

# NeuroVive Pharmaceutical

Company outlook

## Licensing deal and R&D pipeline progress

On 18 June 2018, NeuroVive [announced](#) that it had out-licensed a subset of compounds from its NVP015 programme (succinate prodrugs) to BridgeBio, a private biotech based in California, targeting Leber's Hereditary Optic Neuropathy (LHON) under new subsidiary Fortify Therapeutics. The upfront payment was limited, but the total deal value could reach \$60m. NeuroVive is about to initiate a Phase Ib trial with the second lead drug candidate, KL1333 (NAD<sup>+</sup> modulator), while both the EMA and FDA have provided positive views on the lead NeuroSTAT Phase IIb programme (TBI). We value NeuroVive at SEK1.64bn or SEK17.9/share.

| Year end | Revenue (SEKm) | PBT* (SEKm) | EPS* (SEK) | DPS (SEK) | P/E (x) | Yield (%) |
|----------|----------------|-------------|------------|-----------|---------|-----------|
| 12/16    | 0.0            | (70.7)      | (1.7)      | 0.0       | N/A     | N/A       |
| 12/17    | 0.6            | (70.1)      | (1.5)      | 0.0       | N/A     | N/A       |
| 12/18e   | 1.5            | (83.0)      | (1.2)      | 0.0       | N/A     | N/A       |
| 12/19e   | 1.5            | (130.1)     | (1.5)      | 0.0       | N/A     | N/A       |

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

## R&D events in H218/H119

The near-term R&D events are related to NeuroVive's core portfolio of assets and include initiation of its Phase Ib study with KL1333 for mitochondrial diseases (H218), initiation of the Phase IIb trial with NeuroSTAT for TBI and the results of the first part of the Phase Ib study with KL1333 (potentially in H119). The recent fund-raise (SEK78.5m) will be used in funding these trials, but further capital will likely be required to ramp up the NeuroSTAT Phase IIb trial, a proof-of-concept study in traumatic brain injury where there is no approved, specific therapeutic treatment (management indicates this could be done via non-dilutive or partnership funding). Out-licensing common disease preclinical assets in the non-core portfolio, especially NV556 (NASH), could be a catalyst and a source of cash.

## Positive news in the mitochondrial medicine space

NeuroVive's partner, Yungjin Pharm, reported positive Phase I results with KL1333 in May 2018. We believe this diminishes the likelihood of negative surprises from NeuroVive's own Phase Ib trial with KL1333. Other recent industry news includes Stealth BioTherapeutics raising \$100m in June 2018 in a private round to develop elamipretide. This drug also improves the electron transport chain function, so the next data readout from its Phase III MMPOWER-3 trial in primary mitochondrial myopathy (Q119) could also be a catalyst for NeuroVive's. In addition, Astellas Pharma acquired Mitobridge (Phase I) in November 2017 for \$225m upfront and another \$225m in milestones, suggesting M&A interest from pharma in the space. Finally, the valuation of NASDAQ-listed Reata at \$2.1bn after the recent \$115m raise indicates capital markets' appreciation for mitochondrial medicine companies.

## Valuation: Marginally up to SEK1.64bn or SEK17.9/sh

Our updated valuation of NeuroVive is largely similar at SEK1.64bn or SEK17.9/share compared to SEK1.62bn or SEK17.7/share previously. The positive effect of rolling our model forward was partially offset by a lower net cash position. We maintain the R&D assumptions set out in our [initiation](#) report.

## Pharma & biotech

5 October 2018

**Price** **SEK4.06**

**Market cap** **SEK372m**

SEK8.83/US\$

Net cash (SEKm) at 30 June 2018 51.9

Shares in issue 91.6m

Free float 98%

Code NVP

Primary exchange NASDAQ Stockholm

Secondary exchange OTCQX

## Share price performance



% 1m 3m 12m

Abs (1.6) (5.7) 8.9

Rel (local) (2.1) (13.0) 5.5

52-week high/low SEK5.6 SEK2.1

## 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

Start of Phase Ib with KL1333 (MAD EU) H218

Initiation of NeuroSTAT Phase IIb 2019

News about assets in licensing portfolio H218/H119

## Analysts

Jonas Peculius +44 (0)20 3077 5728

Alice Nettleton +44 (0)20 3077 5700

[healthcare@edisongroup.com](mailto:healthcare@edisongroup.com)

[Edison profile page](#)

**NeuroVive Pharmaceutical is a research client of Edison Investment Research Limited**

## Investment summary

---

### **Description: Targeting mitochondria to treat a range of diseases**

NeuroVive is a global biopharma company based in Sweden with broad expertise in mitochondrial medicine. The company traces its roots to the discovery by co-founder and current CSO Eskil Elmér and his colleagues that ciclosporin 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 since maintained its focus on mitochondrial medicine. As of end-H118, it employed around 10 employees. However, the company emphasises its wide network of academic partners and R&D organisations, which facilitates innovative and flexible studies to advance the R&D programmes. NeuroVive owns 82.5% of the 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 in 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. The company's shares also trade on the US OTC Markets Group's OTCQX segment.

### **Valuation: Mix of preclinical and clinical assets underpin rNPV**

We value NeuroVive at SEK1.64bn or SEK17.9/share, based on a risk-adjusted NPV model using a 12.5% discount rate, including SEK51.9m net cash at end-Q218. We include five of the company's seven programmes/assets, but for the time being exclude the earliest assets NVP025 and NVP022 as NeuroVive is yet to provide more details about the further development plan 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 SEK51.9m at the end of Q218 and was debt free. We have fine-tuned our estimates and expect operating losses of SEK83.7m and SEK130.1m in 2018 and 2019 respectively. NeuroVive does not provide guidance on timing for its cash reach (instead it breaks down the milestones that can be achieved with current cash) but, according to our model and based on current R&D plans, cash reach is into 2019, beyond several R&D events. 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, and value creation in the foreseeable future will therefore 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. NeuroVive continues to be in an arbitration dispute with CicloMulsion AG regarding the royalty payments in the original licensing deal, when NeuroVive in-licensed CicloMulsion technology. NeuroVive subsequently discontinued the CicloMulsion product for cardiovascular indications and, so far, the outcome in the arbitration case remains uncertain.

