

# BIO STOCK

## COMPANY ANALYSIS

NEUROVIVE  
FEBRUARY, 2017

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# NEUROVIVE

## ANALYTICAL SUMMARY

Swedish pharmaceutical company NeuroVive Pharmaceutical AB is a leader in mitochondrial medicine. Its lead candidate – NeuroSTAT – is currently being evaluated in a phase 1/2 trial with results expected later this year. The company has gone through some rough times but is currently picking up speed after having released exciting new data within one of the industry hottest indications – NASH – and within the cancer type HCC, which is characterized by high unmet needs. About a year ago, CEO Erik Kinnman was appointed. Since then, Erik Kinnman has established a new portfolio strategy where development for smaller indications aims for the clinic while assets targeting large indications are out-licensed when preclinical testing has been completed.

The company finished the last year in a strong way and BioStock has analyzed the outlook for the company. In this report, the market potential of NeuroVive's NV556 program within NASH is explored. Driven by a huge market, great unmet needs and no current treatments – NASH holds high potential. This is confirmed by the high-value deals that have been carried out recently and the interest among pharma companies to enter this space.

Overall, we believe that NeuroVive is currently regaining its position among investors as a leader in mitochondrial medicine and that the new business model is an interesting move.

### Important catalysts for investors to watch:

- Results from the CHIC phase 1/2 trial in TBI. Expected in H1 2017.
- Results from the experimental study in TBI. Expected in H1 2017.
- Results from confirming NASH and fibrosis studies with NV556. Lead candidate selection in the second NASH program NVP022. Expected in H1 2018.
- NVP015 lead candidate selection within energy regulation. Expected in H2 2017.
- Lead candidate selection within HCC program. Expected in H1 2018.

## ABOUT THE COMPANY

### Background

NeuroVive Pharmaceutical AB (publ) is a Swedish biotech company listed on Nasdaq, Stockholm, Sweden. The company is committed to the discovery and development of drug candidates that preserve mitochondrial integrity and function in areas of therapeutic need. NeuroVive's strategy is to take drugs for rare diseases through clinical development and into the market, while projects targeting larger indications - outside the core focus area - are aiming to be out-licensed in a preclinical phase. Through a team of 12 employees, the company manages preclinical and clinical projects in a semi-virtual environment together with key opinion leaders, regulatory consultants, clinical research organizations, contract manufacturers and other specialized suppliers. Moreover, by forming strong international partnerships and a network of mitochondrial research institutions, NeuroVive has established a position as a leading mitochondrial company.

NeuroVive's research currently covers four segments where the company's in-depth expertise within mitochondrial dysfunction has the potential to make a substantial improvement to care. These are traumatic brain injury (TBI), genetic mitochondrial disorders (including Complex I Dysfunction), Non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC). The company's lead asset - NeuroSTAT - is a neuroprotective agent in early clinical phase 2 development for the prevention of moderate to severe TBI. Next in line, is the company's preclinical program - NV556 - within organ protection, followed by the NVP015 program - that has yet to choose a candidate drug - within genetic mitochondrial disorders. These three programs are complemented by an R&D portfolio that NeuroVive aims to out-license

in a preclinical phase. There are currently three early development programs within this group, two focused on NASH (NV556 and NVP022) and one targeting HCC. This dual business model separates NeuroVive from many of its peers - where the norm is to bring preclinical candidates to a phase 2 proof-of-concept before partnering with a larger player - by establishing a long-term vision to achieve profitable growth in 5-10 years.

### Reinforced strategic direction

NeuroVive's strategic move towards a more balanced portfolio, demonstrates that the company continues to adapt and learn from its history. Shares in NeuroVive have been shredded twice as the previous flagship candidate - CicloMulsion - failed to reach statistical significance in two clinical trials for reperfusion injuries after myocardial infarction and acute kidney injuries. However, by re-balancing short-time smaller revenues, through preclinical deals for non-orphan opportunities, with long-term revenues based on market approvals in rare indications, risks are being managed more actively to the benefit of company shareholders. This strategic change may also reflect a new leadership style, following the C-level replacement that was made roughly a year ago. During his first year as CEO, Erik Kinnman has delivered several important achievements to counter-balance the reported setbacks related to CicloMulsion and the Arbutus Biopharma deal. Some of the bigger highlights have included the announcement of two new indications (NASH and HCC), a fully subscribed rights issue of 94 MSEK, several new collaborations as well as the expansion of both NeuroVive's management team and KOL panel.



*NV556 has demonstrated positive effects on fibrosis development in an experimental model for NASH. This indication holds huge potential commercial value, and if further preclinical development confirms these findings, we will be able to initiate out-licensing discussions by the second half of 2017.*

*Erik Kinnman, CEO NeuroVive*

### Strategic partnerships

NeuroVive has long time collaborations with Skåne University Hospital, in Lund, Sweden, and the Copenhagen University Hospital, Denmark. These collaborations have been important for the discoveries that originally created the company as well as stable foundations for preclinical experiments and running clinical trials in TBI and acute kidney injuries. Within TBI, the company also has a preclinical collaboration with the University of Pennsylvania, USA.

To develop new compounds for ischemic stroke, mitochondrial disorders and organ protection, NeuroVive has relied on its long-term partnership with UK based company Isomerase. The collaboration between the two companies' researchers is also a creative hotbed for identifying new development platforms and last year NeuroVive determined that Isomerase was important enough to conduct a partial acquisition of the company. This enables NeuroVive to source new compounds based on in-house research as a complement to in-licensing

innovative candidates.

In the past year, NeuroVive has expanded its collaborations within mitochondrial disorders. It was recently announced that the key opinion leader Marni J. Falk had been contracted. Dr. Falk is an attending physician and director of the Mitochondrial Disease Clinical Center at CHOP, US, which is a large center for children and adults with mitochondrial disorders and a leading mitochondrial disease research center. This provides NeuroVive with both expertise and access to patients in upcoming clinical trials. In Sweden, NeuroVive has a collaboration with a research group led by Prof. Håkan Westerblad at Karolinska Institutet. His group will study NV556 and its effects in experimental models of mitochondrial myopathy.



