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	0	0	0	0	(85,738)
Long term borrowings	0	0	0	0	(85,738)
Other long term liabilities	0	0	0	0	0
Net Assets	107,841	154,779	167,133	97,419	45,993
CASH FLOW					
Operating Cash Flow	(44,171)	(67,885)	(57,614)	(49,746)	(51,268)
Net Interest	539	665	237	314	0
Tax	0	0	0	0	0
Capex	(178)	(245)	(139)	(187)	(190)
Acquisitions/disposals	0	0	0	(11,035)***	0
Financing	76,599	138,406	77,332	0	0
Other	10,421	(23,977)	(23,227)	(18,750)	(48,125)
Dividends	0	0	0	0	0
Net Cash Flow	43,210	46,964	(3,411)	(79,405)	(99,584)
Opening net debt/(cash)	(6,488)	(49,698)	(96,662)	(93,251)	(13,846)
HP finance leases initiated	0	0	0	0	0
Other	0	0	0	0	0
Closing net debt/(cash)	(49,698)	(96,662)	(93,251)	(13,846)	85,738

Source: Edison Investment Research, NeuroVive Pharmaceutical accounts. Note: *Includes only costs related to preclinical development. **Includes capitalised costs related to clinical R&D. ***Related to a disposal of a subsidiary; the net effect of the disposal was neutral on cash flows.

Contact details	Revenue by geography
NeuroVive Pharmaceutical AB Medicon Village 223 81 Lund, Sweden +46 (0) 46 275 62 20 www.neurovive.com	N/A

Management team

Chief Executive Officer: Erik Kinnman	Chief Medical Officer: Magnus Hansson
Erik Kinnman has broad experience from the healthcare 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 include clinical and business development, business strategy and investor relations. In addition, he holds an executive MBA from the Stockholm School of Economics and has a PhD from the Karolinska Institutet. Mr Kinnman has trained as a medical doctor.	Magnus Hansson has extensive experience in the area of mitochondrial medicine. He previously served as a senior scientist at NeuroVive since 2008 and as a consultant physician and associate professor in medical imaging and physiology at Skåne University Hospital, Sweden. Mr Hansson holds a PhD in experimental brain research from Lund University, Sweden and has authored more than 30 scientific publications and 10 patent applications.
Chief Financial Officer: Catharina Jz Johansson	**Chief Scientific Officer: Eskil Elmér**
Catharina Jz Johansson has experience working at multinational medtech companies including as interim CFO for medical device company Cellavision, which is listed on Nasdaq Stockholm, and accounting manager for Bong and Alfa Laval Europe. Ms Johansson holds an MSc in business and economics.	Eskil Elmér is associate professor of experimental neurology at Lund University, Sweden, and group leader of the Mitochondrial Medicine lab at the department of Clinical Neurophysiology. Mr Elmér is patentee and co-founder of both Maas Biolab and NeuroVive Pharmaceutical, and CSO of NeuroVive. In addition, Mr Elmér is a practising physician in the department of clinical neurophysiology at Skåne University Hospital in Lund, Sweden.

Principal shareholders	(%)
Baulos Capital Belgium	8.84
Maas Biolab	7.83
Avanza Pension Forsakring	7.13
Nordnet Pension Forsakring	1.51
Handelsbanken	1.08
Elmer Eskil	0.87
Keep Marcus	0.86

Companies named in this report

Novartis, Arbutus Biopharma, Yungjin Pharm, Intercept, Genfit, Inventiva, Tobira, Conatus, Gilead, Bayer

Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
295 Madison Avenue, 18th Floor
10017, New York
US

Sydney +61 (0)2 8249 8342
Level 12, Office 1205
95 Pitt Street, Sydney
NSW 2000, Australia