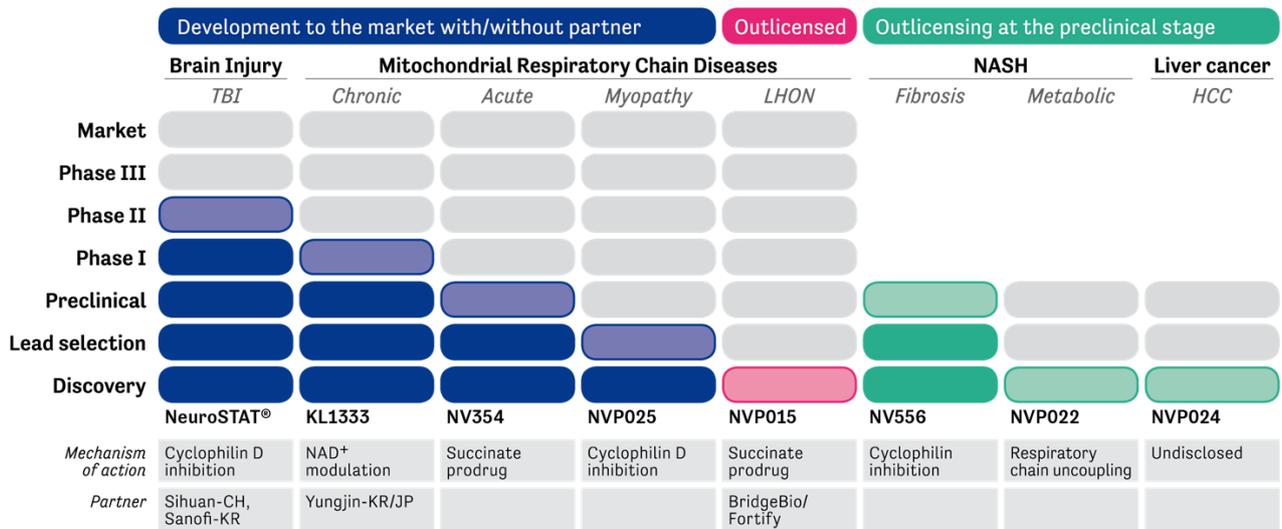
## Outlook: Promising assets for mitochondrial medicine

NeuroVive specialises in mitochondrial medicine, with its most advanced assets in traumatic brain injury and genetic mitochondrial diseases. The company employs a dual business model:

- Orphan drug projects:** 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 programmes for genetic mitochondrial diseases: KL1333 and NVP015 for various genetic mitochondrial diseases, and NVP025 for mitochondrial myopathy. A subset of compounds from the NVP015 programme was recently out-licensed to BridgeBio, while NeuroVive continues internal development with the lead compound from this programme, which has been named NV354.
- Common disease products:** NeuroVive seeks to secure short-term income in the form of upfront and milestone payments by out-licensing assets in the preclinical stage. These assets target larger indications and are therefore likely to require significant R&D investments, but are also of interest to larger pharma companies. Currently, the portfolio includes NV556 and NVP022 for NASH and NVP024 for HCC.

NeuroVive has made recent progress across all of its development programmes (Exhibits 1 and 2).

**Exhibit 1: NeuroVive's R&D pipeline**



Source: NeuroVive

**Exhibit 2: Current status of the development and upcoming newsflow**

| Product                                                                                                                                       | Stage                  | Indication                                | Recent progress and upcoming events                                                                                                                                                                                                                                                                                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------|------------------------|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Projects for internal development</b>                                                                                                      |                        |                                           |                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>NeuroSTAT</b><br>novel ciclosporin formulation<br>-i/v; acute treatment                                                                    | Phase IIb<br>ready     | Traumatic brain injury                    | 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 and EU.                                                                                                                                                                         |
| <b>KL1333</b><br>NAD+ modulator<br>oral; chronic treatment                                                                                    | Phase Ib               | Various genetic<br>mitochondrial diseases | In-licensed from Yungjin Pharm (South Korea) in May 2017. Yungjin retained rights to Korea and Japan and in May 2018 successfully completed a Phase I trial in healthy volunteers. NeuroVive is preparing for a EU Phase Ib trial, with expected initiation in H218. Orphan drug designation by the FDA for inherited mitochondrial respiratory chain disease, and by the EMA for MELAS. |
| <b>NVP354 (from NVP015 programme)</b><br>succinate prodrug<br>i.v. and oral alternative energy source<br>in complex I disorders               | Preclinical            | Various genetic<br>mitochondrial diseases | NVP354 is the lead candidate in the NPV015 programme, which NeuroVive is developing on its own, while a subset of NVP015 compounds was out-licensed to BridgeBio Pharma in June 2018 (see below). The next step is preclinical <i>in vivo</i> results during Q418 and preclinical proof-of-principle.                                                                                    |
| <b>NVP025</b><br>novel sangamide class cyclophilin<br>inhibitor; oral; chronic treatment                                                      | Lead<br>identification | Mitochondrial myopathy                    | Drug class to protect the mitochondria in the muscles from impaired calcium metabolism and slow down muscular dystrophy. Selection of lead candidate ongoing.                                                                                                                                                                                                                            |
| <b>Out-licensed</b>                                                                                                                           |                        |                                           |                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>NVP015</b><br>succinate prodrugs                                                                                                           | Discovery              | Leber's hereditary optic<br>neuropathy    | In June 2018, NeuroVive out-licensed a subset of compounds from its NVP015 programme to BridgeBio Pharma, which will develop a treatment for LHON. Total deal value up to \$60m, of which the majority will come from milestone and royalty payments.                                                                                                                                    |
| <b>Projects for out-licensing</b>                                                                                                             |                        |                                           |                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>NV556</b><br>sangamide class cyclophilin inhibitor<br>oral; chronic treatment                                                              | Preclinical            | NASH – fibrosis                           | In April 2017, NeuroVive released <i>in vivo</i> proof-of-concept data from a second preclinical model confirming that NV556 has antifibrotic effects. Comprehensive preclinical programme completed. A potential near-term opportunity to out-license.                                                                                                                                  |
| <b>NVP022</b><br>protonophore, 'mild' liver-targeted<br>uncoupler                                                                             | Lead<br>identification | NASH – metabolic                          | NeuroVive initiated another programme targeting NASH. New data were presented at the Liver Meeting organised by the American Association for the Study of Liver Diseases (AASLD) in October 2017 that show NVP022 has a mild uncoupling effect specifically in liver cells and that the drug is efficiently transported to the liver. Selection of lead candidate ongoing.               |
| <b>NVP024</b><br>sangamide class cyclophilin inhibitor<br>oral                                                                                | Lead<br>identification | Hepatocellular carcinoma                  | In February 2017, NeuroVive presented <i>in vitro</i> and <i>in vivo</i> proof-of-concept data showing efficacy in HCC. Preclinical development ongoing.                                                                                                                                                                                                                                 |
| Source: Edison Investment Research. Note: TBI – traumatic brain injury; NASH – non-alcoholic steatohepatitis; HCC – hepatocellular carcinoma. |                        |                                           |                                                                                                                                                                                                                                                                                                                                                                                          |

## In-licensed KL1333 quickly became one of lead assets

### Ph Ib to start in H218 following successful Ph I in South Korea

KL1333 is a small molecule in-licensed from Yungjin Pharm (a diversified South Korean pharmaceutical company) in May 2017. It targets genetic mitochondrial diseases and is intended for chronic oral use in a variety of mitochondrial diseases. KL1333 was originally developed by KT&G Life Sciences, which was acquired by Yungjin in January 2017.