### ***What is a mitochondrion?***

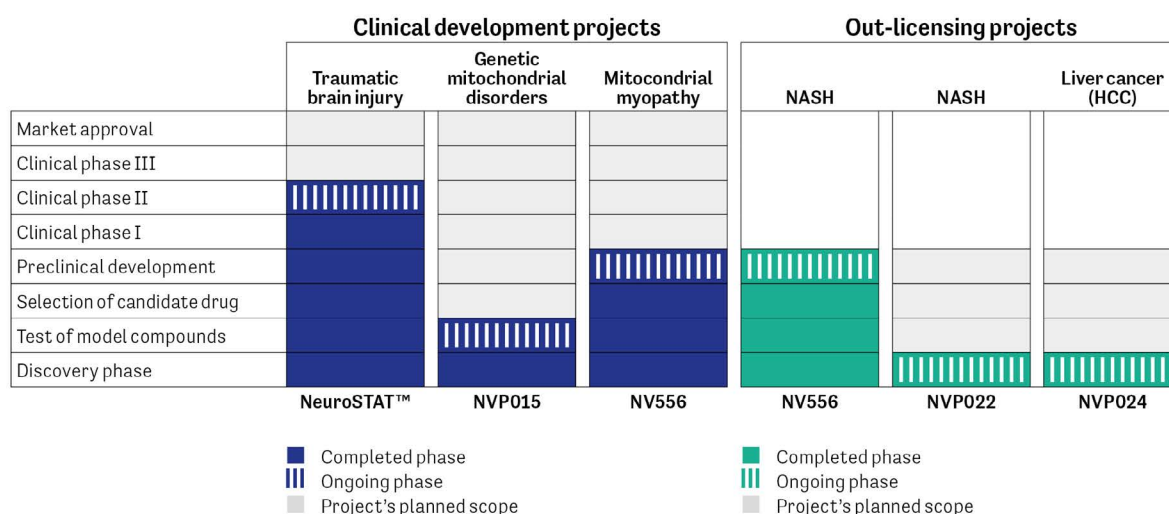
*Mitochondria are present in all cells and serve as the engine and energy supply of the cell, and are decisive for cells being able to withstand and recover from damage. In simple terms, you could say that mitochondria transform the oxygen we breathe in and the food we eat into energy for the cell. The mitochondria serve a crucial role in energy production, thus helping cells to withstand and recover from damage.*

### Major shareholders

NeuroVive Pharmaceutical AB is listed on Nasdaq Stockholm and trades under the ticker NVP. The share is also traded on the OTC Market Group's best market, OTCQX, in the US under the ticker NEVPF. The share capital is 2 472 932.25 SEK, divided between 49 458 645 shares (quotient value of 0.05 SEK). Approximately 6 900 shareholders currently own NeuroVive shares. Each share confer entitlement to one vote and equal participation in the company's assets and earnings. Lead investor and

NeuroVive's largest individual owner is Fredrik Olsson, through his holdings in Baulos Capital Belgium SA and Baulos International AS, together with his private holdings, with a total ownership of 9.11%. Second largest individual owner is Marcus Keep, through his holdings in Maas BioLab and private holdings, with a total ownership of 8.69%. Both CSO Eskil Elmér and the Chairman of the Board Greg Batcheller are found on the list of the company's largest shareholders.

## ASSET PORTFOLIO



## Orphan drug designation portfolio

Region	Designation	Date of designation
Europe	Treatment of moderate and severe closed traumatic brain injury.	Oct 01, 2010
USA	Treatment of moderate to severe traumatic brain injury.	Nov 23, 2010

### Traumatic brain injury

NeuroVive estimates that around three million people are affected by TBI each year. Traffic accidents, sports and more extreme situations (e.g. war, violence) often are the cause of hospitalized cases of TBI. While the patient may be saved from the immediate life threatening situation, the brain injury continues to worsen several days after the accident. This may lead to lower quality of life and long-term disabilities for the individual. Moreover, these patients put an enormous burden on healthcare budgets with costs for severe TBI estimated at 5-14 MSEK per patient. There are currently no pharmaceuticals that can limit the extent of TBI and total healthcare costs have been estimated to 60 BSEK annually in the US. There is clearly a substantial need for effective treatments, which NeuroVive identified early. A research group, led by Eskil Elmér, founder of NeuroVive and CSO, discovered that the generic substance cyclosporine is a potent neuroprotectant. By inhibiting cyclophilin and stabilizing the energy-producing mitochondria, the extent of TBI was hypothesized to be possible to limit. However, standard drugs containing cyclosporine all contained a poisonous substance (called cremophor), which the Lund University researchers did not want to include. A new cyclosporine formulation was therefore created, which NeuroVive called NeuroSTAT. Now – a few years later – NeuroVive has an ongoing clinical phase 1/2 study within TBI that is expected to soon be fully enrolled and results will

be presented later this year. The Copenhagen Head Injury Cyclosporine (CHIC) study is an open label study evaluating two different dosages of NeuroSTAT. This study is complemented by supporting animal studies at the University of Pennsylvania to generate efficacy data for the regulatory process and as guidance for the design of a phase 2b study. NeuroVive intends to bring this candidate to a market approval and is scouting for potential partners. In addition to Big Pharma companies looking to build neuroprotectant portfolios, TBI's high societal costs could possibly open funding-avenues by running a phase 2b and subsequently a phase 3 trial together with funding support from organization plagued by the detriments of TBI. In the US, potential financing may come from the US military or larger sport organizations such as the National Hockey League or the National Football League. Another avenue may be government organizations in Asia where occurrences of traffic accidents are high. NeuroVive's next project-related milestones are the announcement of the PK/safety data from the phase 1/2 CHIC study and efficacy data from the ongoing in vivo study at the University of Pennsylvania, both expected before the summer (2017).

*Next expected project-related milestone within TBI is NeuroVive's presentation of the PK/safety data from the phase 1/2 CHIC study and efficacy data from the PENN study.*