Yungjin Pharm is developing the drug in South Korea and Japan, and NeuroVive has rights to the rest of world (more detailed deal terms can be found in our [initiation report](#)). Recently, NeuroVive announced positive results from the [KL1333 Phase I trial](#) in healthy volunteers performed by partner Yungjin Pharm in South Korea (n=60). The researchers found that KL1333 has a favourable PK profile and no serious adverse events were observed.

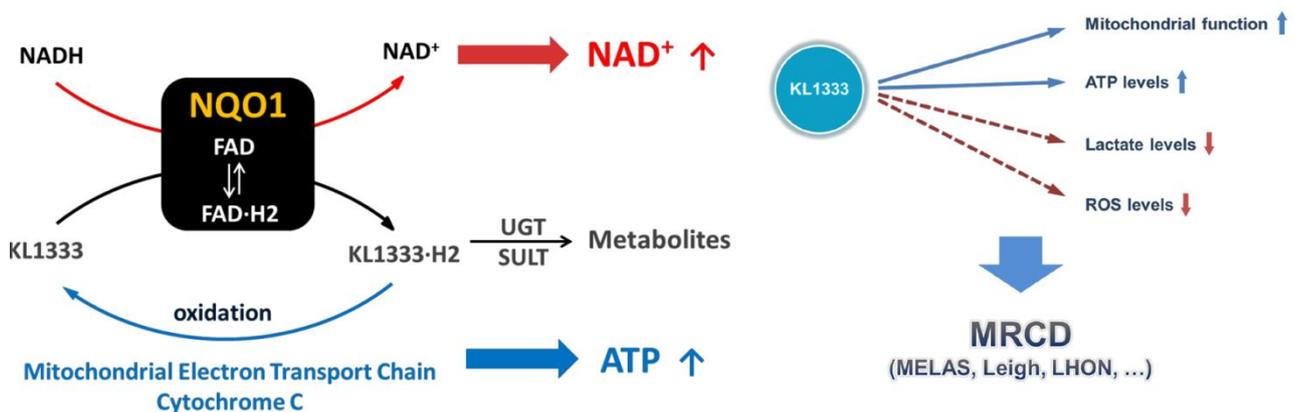
Following this, NeuroVive plans to start its own Phase Ib study in Europe (UK sites) in H218, with results expected in H119. It has not disclosed the full trial design yet, but said that it will be a multiple ascending dose (MAD) trial with KL1333 in healthy volunteers as well as patients with mitochondrial genetic disorders, focusing on MELAS and mitochondrial DNA deletion syndromes (PEO, KSS). According to management, NeuroVive's selected CRO has begun working and the trial is expected to commence in H218.

Exploratory Phase II trial(s) should start within 12–18 months, followed by a confirmatory trial that is expected to be of limited size due to the rarity of the conditions in this orphan drug development space. Open-label studies may also be considered for ultra-rare conditions, which could lead to an early market introduction in 2023, with expansion to the main groups of mitochondrial diseases in subsequent years.

## First peer-reviewed article about KL1333's mechanism of action

KL1333 is a novel NAD<sup>+</sup> modulator, which interacts with NQO1 (NAD(P)H:quinone oxidoreductase 1) as a substrate and regulates the levels of nicotinamide adenine dinucleotide (NAD<sup>+</sup>). NAD<sup>+</sup> is a coenzyme necessary for many cellular metabolism processes including mitochondrial function and production of ATP in the electron transport chain. Increased NAD<sup>+</sup> could therefore improve mitochondrial function in various mitochondrial diseases. NAD<sup>+</sup> can be synthesized *de novo* (from scratch) or via a salvage pathway, which uses compounds acquired via diet (B<sub>3</sub> vitamin niacin). Newer third-party data suggested that NADH conversion to NAD<sup>+</sup> can also be performed by enzymes such as NQO1 ([Gi-Su Oh et al, 2013](#)) (Exhibit 4).

**Exhibit 3: Recently published KL1333 mechanism of action**



Source: [NeuroVive](#)

A recent [peer-reviewed publication](#) from Yungjin researchers described how KL1333 increases intracellular NAD<sup>+</sup> via the enzyme NQO1 in an *in vitro* model of cell cultures taken from MELAS patients. The results include:

- KL1333 treatment of C2C12 and L6 myoblasts increased NAD<sup>+</sup> levels via the action of NQO1, increased energy production and mitochondrial function, and decreased oxidative stress in MELAS fibroblasts;
- KL1333 activated the SIRT1/AMP-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) signalling network, which is involved in mitochondrial biogenesis and function; and
- Compared with idebenone (Raxone, Santhera Pharmaceuticals), KL1333 was a more potent substrate for NQO1 and had a stronger effect on ATP levels in MELAS fibroblasts.

These results suggest that KL1333 could be used to treat MELAS effectively by modulating intracellular NAD<sup>+</sup> levels via NQO1 and may be more effective than idebenone for the treatment of mitochondrial diseases. The indication for KL1333, as an activator of the SIRT1/AMPK/PGC-1α signalling network, could also be extended to age-related and metabolic diseases such as neurodegeneration, diabetes and non-alcoholic fatty liver diseases.

Santhera's idebenone (Raxone, synthetic analogue of Coenzyme Q10), which to our knowledge was the first and remains the only drug approved specifically for mitochondrial disease LHON, also binds to NQO1 and increases NAD<sup>+</sup>. Idebenone is a synthetic analogue of Coenzyme Q10, while

KL1333 is a novel NAD<sup>+</sup> modulator, so differentiated from idebenone. Raxone sales in 2017 were CHF23m, while the consensus estimate for 2024 is CHF628m, which also includes the second indication for which Raxone is being developed, Duchenne muscular dystrophy (EvaluatePharma).

## NeuroSTAT for TBI – preparing for Phase IIb

---

NeuroSTAT is NeuroVive's innovative, patent-protected formulation of ciclosporin without the use of Cremophor or ethanol, hence differentiated from other formulations of ciclosporin in the market (see our [initiation report](#) for detailed analysis of NeuroSTAT's competitive edge). There is still no neuroprotective treatment available for TBI. In May 2017, NeuroVive announced positive findings from both the preclinical and clinical studies it had been conducting at that time and started preparations for the proof-of-concept Phase IIb.

One of these, the Phase IIa Copenhagen Head Injury Ciclosporin (CHIC) study, 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 which factors are important in designing 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 starting efficacy trials.

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), which means it passes the blood-brain barrier. The safety profile was confirmed.

On 4 October 2018, NeuroVive, in collaboration with researchers at the University of Florida released a [biomarker analysis](#) from this study, which appeared to provide initial signs of NeuroSTAT's effect on the secondary brain injury cascade. Four novel biomarkers, GFAP (Glial fibrillary acidic protein), UCH-L1 (Ubiquitin carboxy-terminal hydrolase L1), NF-L (Neurofilament Light) and Tau, were analysed in cerebrospinal fluid samples taken from the severe brain trauma patients in the CHIC study. The results showed that the administration of NeuroSTAT had a positive longitudinal effect on the levels of these biomarkers potentially alleviating secondary brain injury.

This was a non-controlled and open-label study; therefore, no concrete conclusions can be made at this point. On the other hand, it was a Phase IIa study with representative patients and CSF samples were taken on several occasions during the trial, so it represents a good starting point to understand how to best use the biomarkers in upcoming randomised trials, in our view. Having biochemical markers in the trial could lead to better understanding as to which patients NeuroSTAT is best suited to (patient stratification: mild, moderate, severe brain trauma). They also provide a sensitive way to evaluate NeuroSTAT's treatment effect (follow-up) and make prognosis more accurate (outcomes). Detailed data from the CHIC study will be published at a future date.

All four biomarkers analysed in the study come from cutting-edge research, and recently the FDA approved GFAP and UCH-L1 blood tests for diagnosis of mild TBI. Until recently, no biochemical measures existed in practice to evaluate TBI patients; this mainly depended on physical examination and imaging studies. Given that NeuroSTAT's mechanism of action is to limit secondary injury to brain tissue, the availability of biochemical biomarkers adds a new dimension of patient evaluation.

## Experimental study results published

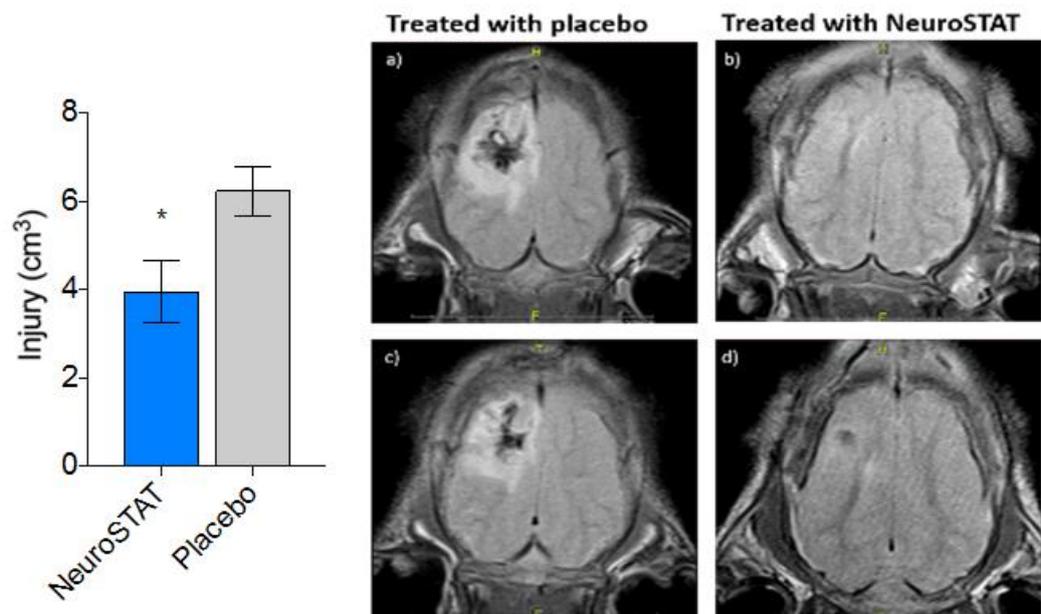
Until recently, only headline findings have been released from the experimental preclinical study with large animals (piglets), but a new [peer-reviewed paper](#) published in the Journal of Neurotrauma in July 2018 described the findings in detail. The importance of this study is that, while it is preclinical, it was carried out in a highly controlled manner similar to clinical trials, ie blinded and placebo controlled. There is a high degree of translatability of findings into humans due to the substantial structural, anatomical similarities between human and pig brains (similar gyral pattern and distribution of grey and white matter). In addition, the outcome was measured using MRI and the upcoming Phase IIb trial is likely to use same method.

The model involved standardised focal cranial impact resulting in a brain injury while the piglets were sedated. The study consisted of three different sub-studies, all of which were randomised. The first two sub-studies established the PK/PD profile, proving that NeuroSTAT reaches the CNS in a dose-dependent manner and established the recommended dose of 20mg/kg/day for the efficacy part of the trial.

The third sub-study evaluated the efficacy of the recommended dose after five days of treatment (randomized, blinded). A total of 37 animals underwent randomisation, of which 24 received the full dose (n=11 NeuroSTAT; and n=13 placebo; the remaining 13 animals did not receive the full dose due to various technical issues, such as failed intubation or anaesthesia). The findings include:

- **The volume of brain injury was reduced by 35% in the NeuroSTAT group** compared to the placebo group five days after TBI (measured with MRI; Exhibit 5).
- **Brain tissue metabolism and mitochondria biomarkers.** The researchers measured various neurotransmitters, neuronal and mitochondrial activity biomarkers, and reported a consistent trend towards positive improvements in brain metabolism and mitochondrial function in the brain tissue around the contusion area.