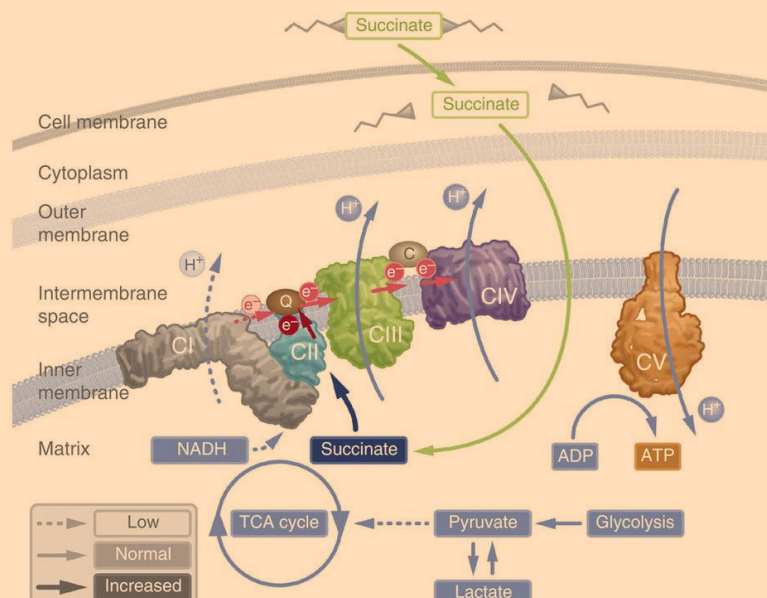
## Genetic mitochondrial disorders

Approximately 12 in 100 000 people suffer from mitochondrial disorders, which makes this a group of rare conditions with a common denominator. Many are hereditary disorders that affect the energy conversion of cells that mitochondria normally maintain. Several of these are caused by complex 1 deficiency, which can be simplified as a fatal error in one of the key gears in the mitochondrial engine. Energy generation in mitochondria relies on a sequence of conversions in the electron transport chain and complex 1 is the first gatekeeper for this process. For this reason, NVP015 is an intriguing program. NeuroVive's compounds, in the NVP015 program, skips the first step of the sequential process by entering the electron transport chain downstream of complex 1. This means that a complex 1 dysfunction may be bypassed (by entering the chain where succinate normally enters the chain) and energy will still be generated by the normal respiratory process. If this works, this is certainly groundbreaking and the new strategy to regulate energy was recently published by NeuroVive's team in Nature Communications (Ehinger JK et al. (2016), Nat. Commun. 7:12317), **for an overview of the concept see the illustration below**. Nature Communications is the third highest-ranked multidisciplinary science journal in the world and the fact that this article was accepted indicates that the scientific community agrees that this is forefront research.

The published study was conducted by NeuroVive in partnership with Lund University, Newcastle University, Selcia/Mitopharm Ltd and Isomerase Therapeutics Ltd. The article describes how the team managed to select three candidates, from a library exceeding 50+ pro-drugs of succinate, resulting in a new pharmacological strategy to metabolically support patients during time of metabolic decompensation. The article notes that these compounds currently lack sufficient plasma stability to be suitable for in vivo use, and NeuroVive together with Isomerase are therefore working hard on solving this issue. According to the latest interim report, work is ongoing to develop a new series of succinate prodrugs with improved stability in the bloodstream and the most promising compounds from this series are currently being tested in various experimental models. When an appropriate level of plasma stability has been obtained, BioStock expects NeuroVive's next project-related milestone will be the selection of a lead candidate drug late 2017.

*Next expected project-related milestone for NVP015 is the selection of a candidate drug, which is expected later this year.*

## NVP015 CONCEPT - SUCCINATE PRO-DRUG DELIVERY



*Cell membrane-permeable prodrugs of succinate access the intracellular space and release succinate, enabling increased electron transport, respiration and ATP production through complex II, thus bypassing the deficiency in mitochondrial complex I.*

*Ehinger JK et al. (2016), Nat. Commun.*



## ASSET PORTFOLIO

### Organ protection and NASH

NeuroVive's candidate, NV556, inhibits cyclophilins, which results in a reaction that preserves mitochondrial function and thus potentially may limit the progression of injury in various organs of the body. Cyclophilin inhibition is certainly an area where NeuroVive has profound expertise. Both NeuroSTAT, NVP018 and multiple discontinued candidates (e.g. CicloMulsion and NVP014) fall under this category. NeuroVive's candidate, NV556, inhibits cyclophilins, which results in a reaction that preserves mitochondrial function and thus potentially may limit the progression of injury in various organs of the body. Cyclophilin inhibition is certainly an area where NeuroVive has profound expertise. Both NeuroSTAT, NVP018 and multiple discontinued candidates (e.g. CicloMulsion and NVP014) fall under this category. Over

the years, NeuroVive has accumulated a broad knowledge base within organ protection. One example was CicloMulsion that was clinically tested to limit the extent of reperfusion injuries following myocardial infarction and was tested as a preventive treatment to reduce the incidence of acute kidney injury in patients undergoing major surgery. Another example of a non-cyclosporine – but yet cyclophilin inhibiting – project was NVP014 that was previously developed to limit brain injury as a result of ischemic stroke. According to the company, both the NVP019 project and additional candidates are currently being assessed in a range of organ protection related indications, in acute and chronic conditions. NV556 for organ protection is certainly an exciting development track with many applications (e.g. mitochondrial myopathies).

### Patent portfolio

Product	Description	Regions granted (estimated expiry)
NeuroSTAT (CicloMulsion)	<b>Lipid emulsion with cyclosporine containing medium long fatty acids.</b> WO 12042023 comprises a lipid emulsion containing CsA, which is free from Cremophor and ethanol, for oral or parenteral administration. The application entered PCT in Oct 2011 and has entered national phase in March 2013 in the US, EPO, and other countries. It applies to the NeuroSTAT project. A separate patent has been filed in China in 2012. Neurovive is applicant and owns the application.	AU, US (2031)
NV556 NVP024	<b>Macrocyclic compound and methods for its production.</b> These applications (WO 10034243, WO 11098809, WO12085553, WO012131371 and WO 13061052) apply to project NCEs for next generation of cyclophilin inhibitors. They have international filing date of 29 March 2012 and were published on 4 October 2012. The applications were acquired by NeuroVive in Feb 2013.	AT, BE, BG, HR, CY, CZ, EP, FI, FR, DE, GR, HU, IS, IE, IT, LV, MK, NL, NO, PK, PA, PL, PT, RO, RS, SK, SI, ES, SE, CH, TR, GB, DK, ZA (2032)
NVP015	<b>Protected succinates for enhancing mitochondrial ATP-production.</b> WO 14053857 comprises the use of phosphate ester pro-drugs of succinate for enhancing mitochondrial ATP-production. It is currently co-owned 50-50 by NeuroVive and Mitopharm Ltd, and applies to the NVP015 project. The patent will expire in 2032. Patent was filed October 5, 2012. 1. WO/2015/155238: Succinate prodrugs for use in the treatment of lactic acidosis or drug-induced side-effects due to complex i-related impairment of mitochondrial oxidative phosphorylation. 15.10.2015. 2. WO/2015/155230: Prodrugs of succinic acid for increasing ATP production. 15.10.2015. 3. WO 2015/155231: Prodrugs of succinic acid for increasing ATP production. 15.10.2015.	Pending in USA and EU (2032)  Patents 1-3 pending (~2035)
ToxPhos	<b>Mitochondrial toxicity test.</b> WO 1405317 comprises an invention based on a novel method that is useful in drug screening. In particular the method is useful for testing effects of substances on the mitochondria, notable toxic or beneficial effects of drug substances or candidate drug substances. Neurovive is applicant and owns the application.	Pending in all regions (2033)

NV556's primary indication, however, is NASH. NeuroVive already has much preclinical data in its hands, which positions this candidate in a late preclinical stage. NV556 has been shown to prevent fibrosis development in a well-validated experimental model of NASH and confirmatory long term studies are currently ongoing. NeuroVive also has an earlier project, called NVP022, where a group of substances are tested for NASH. This project complements NV556 well since the NVP022 substances seem to have properties that modify the development of fibrosis in an earlier stage of the disease. BioStock expects that the next project-related milestone will be an announcement of further NASH related NV556 data. Moreover, NeuroVive has communicated that efforts are currently underway to compile a package for the commencement of out-licensing activities, in H2 2017. Lead candidate selection in the second NASH program, NVP022, is expected in H1 2018.