**Exhibit 4: NeuroSTAT demonstrated a reduced neuronal injury volume of 35% compared to placebo (n=10 NeuroSTAT; n=13 placebo)**



Source: [M. Karlsson et al.](#)

## Next steps: Positive FDA and EMA opinions on Phase IIb design

NeuroVive is making preparations for the Phase IIb trial and has now received positive opinions from both the FDA and EMA. The details of the trial design have not yet been released, but

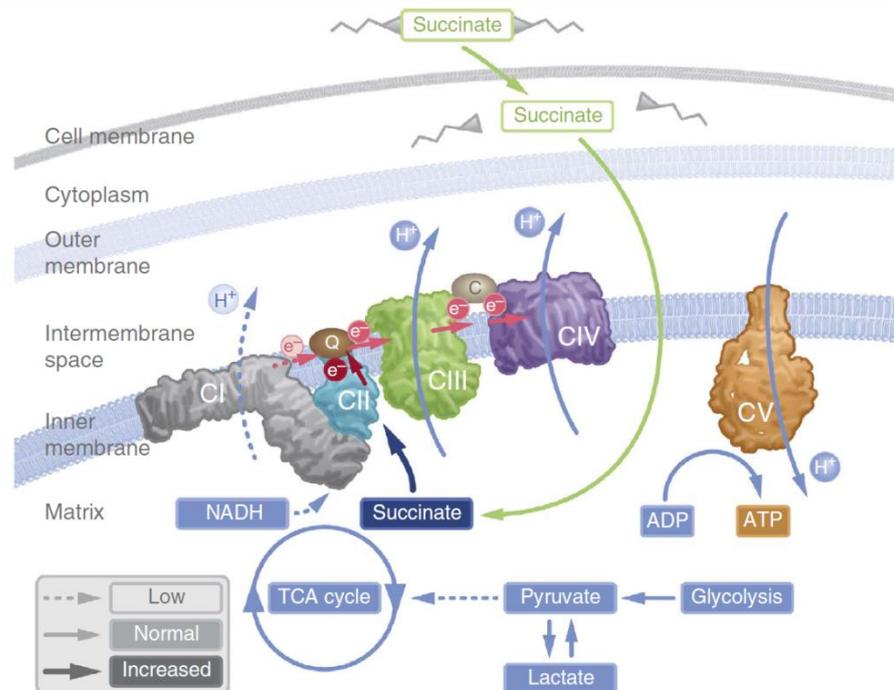
important elements include novel biomarker endpoints and a subpopulation of TBI patients with defined trauma. The latter is especially beneficial for NeuroVive, in our view, as TBI can present a very diverse pathology. The ability to select patients with similar trauma-features greatly improves the consistency of the study. NeuroVive appears to be the first company to adopt a precision medicine approach in the TBI field, also highlighted by the recent partnerships with University of Florida for biomarker development and the TRACK-TBI consortium.

Submission of the IND application is the next step. The precise timing of the start of the study has not been announced yet. We believe NeuroVive's current cash position is sufficient to continue the preparations, but it will need new funds or a partner to start and run the study. Our model includes patient enrolment start in 2019. Enrolment rate is inherently unpredictable in acute treatment studies, but NeuroVive has indicated plans for a multi-centre design in Europe and the US. We expect data readout to be possible by 2021, which can be a substantial value trigger for the programme and enable progress to a confirmatory Phase III trial thereafter.

## NVP015 programme partnered with BridgeBio Pharma

In November 2017, NeuroVive [announced](#) that it had selected the lead compound NV354 for the NVP015 programme, which is focusing on the development of succinate prodrugs targeting complex I deficiency (Exhibit 7). 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 the nuclear or mitochondrial genome.<sup>1</sup> *In vivo* preclinical proof-of-principle results for the lead compound are expected in 2018. See our [initiation](#) for a more detailed background on the NVP015 programme and mitochondrial complex I deficiency.

### Exhibit 5: NVP015 mechanism of action – targeting mitochondrial complex I deficiency by increasing the presence of succinate in the electron transport chain



Source: J. K. Ehinger et al. Note: CI to CIV – complex I to IV, H<sup>+</sup> – hydrogen, e<sup>-</sup> – electron flow, Q – coenzyme Q, C – cytochrome, ADP/ATP – adenosine di(tri)phosphate, NADH – nicotinamide adenine dinucleotide.

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

As part of the NPV015 discovery programme, NeuroVive evaluated many other succinate prodrugs. On 18 June 2018, the company announced that it had out-licensed a subset of these succinate prodrugs to private biotech BridgeBio, based in California, US. BridgeBio plans to develop these compounds for the localized treatment of Leber's Hereditary Optic Neuropathy (LHON) in its new subsidiary Fortify Therapeutics. The total deal value could reach \$60m (a 'limited' amount will be provided upfront for research funding). The disclosed deal terms are shown in Exhibit 8.

#### Exhibit 6: NeuroVive and BridgeBio licensing deal (June 2018)

##### Deal overview

NeuroVive out-licensed a subset of the NVP015 programme to BridgeBio's subsidiary Fortify Therapeutics for the treatment of LHON.

##### Deal terms

- Total deal value up to \$60m. This includes 'limited' research funding, milestone payments and single-digit royalties (dependent on successful development and marketing approval). Fortify Therapeutics to develop 'selected lead compounds derived from NeuroVive's novel NVP015 succinate prodrug programme' into drug candidates for localised treatment of LHON.

Source: NeuroVive Pharmaceutical. Note: LHON = Leber's Hereditary Optic Neuropathy.

BridgeBio has a unique business model which involves acquiring rare genetic disease assets and forming subsidiaries around the assets for further development, a so-called [hub and spoke](#) corporate structure. It now has 19 assets in its subsidiaries. BridgeBio [believes](#) that this new approach to drug development will facilitate focused R&D at the level of each asset. Most recently, in June 2018, it in-licensed Phase II asset infigratinib from Novartis to treat rare cancers, and created a new subsidiary around it, QED Therapeutics, along with a \$65m commitment.

Only a subset of NVP015 chemistry has been out-licensed which, BridgeBio believes, has best potential specifically for local delivery to the eye in LHON patients. The NPV015 programme could potentially cover various different mitochondrial diseases and NeuroVive stressed that it is continuing its internal programme for NVP015 outside local delivery for LHON. We believe the new partnership:

- provides external validation of the science behind the NVP015 programme;
- means that any data generated by the collaboration could read through to other applications of molecules from the NVP015 programme. NeuroVive recently selected a lead compound for mitochondrial diseases, which is expected to reach experimental proof-of-concept in 2018; and
- could generate future revenue for NeuroVive. While this very much depends on the R&D milestones met, at least BridgeBio appears to be a financially strong and committed partner. BridgeBio has already raised c \$200m from just two private rounds, and has the backing of some high-profile investors including KKR, Viking Global Investors, Aisling Capital, Cormorant Asset Management, Perceptive Life Sciences Fund and RA Capital.

The aforementioned Raxone (Santhera Pharmaceuticals) is the only drug currently marketed for LHON. It was approved by the EMA in 2015 and fully reimbursed in eight European countries, but is not yet approved by the FDA. Other late-stage programmes in the LHON space include GS010 (GenSight), an NADH-ubiquinone oxidoreductase chain 4 gene therapy currently in Phase III, and Ocuvia (Stealth BioTherapeutics), which also improves the function of the electron transport chain currently in Phase II. All three of these therapies have orphan drug designation from the EMA and/or FDA.

## NeuroVive's other assets

### NVP025 for mitochondrial myopathy

The NVP025 programme targets mitochondrial myopathies, which 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 of developing 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 and comes from NeuroVive's sangamide class of compounds. In January 2017, NeuroVive signed an agreement with Karolinska Institutet to study a potent sangamide 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.

## Novel NV556 and NVP022 compounds for NASH

NV556 is a novel cyclophilin inhibitor originating from NeuroVive's sangamide class compounds, which are derivatives of sanglifehrin A. Sanglifehrin A, like ciclosporin, inhibits cyclophilin but binds to a different site from ciclosporin. NV556 has a direct antifibrotic mechanism of action in the liver. The asset has undergone extensive preclinical development, has favourable drug-like properties and confirmed antifibrotic effect in several animal models.<sup>2</sup> It is the most advanced asset in the portfolio for out-licensing and NeuroVive aims to license it as soon as possible.

NeuroVive initiated another programme targeting NASH, in which the company is testing model compounds. Few details had been disclosed about NVP022, until the company [reported data](#) at the Liver Meeting organised by the AASLD on 20-24 October 2017. NVP022 is a protonophore, which acts as a 'mild' liver-targeted uncoupler. Protonophores can transport protons across mitochondria membranes and disrupt the proton gradient that is needed to produce ATP in mitochondria. Mitochondrial protonophores have been shown in the past to positively affect NASH and diabetes biomarkers, but had limitations due to the risk of overdosing easily (maximum uncoupling effect). NVP022 is a mild, liver-targeted uncoupler and could have a direct effect on metabolic components of NASH. NeuroVive is currently evaluating compounds with the expectation of selecting a lead compound in 2018.

## 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. 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. See our [initiation](#) report for more detail. Currently, NeuroVive continues early preclinical development.

## 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, and in the foreseeable future value creation will therefore 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. NeuroVive continues to be in an arbitration dispute with CicloMulsion regarding the royalty payments in the original licensing deal. NeuroVive in-licensed CicloMulsion technology, which was used in post-operative acute kidney injury and myocardial

---

<sup>2</sup> 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.

infarction studies, but has discontinued the development of CicloMulsion product for cardiovascular indications. The outcome of the arbitration case remains uncertain.

## Valuation

Our updated valuation of NeuroVive is largely similar at SEK1.64bn or SEK17.9/share compared to our last published SEK1.62bn or SEK17.7/share. As previously, in our valuation we include clinical-stage NeuroSTAT (traumatic brain injury) and KL1333 (genetic mitochondrial disorders) and the advanced preclinical products. We continue to exclude NVP025 (mitochondrial myopathy) and NVP022 (NASH) for the time being, as both are at an early stage. We maintain all our previous valuation assumptions.

We have already included a licensing deal for NVP015 in our model and for the time being we do not make any adjustment to it. This is primarily because our risk-adjusted NPV includes the potential of NVP015 in a broad set of mitochondrial diseases with impaired complex I function. Only a subset of NPV015 chemistry has been out-licensed and only for local treatment of one indication, therefore we consider the potential \$60m in milestones (not risk-adjusted, not discounted) to be already reflected in our calculated, risk-adjusted and discounted present value for the whole NVP015 project of \$33m.

| Exhibit 7: NeuroVive sum-of-the parts valuation |        |                   |                |                |             |              |                 |
|-------------------------------------------------|--------|-------------------|----------------|----------------|-------------|--------------|-----------------|
| Product                                         | Launch | Peak sales* (\$m) | NPV (\$m)      | NPV/share (\$) | Probability | rNPV (\$m)   | rNPV/share (\$) |
| NeuroSTAT                                       | 2024   | 454               | 336.6          | 3.7            | 15%         | 40.2         | 0.4             |
| KL1333                                          | 2023   | 574               | 650.7          | 7.1            | 10%         | 60.3         | 0.7             |
| NVP015                                          | 2024   | 875               | 816.8          | 8.9            | 5%          | 32.9         | 0.4             |
| NV556                                           | 2026   | 1,716             | 200.4          | 2.2            | 8%          | 39.5         | 0.4             |
| NVP024                                          | 2029   | 702               | 34.5           | 0.4            | 3%          | 6.8          | 0.1             |
| Net cash at end-Q218                            |        |                   | 5.9            | 0.1            | 100%        | 5.9          | 0.1             |
| <b>Valuation</b>                                |        |                   | <b>2,045.0</b> | <b>22.3</b>    |             | <b>185.5</b> | <b>2.0</b>      |

|                      | SEKm            | SEK          |      | SEKm           | SEK         |
|----------------------|-----------------|--------------|------|----------------|-------------|
| NeuroSTAT            | 2,972.0         | 32.5         | 15%  | 354.8          | 3.9         |
| KL1333               | 5,745.5         | 62.7         | 10%  | 532.1          | 5.8         |
| NVP015               | 7,212.7         | 78.8         | 5%   | 290.5          | 3.2         |
| NV556                | 1,770.0         | 19.3         | 8%   | 348.5          | 3.8         |
| NVP024               | 304.9           | 3.3          | 3%   | 60.4           | 0.7         |
| Net cash at end-Q218 | 51.9            | 0.6          | 100% | 51.9           | 0.6         |
| <b>Valuation</b>     | <b>18,057.0</b> | <b>197.2</b> |      | <b>1,638.3</b> | <b>17.9</b> |

Source: Edison Investment Research. Note: \*Peak sales reached six years after launch. WACC = 12.5% for product valuations. Number of shares outstanding 91.6m.

## Financials

NeuroVive reported other income of SEK1.5m comprising a research contribution from BridgeBio of SEK876k and a research grant from Vinnova (a Swedish innovation agency) of SEK576k in. Total operating H118 expenses were SEK39.6m, of which SEK23.0m was spent on R&D. Given that NeuroVive plans to initiate two clinical studies in the near term, we expect R&D costs to pick up. Consequently, we maintain our increasing R&D cost estimates of SEK56.6m and SEK103.2m for 2018 and 2019 respectively. We have slightly fine-tuned our other estimates (other operating income/expenses and net financial loss) with minimal net effect on EPS.