*NASH is currently one of the hottest indications in the industry and BioStock has therefore made a deeper assessment, further down in this document, about the market potential in this space.*

*Next expected project-related milestone in the NV556 program is the announcement of further NASH related NV556 data.*

### **Hepatocellular carcinoma**

Lastly, NeuroVive recently published some exciting news related to HCC, which is a completely new indication for the company. Preclinical data was presented at the EASL HCC Summit from a new generation of sanglifehrin-based compounds with potent inhibitory effects on hepatocellular carcinoma cells and anti-cancer activity in an experimental model of HCC. At first, this may come off as unrelated to the mitochondrion. However, sanglifehrin A is a molecule that acts as a potent inhibitor of the mitochondrial permeability transition pore by binding to cyclophilin D at a different site from cyclosporine. As experts in the cyclophilin inhibition game, NeuroVive has known this a long time and acquired an asset portfolio for this very reason from Cambridge based Biotica Technology Limited back in 2013. Biotica was developing sangamides, which are derivatives of sanglifehrin A, and the transaction provided NeuroVive with a library of cyclophilin inhibiting assets. One of these projects was used in the hepatitis B licensing deal with Arbutus Biopharma. Although this

deal was subsequently discontinued, it led to a situation where NeuroVive now owns the project and have received an upfront payment and preclinical/CMC material valued at \$1.5 million. Now new derivatives of the sanglifehrin-compounds, from the Biotica acquisition in 2013, with completely new mechanisms of action have demonstrated potency in HCC. Against this background, the Biotica transaction must be considered to have been a very successful deal. In a press release, NeuroVive reported that it had explored anti-cancer effects in a new proprietary subset of its sanglifehrin-based compounds. Anti-cancer activity of the model compound was reported to show up to 500 times more potent inhibitory effects on human HCC cells compared to sorafenib, more commonly known as Nexavar. Sorafenib is currently marketed by Bayer and Onyx Pharmaceuticals for the treatment of unresectable HCC and advanced renal cell carcinoma, which makes it a relevant comparator drug in this context. Apparently, the sanglifehrin-based compound class also demonstrated relevant activity when administered in experimental models both orally and through intraperitoneal dosing. Furthermore, the compounds were reported to not have shown toxicity in normal cells and to have been well tolerated in vivo. While the reported data is still early, these are positive news for the prospects of making a convenient dosing formulation and a future drug. Based on the fact that there are 50 US orphan designations for HCC, the prospects of arguing that the indication qualifies for orphan drug designations seem likely. It is also worth noting that sorafenib is the only drug on this list that has been approved and enjoyed the market exclusivity that the orphan designation offers before the exclusivity expired in Nov, 2014. It is not clear, at this stage, whether NeuroVive considers this project to be one of the core rare disease programs that will be advanced through clinical trials or one of the out-licensing projects that will be divested in a preclinical stage. Either way, BioStock expects that the next project-related milestone that will be announced will be the selection of a candidate drug followed by the decision to initiate a preclinical program..

*Next expected project-related milestone within HCC is the selection of a candidate drug and the decision to initiate a preclinical program.*

## **Liver cancer**

*HCC is the most common type of liver cancer (representing 85% of all cases). Liver cancer qualifies as a rare disease in many regions (approx. 105 000 cases per year in the US, EU5 and Japan), but is the third most common cancer type in Asia. In fact, more than 400 000 new cases are diagnosed with liver cancer in China per year.*

## **Hepatocellular carcinoma**

*Each year, more than half a million people worldwide receive a diagnosis of hepatocellular carcinoma, and hepatocellular carcinoma related to HCV is the fastest rising cause of US cancer-related deaths. HCC is a silent disease, which means that it is often diagnosed in a later stage. If it is discovered in an early stage, surgery and liver transplants are typically first-line options. Tragically, most patients do not escape the disease and more than 70% of all cases relapse within five years.*

## **Current treatments**

*Nexavar (sorafenib), marketed by Bayer/Amgen, was first approved for first-line treatment of advanced or metastatic hepatocellular cancer (HCC) in 2007, and remains the only approved pharmacological HCC therapy. Its use is limited to cases when surgery is not an option and has a limited effect on overall survival (12 weeks). However, Nexavar is selling at blockbuster levels in HCC and kidney cancer.*

## **Unmet clinical needs**

*There is a clear need for novel treatments with clear effects on overall survival. Another area is the early-stage adjuvant HCC setting that will continue to be an area of high unmet need as there are no approved pharmacological therapies to prevent disease recurrence in patients who have received potentially curative surgical resection or local ablation.*

# 84 million SEK

*estimated cash in bank*

# 5.25 million SEK

*estimated burn-rate per month*

# 16 months

*estimated life time, until cash needed*

## Financial summary

NeuroVive Pharmaceutical, like many of its industry peers, is financed by its shareholders. No income was reported in the latest interim report (Jan-Sep 2016) and should not be expected in the short-term by investors. Per the consolidated statement of comprehensive income, costs during the first nine months of 2016 amounted to 57.3 MSEK (42% external costs, 20% personnel and 36% other operating costs). NeuroVive notes that close to 20.6 MSEK relates to former capitalized costs for the now discontinued CicloMulsion program and that roughly 8.2 MSEK of the total cost relates to non-clinical projects. It is therefore likely that the costs during 2017 will be substantially less, since there will be no new costs for CicloMulsion. Costs of 57.3 MSEK, in the first 9 months, results in a 6.4 MSEK monthly burn-rate, which may be compared to a burn-rate at 4.1 MSEK per month, if the capitalized costs for Ciclomulsion are subtracted. As a conservative assumption, based on an average of the two values, is a monthly burn-rate of 5.25 MSEK/month. With current assets of 115.1 MSEK reported on Sep 30, 2016, this results in a theoretical company survival time of roughly 22 months after the quarterly report. A conservative estimate thus results in a projected life time that brings the company into Q1, 2018.