Cash at end-Q218 was SEK51.9m which, according to our model, should fund the company's activities into 2019. Further capital will be required to complete the NeuroSTAT Phase IIb trial, but results from the Phase I MAD study with KL1333 should be in H119, which could provide a catalyst for the share price. NeuroVive indicated that it is also working towards securing co-funding for the

Phase IIb NeuroSTAT trial, as well as non-dilutive funding from a potential licensing deal for NV556 (NASH) in H119 and potential further research grants. None of the milestones from the BridgeBio deal is included in our model, which could provide additional runway. Furthermore, warrants exercisable in November 2018 could bring in another SEK37.3m gross in cash (at a strike price of SEK3.80).

**Exhibit 8: Financial summary**

|                                              | SEK'000s | 2016     | 2017     | 2018e    | 2019e     |
|----------------------------------------------|----------|----------|----------|----------|-----------|
| December                                     |          | IFRS     | IFRS     | IFRS     | IFRS      |
| <b>PROFIT &amp; LOSS</b>                     |          |          |          |          |           |
| Revenue                                      |          | 14       | 585      | 1,500    | 1,500     |
| Cost of Sales                                |          | 0        | 0        | 0        | 0         |
| Gross Profit                                 |          | 14       | 585      | 1,500    | 1,500     |
| Research and development                     |          | (12,000) | (27,926) | (56,565) | (103,243) |
| EBITDA                                       |          | (69,868) | (67,897) | (82,615) | (129,980) |
| Operating Profit (before amort. and except.) |          | (70,989) | (69,492) | (70,989) | (69,492)  |
| Intangible Amortisation                      |          | 0        | 0        | 0        | 0         |
| Exceptionals                                 |          | (1,121)  | (1,595)  | (942)    | 0         |
| Other                                        |          | 0        | 56       | 0        | 0         |
| Operating Profit                             |          | (72,110) | (71,031) | (83,699) | (130,133) |
| Net Interest                                 |          | 265      | (571)    | (200)    | 0         |
| Profit Before Tax (norm)                     |          | (70,724) | (70,063) | (82,957) | (130,133) |
| Profit Before Tax (reported)                 |          | (71,845) | (71,602) | (83,899) | (130,133) |
| Tax                                          |          | 0        | 0        | 0        | 0         |
| Profit After Tax (norm)                      |          | (70,724) | (70,007) | (82,957) | (130,133) |
| Profit After Tax (reported)                  |          | (70,240) | (66,727) | (79,899) | (126,133) |
| Average Number of Shares Outstanding (m)     |          | 42.0     | 50.2     | 71.9     | 91.6      |
| EPS - normalised (SEK)                       |          | (1.72)   | (1.49)   | (1.21)   | (1.46)    |
| EPS - normalised & fully diluted (SEK)       |          | (1.72)   | (1.49)   | (1.21)   | (1.46)    |
| EPS - reported (SEK)                         |          | (1.67)   | (1.33)   | (1.11)   | (1.38)    |
| Dividend per share (SEK)                     |          | 0.0      | 0.0      | 0.0      | 0.0       |
| Gross Margin (%)                             |          | 100.0    | 100.0    | 100.0    | 100.0     |
| EBITDA Margin (%)                            |          | N/A      | N/A      | N/A      | N/A       |
| Operating Margin (before GW and except.) (%) |          | N/A      | N/A      | N/A      | N/A       |
| <b>BALANCE SHEET</b>                         |          |          |          |          |           |
| Fixed Assets                                 |          | 84,645   | 87,579   | 87,579   | 87,579    |
| Intangible Assets                            |          | 71,151   | 74,315   | 74,315   | 74,315    |
| Tangible Assets                              |          | 274      | 162      | 162      | 162       |
| Investments                                  |          | 13,220   | 13,102   | 13,102   | 13,102    |
| Current Assets                               |          | 94,901   | 30,560   | 20,452   | 1,568     |
| Stocks                                       |          | 0        | 0        | 0        | 0         |
| Debtors                                      |          | 0        | 0        | 0        | 0         |
| Cash                                         |          | 93,251   | 28,992   | 18,884   | 0         |
| Other                                        |          | 1,650    | 1,568    | 1,568    | 1,568     |
| Current Liabilities                          |          | (12,413) | (14,259) | (14,259) | (14,259)  |
| Creditors                                    |          | (12,413) | (14,259) | (14,259) | (14,259)  |
| Short term borrowings                        |          | 0        | 0        | 0        | 0         |
| Long Term Liabilities                        |          | 0        | 0        | 0        | (111,203) |
| Long term borrowings                         |          | 0        | 0        | 0        | (111,203) |
| Other long term liabilities                  |          | 0        | 0        | 0        | 0         |
| Net Assets                                   |          | 167,133  | 103,880  | 93,772   | (36,315)  |
| <b>CASH FLOW</b>                             |          |          |          |          |           |
| Operating Cash Flow                          |          | (57,614) | (58,039) | (83,557) | (129,980) |
| Net Interest                                 |          | 237      | (84)     | (200)    | 0         |
| Tax                                          |          | 0        | 0        | 0        | 0         |
| Capex                                        |          | (139)    | (40)     | (141)    | (107)     |
| Acquisitions/disposals*                      |          | 0        | (11,035) | 0        | 0         |
| Financing                                    |          | 77,332   | 9,031    | 73,790   | 0         |
| Other                                        |          | (23,227) | (4,092)  | 0        | 0         |
| Dividends                                    |          | 0        | 0        | 0        | 0         |
| Net Cash Flow                                |          | (3,411)  | (64,259) | (10,108) | (130,087) |
| Opening net debt/(cash)                      |          | (96,662) | (93,251) | (28,992) | (18,884)  |
| HP finance leases initiated                  |          | 0        | 0        | 0        | 0         |
| Other                                        |          | 0        | 0        | 0        | 0         |
| Closing net debt/(cash)                      |          | (93,251) | (28,992) | (18,884) | 111,203   |

Source: Source: NeuroVive's accounts, Edison Investment Research. Note: \*Related to the disposal of a subsidiary in 2017, the net effect of which was neutral on cash flows.