## Consolidated statement of comprehensive income (Q1-Q3, 2016, report)

[kSEK]	Jan-Sep, 2016	Jan-Sep, 2015	Jan-Dec, 2015
Net sales & operating income	90	3 001	3 024
Other external expenses	-24 308	-44 672	-48 514
Personnel cost	- 11 332	-12 689	-15 556
Depreciation and write-downs	-808	-565	-1 200
Other operating expenses	-20 888	-29 174	-29 220
Operating income (before tax and financial items)	-57 247	-84 099	-91 466

## Consolidated statement of financial position (Q1-Q3, 2016, report)

[kSEK]	2016-09-30	2015-09-30	2015-12-31
<b>ASSETS</b>			
<i>Intangible assets</i>	64 339	72 563	74 904
<i>Tangible assets</i>	290	347	316
<i>Financial assets</i>	13 220	161	149
<b>Total non-current assets</b>	<b>77 849</b>	<b>73 071</b>	<b>75 369</b>
<i>Other receivables</i>	1 574	796	2 368
<i>Prepaid expenses and accrued income</i>	665	277	528
<i>Cash and cash equivalents</i>	112 889	116 966	96 662
<b>Total current assets</b>	<b>115 128</b>	<b>118 039</b>	<b>99 558</b>
<b>TOTAL ASSETS</b>	<b>192 978</b>	<b>191 109</b>	<b>174 927</b>
<b>EQUITY AND LIABILITIES</b>			
<i>Total equity attributable to the shareholders of the parent</i>	169 169	147 644	141 128
<i>Total equity</i>	182 385	161 965	154 779
<i>Total liabilities</i>	10 593	29 145	20 148
<b>TOTAL EQUITY AND LIABILITIES</b>	<b>192 978</b>	<b>191 109</b>	<b>174 927</b>

## BOARD OF DIRECTORS

### GREG BATCHELLER LL.M. J.D. CHAIRMAN

Executive Chairman since 2008 and board member since 2000. Commercial lawyer, business developer and project manager with many years in the Life Science industry.



### HELENA LEVANDER BOARD MEMBER

Board member since 2012. Founder of nordic Investor Services with extensive experience in financial markets and asset management, through working with SEB, Nordea and Odin Funds.



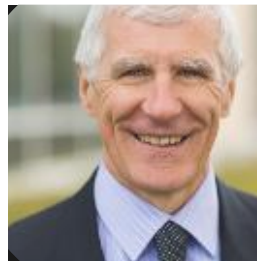
### ANNA MALM BERNSTEN BOARD MEMBER

Board member since 2013. Extensive international experience in strategic marketing, product launching and business development within pharma and biotech companies.



### DAVID LASKOW-POOLEY BOARD MEMBER

Board member since 2016. Laskow-Pooley is a member of the board of TapImmune Inc, USA, OBN Ltd, England and Pharmafor Ltd, England.



### ARNE FERSTAD BOARD MEMBER

Board member since 2010. Co-owner Ankor Consultants (London), previous Chairman of Baxter (Nordic & Benelux) and European President of Baxter Healthcare's Renal Division.



### MARCUS KEEP M.D. BOARD MEMBER

Board member since 2000. Neurosurgeon, CEO and Executive Chairman of Maas Biolab, LLC, one of the largest shareholders in NeuroVive.



### BOEL FLODGREN Ph.D Prof. BOARD MEMBER

Board member since 2013. Professor in commercial law and former principal at Lund University. Extensive experience in research and teaching within the field of business law





## OPERATIONAL TEAM

M.D. Ph.D. MBA **ERIK KINNMAN**

**CEO**

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strategy, IR, business  
development.



**ESKIL ELMÉR M.D. Ph.D.**

**CSO & FOUNDER**

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research.

**CATHARINA JOHANSSON**

**CFO**

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multinational operations and  
partnership activities.



**MAGNUS HANSSON M.D. Ph.D.**

**CMO**

Preclinical and  
clinical research and  
development.

**CECILIA HOFVANDER**

**IR & COMM DIRECTOR**

More than 15 years experience  
from investor relations within  
small/mid cap biotech.

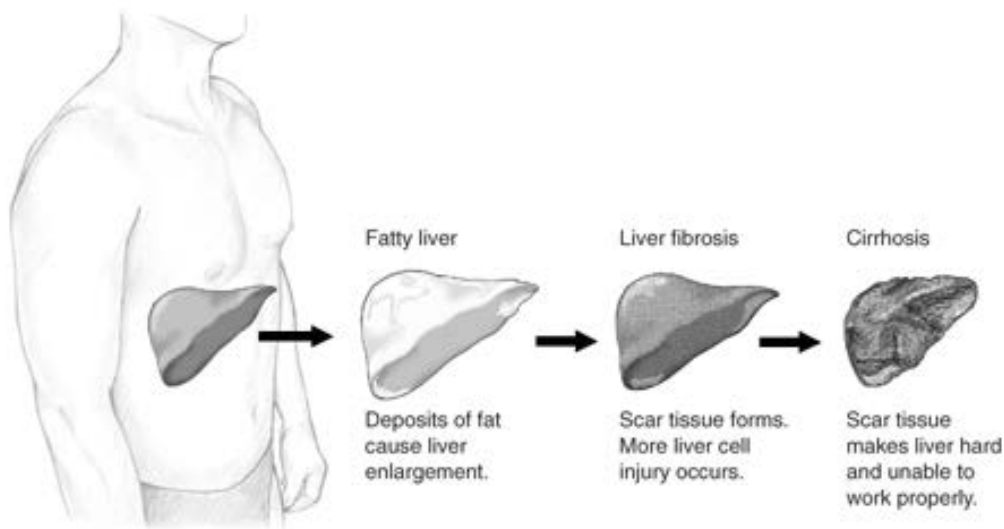


### Management team

Negative news made NeuroVive's market cap suffer last year but in the past four months this has changed. CEO Erik Kinnman joined the company less than a year ago and seems to have regained the confidence among the company's shareholders. With a new business model in place and with recent progress within NASH and HCC, Erik Kinnman's team seems well positioned for a strong 2017. Kinnman is a trained physician, Ph.D., and Associate Professor (Karolinska Institutet), with a combined background within business development, financing and investor relations. A small selection of the companies that Kinnman has worked for in the past include Wilson Therapeutics, PledPharma, Index Pharma, SOBI and AstraZeneca. Responsibilities across Erik Kinnman's management team are distributed between scientific operations, medical affairs, financials and investor

relations. CSO Eskil Elmér, M.D., Ph.D., Assoc. Prof., is a serial inventor and founder of NeuroVive with extensive knowledge within mitochondrial medicine and clinical neurophysiology. Day-to-day medical activities are run by Magnus Hansson, M.D., Ph.D., Assoc. Prof., who together with Eskil Elmér has specialized in research related to the mitochondrion's role in acute and chronic diseases. Catharina Johansson is NeuroVive's CFO with over 15 years experience from different financial positions within growth companies in the medical technology field and multinational operations. Cecilia Hofvander, IR & Comm Director, comes from a 20+ year background at Active Biotech and manages communication with NeuroVive's external stakeholders.