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Contact details</b><br>NeuroVive Pharmaceutical AB<br>Medicon Village<br>223 81 Lund,<br>Sweden<br>+46 (0) 46 275 62 20<br><a href="http://www.neurovive.com">www.neurovive.com</a>                                                                                                                                                                                                                                                                                                                                                                                                      | <b>Revenue by geography</b><br>N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Management team</b><br><b>Chief Executive Officer: Erik Kinnman</b><br>Erik Kinnman has broad experience in 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 a PhD from the Karolinska Institutet. Mr Kinnman has trained as a medical doctor. | <b>Chief Medical Officer: Magnus Hansson</b><br>Magnus Hansson has extensive experience in the area of mitochondrial medicine. He has worked 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 written more than 30 scientific publications and 10 patent applications. |
| <b>Chief Financial Officer: Catharina Jz Johansson</b><br>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.                                                                                                                                                                                                                                | <b>Chief Scientific Officer: Eskil Elmér</b><br>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. He 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, Sweden.           |
| <b>Principal shareholders</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Avanza Pension Försäkrings AB                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 14.34                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| EuroClear Bank S.A/N.V                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 4.90                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Nordnet Pensionförsäkring AB                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 4.11                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Baulos Capital Belgium SA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 3.28                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Rothsay Limited                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 3.19                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Danske Bank International S.A.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 2.29                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Handelsbanken Liv                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 1.83                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Companies named in this report</b><br>Yungjin Pharm, BridgeBio Pharma, Santhera Pharmaceuticals, Stealth, Reata, Mitobridge, Astellas                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

Edison is an investment research and advisory company, with offices in North America, Europe, the Middle East and AsiaPac. The heart of Edison is our world-renowned equity research platform and deep multi-sector expertise. At Edison Investment Research, our research is widely read by international investors, advisers and stakeholders. Edison Advisors leverages our core research platform to provide differentiated services including investor relations and strategic consulting. Edison is authorised and regulated by the [Financial Conduct Authority](https://www.fca.org). Edison Investment Research (NZ) Limited (Edison NZ) is the New Zealand subsidiary of Edison. Edison NZ is registered on the New Zealand Financial Service Providers Register (FSP number 247505) and is registered to provide wholesale and/or generic financial adviser services only. Edison Investment Research Inc (Edison US) is the US subsidiary of Edison and is regulated by the Securities and Exchange Commission. Edison Investment Research Pty Limited (Edison Aus) [46085869] is the Australian subsidiary of Edison. Edison Germany is a branch entity of Edison Investment Research Limited [4794244]. [www.edisongroup.com](http://www.edisongroup.com)

#### DISCLAIMER

Copyright 2018 Edison Investment Research Limited. All rights reserved. This report has been commissioned by NeuroVive Pharmaceutical and prepared and issued by Edison for publication globally. All information used in the publication of this report has been compiled from publicly available sources that are believed to be reliable, however we do not guarantee the accuracy or completeness of this report. Opinions contained in this report represent those of the research department of Edison at the time of publication. The securities described in the Investment Research may not be eligible for sale in all jurisdictions or to certain categories of investors. This research is issued in Australia by Edison Investment Research Pty Ltd (Corporate Authorised Representative (1252501) of Myonlineadvisers Pty Ltd (AFSL: 427484) and any access to it, is intended only for "wholesale clients" within the meaning of the Corporations Act 2001 of Australia. The Investment Research is distributed in the United States by Edison US to major US institutional investors only. Edison US is registered as an investment adviser with the Securities and Exchange Commission. Edison US relies upon the "publishers' exclusion" from the definition of investment adviser under Section 202(a)(11) of the Investment Advisers Act of 1940 and corresponding state securities laws. As such, Edison does not offer or provide personalised advice. We publish information about companies in which we believe our readers may be interested and this information reflects our sincere opinions. The information that we provide or that is derived from our website is not intended to be, and should not be construed in any manner whatsoever as, personalised advice. Also, our website and the information provided by us should not be construed by any subscriber or prospective subscriber as Edison's solicitation to effect, or attempt to effect, any transaction in a security. The research in this document is intended for New Zealand resident professional financial advisers or brokers (for use in their roles as financial advisers or brokers) and habitual investors who are "wholesale clients" for the purpose of the Financial Advisers Act 2008 (FAA) (as described in sections 5(c) (1)(a), (b) and (c) of the FAA). This is not a solicitation or inducement to buy, sell, subscribe, or underwrite any securities mentioned or in the topic of this document. This document is provided for information purposes only and should not be construed as an offer or solicitation for investment in any securities mentioned or in the topic of this document. A marketing communication under FCA Rules, this document has not been prepared in accordance with the legal requirements designed to promote the independence of investment research and is not subject to any prohibition on dealing ahead of the dissemination of investment research. Edison has a restrictive policy relating to personal dealing. Edison Group does not conduct any investment business and, accordingly, does not itself hold any positions in the securities mentioned in this report. However, the respective directors, officers, employees and contractors of Edison may have a position in any or related securities mentioned in this report. Edison or its affiliates may perform services or solicit business from any of the companies mentioned in this report. The value of securities mentioned in this report can fall as well as rise and are subject to large and sudden swings. In addition it may be difficult or not possible to buy, sell or obtain accurate information about the value of securities mentioned in this report. Past performance is not necessarily a guide to future performance. Forward-looking information or statements in this report contain information that is based on assumptions, forecasts of future results, estimates of amounts not yet determinable, and therefore involve known and unknown risks, uncertainties and other factors which may cause the actual results, performance or achievements of their subject matter to be materially different from current expectations. For the purpose of the FAA, the content of this report is of a general nature, is intended as a source of general information only and is not intended to constitute a recommendation or opinion in relation to acquiring or disposing (including refraining from acquiring or disposing) of securities. The distribution of this document is not a "personalised service" and, to the extent that it contains any financial advice, is intended only as a "class service" provided by Edison within the meaning of the FAA (ie without taking into account the particular financial situation or goals of any person). As such, it should not be relied upon in making an investment decision. To the maximum extent permitted by law, Edison, its affiliates and contractors, and their respective directors, officers and employees will not be liable for any loss or damage arising as a result of reliance being placed on any of the information contained in this report and do not guarantee the returns on investments in the products discussed in this publication. FTSE International Limited ("FTSE") © FTSE 2018. "FTSE®" is a trade mark of the London Stock Exchange Group companies and is used by FTSE International Limited under license. All rights in the FTSE indices and/or FTSE ratings vest in FTSE and/or its licensors. Neither FTSE nor its licensors accept any liability for any errors or omissions in the FTSE indices and/or FTSE ratings or underlying data. No further distribution of FTSE Data is permitted without FTSE's express written consent.