## NAFLD and NASH

Heavy use of alcohol causes fat to build up in the liver, resulting in a condition known as alcoholic liver disease. Nonalcoholic fatty liver disease (NAFLD), in contrast, is a condition in which fat builds up in the liver, in the absence of significant alcohol consumption. NAFLD, in turn, may be segmented into non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) patients. People with NAFLD have a greater chance of developing cardiovascular disease and is the most common cause of death in people who have either form of NAFLD. People with NASH have an increased chance of dying from liver-related causes and the disease may lead to cirrhosis or liver cancer. Developing cirrhosis may lead to liver failure, which in turn may require a liver transplant for the patient to survive. Needless to say, NAFLD and NASH cause suffering and huge societal costs.

NAFLD is one of the most common causes of liver disease and has therefore generated a high interest among pharmaceutical companies and investors. NIDDK

(National Institute of Diabetes and Digestive and Kidney Diseases) estimates that about 30-40% of adults in the US have NAFLD. Roughly 20% of the people with NAFLD have NASH, which makes NASH a huge indication (3-12% of adults in the United States). The condition is even more common in people who have certain conditions, especially conditions related to obesity. Researchers (e.g. Chalasani N et al., 2012) have found that 40-80% of type 2 diabetes patients, 30-90% of obese patients and more than 90% of severely obese (undergoing bariatric surgery) patients had NAFLD. It is safe to say that NAFLD has reached epidemic proportions. Some experts (e.g. Fuchs M, Curr Treat Options Gastroenterol. 2015 Jun;13(2):259-73) therefore believe that NASH will replace chronic hepatitis C as leading indication for liver cirrhosis and liver transplantation. This is an alarming trend and there is an urgent need for safe pharmacologic therapy that successfully reverses or prevents progression of liver injury and fibrosis in patients with NASH.

## Non-alcoholic fatty liver and steatohepatitis types

Type	Description
NAFLD	Encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from NAFL to NASH patients with stage 4 fibrosis (cirrhosis).
NAFL	Hepatic steatosis is present, but there is no evidence of hepatocellular injury (in the form of ballooning of the hepatocytes) or fibrosis.
NASH	Hepatic steatosis is present and there is evidence of hepatocellular injury (in the form of ballooning of the hepatocytes) with or without fibrosis.

## MARKET OPPORTUNITY

### Disease characteristics

Both NAFL and NASH are silent diseases with few or no symptoms. Symptoms sometimes don't even show when cirrhosis have developed due to NASH. When symptoms of NASH do show, these include fatigue, nausea, jaundice or discomfort in the upper right side of the abdomen. It is not known why some people with NAFLD have NASH and others have simple fatty liver. Research suggests that certain genes may play a role. People with NAFLD are more likely to have NASH if they have one or more of certain conditions (obesity, high blood pressure, high levels of triglycerides, abnormal levels of cholesterol in their blood, type 2 diabetes or metabolic syndrome). While there are many tools to help diagnose NAFLD (e.g. ultrasound, CT scans, MRI), a liver biopsy is the only way to diagnose NASH by detecting liver inflammation and damage.

In addition to the build-up of fat in the liver, NASH patients also have inflammation and liver cell damage – both of these can cause fibrosis, or scarring, of the liver. Although the presence of fibrosis is not required for a diagnosis of NASH, fibrosis is present in over 80% of NASH patients. For this reason, NASH patients are often further segmented by their fibrosis stage and is frequently used to quantify the progression of the disease.

### Current treatments

Today, recommended treatments for NAFL and NASH rely on weight loss (through dietary interventions and physical exercise) and to some extent: vitamin E. In the US, guidelines (by the American Association for the Study of Liver Diseases) tentatively recommend the use of vitamin E as a first-line treatment option in non-diabetic NASH patients. This is different in the UK where the NICE (National Institute for Health and Care Excellence) guidelines only prescribe dietary and lifestyle changes, but no pharmacological intervention.

*Currently there are no market approved drugs to treat NAFL or NASH and disease guidelines do not recommend specific interventional treatments.*

Despite this lack of treatment recommendations, primary research by Datamonitor shows that about half of all patients in the US, EU5 and Japan are still being prescribed generic medicines off-label. According to the study, monotherapy with metformin – first-line medication for the treatment of type 2 diabetes – is the most commonly prescribed treatment in the US and EU5 for NAFL. Whereas monotherapy with ursodeoxycholic acid – a treatment designed to reduce gallstone formation and

improve bile flow – is the preferred NAFL therapy in Japan.

A growing consensus suggests that only NAFLD patients with NASH require treatment and only they should be the targets of future clinical trials. One of the most common types of treatment prescribed to NASH patients is insulin-sensitizing agents. These have been shown in studies to be the more promising therapeutic candidates (e.g. by Kadayifci A, Clin Liver Dis. 2007 Feb;11(1):119-40, ix.) among categories that include antioxidants, lipid-lowering agents, and anti-obesity drugs.

Given the potential role of oxidative stress in the pathogenesis of NASH, some investigators have focused on the use of antioxidants to protect cellular structures against damage from oxygen free radicals and from reactive products of lipid peroxidation. Two small pilot trials have showed improved liver enzymes with vitamin E treatment, while three randomized, controlled trials have failed to show any benefit. Other potential anti-oxidant therapies for NASH include betaine and N-acetylcysteine. Initial open-label studies of ursodeoxycholic acid, a potential cytoprotective agent, in generated considerable enthusiasm when tested in NAFLD. However, no benefit was observed in a relatively large, well-designed randomized, double-blind, placebo-controlled trial involving 166 NASH patients who were randomized to UDCA 13-15 mg/kg/day or placebo for about 1 year.

Some encouraging data has been demonstrated using insulin-sensitizing agents – such as a clinical trial in patients with biopsy-proven NASH randomized to a regimen containing pioglitazone and diet restrictions – but the drawbacks of these agents are weight gain and the temporary nature of the improvements. Scientifically the hypothesis of using insulin-sensitizing agents is based on their abilities to decrease levels of lipolysis. When lipolysis levels are normal, less free fatty acids are produced and the amount of fat that could potentially build up in a patient's liver is limited (i.e. reducing inflammation and fibrosis). In spite of good hypotheses and encouraging data, none of these agents have been approved for NASH and these agents are currently prescribed off-label.

This lack of strong recommendations has led to physicians developing their own treatment regimens based on the hypotheses above. If a patient stops responding to the treatment that the physician has used as the first-line choice, the patient will progress to the next logical treatment as second- or third-line therapies. This varies between individual physicians, disease staging and geographies. However, a study by Datamonitor shows that most NASH patients across all stages of fibrosis receive metformin as second-line therapy in the US and Europe.

In the last development stages of the clinical pipeline, a number of potential competitors have reached, or advanced through, clinical phase 3 testing. The two most important drugs for investors to keep their eyes on are:

## Late-stage: clinical competition

Candidate (active ingredient)	Development stage	Target patients	Company	Reference
Ocaliva (obeticholic acid)	Phase 3 (expected NDA filing: Q3-Q4, 2018)	Biopsy-confirmed, stage 1 to 3, NASH (age: 18+)	Intercept Pharma and Dainippon Su- mitomo	NCT02548351
- (elaftibranor)	Phase 3 (expected NDA filing: Q4, 2018)	Biopsy-confirmed, stage 1 to 3, NASH (age: 18+)	Genfit SA	NCT02704403

### Phase 3 competition

Most of the market analysts are placing their bets on **Intercept Pharma** being the first to reach the NASH market with an approved drug. In 2011, **Dainippon Sumitomo** struck a \$315 million deal (+ double digit royalties) with **Intercept** in exchange for the rights to NASH and PBC in Japan and China (with an exclusive option to add more Asian countries). **Ocaliva** is a once daily oral agonist of a receptor that regulates bile acids, lipids and possibly glucose. The drug received conditional approvals last year in the US and Europe for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. It was approved under the FDA's accelerated approval pathway, based on a reduction in alkaline phosphatase, and an improvement in survival or disease-related symptoms has not been established. Despite some concerns over elevated cholesterol levels and pruritus, strong uptake is expected if the drug manages to achieve a market approval in NASH based on its broad efficacy profile and the fact that physicians already are familiar with the drug. The drug is currently being tested in the randomized, global, phase 3 REGENERATE study that is planned to enroll 2000 patients. In February (2017), Intercept communicated that FDA had agreed on a protocol revision that increases its chances of success and its plans for accelerated approval, based on the data from the first 750 patients of the trial.

Runner-up and main competitor to **Ocaliva** is **Genfit's** phase 3 candidate **elaftibranor**. This candidate is an oral agonist of a receptor that control gene expression related to insulin sensitivity and fatty acid oxidation. Almost a year ago (March, 2016), **Genfit** announced that it had enrolled its first patient in the pivotal trial in NASH, called RESOLVE-IT. This has created a race between the two where the market is currently guessing that Intercept will be able to submit its NDA first. **Genfit** is seen as the

underdog since its drug failed to show a significant benefit over placebo in its phase 2b GOLDEN trial, before the company adopted a modified endpoint. This modification led to a statistically significant increase in the number of patients who experienced NASH resolution without fibrosis worsening as compared to placebo. Intercept believed that this was enough to place its bets on the 2000 patient RESOLVE-IT trial. Factors speaking in favor of **elaftibranor** include its HDL increasing effect (could have cardiovascular benefits) and its ongoing development of a diagnostic test to identify eligible patients for the drug.

### Market dynamics

Over the last few years, biotech investors have seen the multi-billion dollar boom in the liver disease space as **Gilead Sciences** greatly exceeded market expectations with its wonder drug **Sovaldi** and the huge \$3.85 billion buyout deal was completed between **Merck & Co** and **Idenix Pharmaceuticals**. NASH, much like hepatitis C, is a common and serious liver indication causing huge costs for the healthcare system. In fact, NASH is now the third-leading cause of liver transplants in the US and is predicted to grab the first place by 2020.

*The predicted \$40 billion NASH opportunity, in 2025, has not gone unnoticed by the pharma industry.*

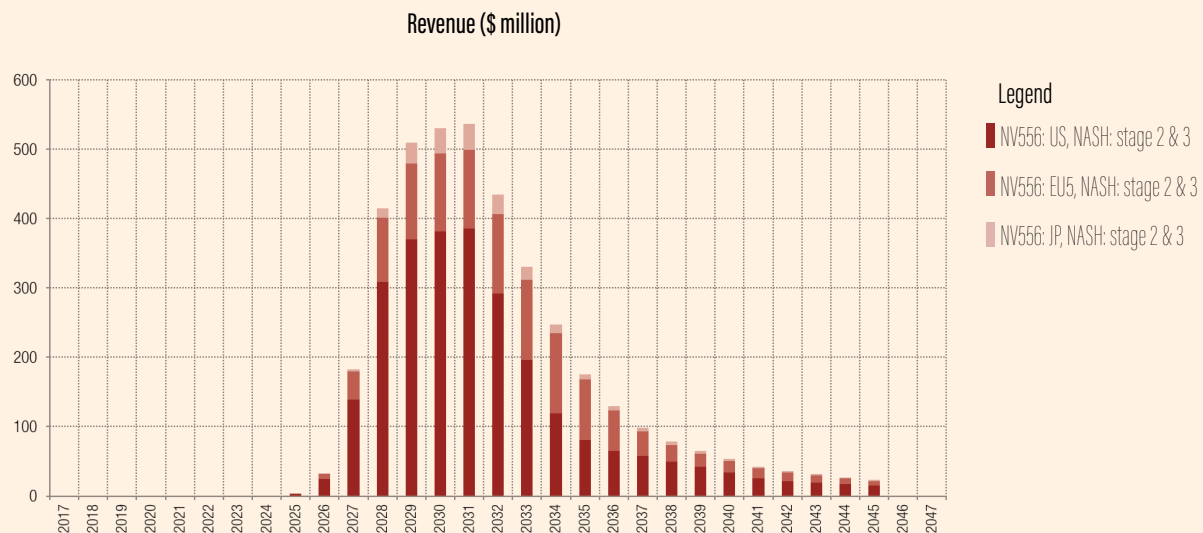
This \$40 billion opportunity (in 2025) has not gone unnoticed by the pharma industry and there is a plethora of novel compounds in clinical phase 2 testing or earlier. No single product appears to be a new cure for the disease and large pharmaceutical companies have started to stockpile promising assets through license deals and M&As.

## **BioStock briefing about presented rNPV values**

*To estimate the potential value of an asset in a company portfolio, BioStock determines a risk-adjusted net present value (rNPV). Assumptions about the market, pricing, timelines, costs, expected market share at peak, etc., are discussed with the analyzed company – these assumptions are then used to create a financial projection of future revenues. If nothing else is stated, peak sales are assumed to be reached within 5 years from market approval and an aggressive sales erosion rate is assumed to begin on the expiry year of the main patent, orphan protection or otherwise. Revenues are transformed into profits by assuming costs and tax for the licensee/acquirer. A standardized discount rate of 15% is then applied to calculate what those future cash flows would be worth today. Drug development projects, in general, have a low likelihood of reaching a market approval and to account for this risk, indication specific attrition data from Hay et al., 2014, Nature, is applied. These assumptions and estimations are then used as input in a simplified version of Monocl Strategy Services' proprietary valuation model to calculate an rNPV.*

*Financial modeling using rNPV is the industry standard for most Big Pharma companies. The calculation is done to appreciate what the value of an asset would be worth today, based on the profit the Big Pharma would expect to make if it would commercialize the asset. If the asset is successfully out-licensed, this value is typically split between the biotech company and the Big Pharma in a risk-sharing structure (e.g. 15/85 or 25/75). The share of the value that the biotech company receives is often realized in payments divided into an upfront lump sum, milestones (R&D and commercial) and royalties. A presented rNPV thus represents the theoretical total project value that a larger company would consider to pay for an asset, not the company share price.*

## PROJECT VALUE



### Market potential

It is no exaggeration to conclude that the size of this market is huge. In the US, EU5 and Japan approximately 10.9 million prevalent cases are estimated to be pharmacologically treated for any form of NASH, in 2017. Even when the patient population is limited to fibrosis in stage 2 and 3 (i.e. excluding both the earliest and latest stages), the total calculated prevalent population is still 4.96 million patients in 2017. With an estimated annual price of \$5000 per patient in the US and \$2500 in EU5 and Japan, a theoretical total market value of \$19 billion per year results in the stage 2-3 NASH segment. To get an understanding how a Big Pharma may value the NV556 opportunity, after it has completed the preclinical stage, a risk-adjusted net present value has been calculated and is presented below.

### NV556 project value: NASH

A financial model built around NV556's projected market approvals in the stage 2 and 3 populations within NASH results in the revenue diagram shown above. Based on the presented base assumptions (below), NV556's peak year would occur in 2031 with a \$536 million turnover from 137 500+ patients being treated in the modeled regions (USA, Japan and EU5). During the modeled period above, NV556 would generate total revenues, exceeding \$4.0 billion with an accumulated NOPLAT of \$2.0 billion (Net Operating Profit Less Adjusted Taxes). Naturally because the price in the US is twice the amount (compared to the

other modeled regions), revenues from this geography represents the majority (78%) of the total revenue. Pharmaceutical pricing in the US, however, is currently under scrutiny and pricing pressure would alter the modeled revenues considerably. If NeuroVive manages to bring NV556 through preclinical testing and thus has a phase 1 asset available for out-licensing later this year. A risk-adjusted net present calculation, with a number of base assumptions (see below) results in \$35 million value for a clinical phase 1 ready asset, at the end of 2017. In a bear scenario, where the assumed prices are sliced by 25% and the market share is cut in half (to 5%), an rNPV of \$6 million still holds, which is telling of the huge market opportunity that NASH presents.

*NASH holds huge market potential and a phase 1 asset projected to capture a 10% market share thus results in a risk-adjusted net present value of \$35 million.*

*As a note, it is worth mentioning that the presented rNPV only represents the estimated project value for a acquirer of NV556 (within the NASH program) based on the presented assumptions. It does not represent the share price of NeuroVive neither does it account for potential label extensions, company assets (physical, intangible or cash in the bank) or other external factors.*



## PROJECT VALUE

### Base assumptions

To estimate the market opportunity, it was assumed that NASH patients with stage 2 and 3 fibrosis were eligible for NV556. It was assumed that NeuroVive would target markets through strategic partnership in the US, Europe and Japan and that 20% of the population would be too old or too frail to receive treatment. All in all, this resulted in a total theoretical market of 3.96 million in 2017. The market share percentage at peak was assumed to be affected by the expected competition and a market share of 10% of the total patients at peak were assumed to receive NV556 treatment. NASH is a growing disease and an annual growth rate was assumed in the US and Japan of 1.03% and 0.68% in Europe.

Pricing in the different regions were assumed to 5 000 USD/year in the US, 2500 USD/year in Europe and in Japan - in line with the expectations for **Ocaliva**.

NV556 is currently in preclinical testing, but the assumption for the valuation was that the candidate would complete preclinical testing and be in a clinical phase 1 ready stage later this year and that the valuation would be done for when phase 1 can start. This statistically translates to a likelihood of approval of 18.2% according to attrition data.

To be able to model a market launch, the assumption was made that NV556 enters phase 1 testing in 2018, phase 2 testing in 2019 and phase 3 testing in 2021, files its regulatory submission in 2024 and reaches a market approval in 2025 in the US and Europe and 2026 in Japan.

Market exclusivity based on orphan exclusivity was modeled until 2032 in the US and 2035 in Europe, and patent exclusivity in Japan until 2031. A rough estimation of the total development costs was made of \$50 million and an additional 20% overhead costs (\$10 million).

### Comparable deals

Arguably, the calculated rNPV value for NV556 seems high - but it is, in fact, comparable to other deals in this space. One recent example is the exclusive option deal between **Boehringer Ingelheim** and the Australian company **Pharmaxis** that was announced in 2015. The option provided worldwide rights to **PXS4728A** and related SSAO/VAP-1 inhibitor molecules, that **Boehringer** later chose to execute. In exchange for its discovery assets, **Pharmaxis** is eligible to receive upfront payment of €29

million, option payment €1.3 million, milestone payments of €223 million and high digit royalties.

A few years ago **AstraZeneca** partnered with **Regulus Therapeutics** around its micro-RNA therapeutic **RG125**. At the time of the deal, **RG125** was in phase 1 testing in NASH. AstraZeneca has paid more than \$30 million, so far, and has communicated that **Regulus** is eligible to receive up to \$495.5 million in future milestone payments.

Another notable deal that was announced a few months ago is the one between **Novartis** and San-Diego based **Conatus Pharmaceuticals**. The option and license agreement was made for the phase 2 asset emricasan to jointly develop treatments for chronic liver diseases. In exchange for these rights, **Conatus** will receive \$50 million in an upfront payment, \$7 million, subject to certain usual and customary closing conditions and may receive up to an aggregate of \$650 million in milestone payments and tiered royalties ranging from the high-teens to the high-twenties from **Novartis**. These deals illustrate the huge potential that Big Pharma sees in this space – even in early stage.

### Potential partners

Many companies are currently entering this space and companies such as **Allergan** and **Gilead** have been especially active deal-makers. **Allergan** recently acquired **Akarna Therapeutics** to gain access to its non-bile acid FXR agonist (AKN-083) and **Tobira Therapeutics** with its two NASH programs. **Gilead** is keen to expand its successful dominance within hepatitis C to new liver diseases and currently have five NASH candidates, including **Nimbus Apollo's** ACC inhibitor program and simtuzumab that was acquired from **Arresto BioSciences**. In 2015, **Gilead** struck a \$470 million deal with German **Phenex Pharmaceuticals** around its three clinical FXR agonist assets.

If nothing else, it is demonstrated by these early stage deals and stockpiling of NASH assets that the pharma industry is keen on finding the next **Sovaldi** in this space.

## CONCLUDING REMARKS

NeuroVive Pharmaceutical has gone through some tough times with its unsuccessful CicloMulsion development and termination of the Arbutus deal. It is therefore refreshing to see that the company's new leadership is re-directing the ship by establishing a new portfolio strategy. For shareholders, this may spread some of the risk that comes with a business model based on bringing molecules through proof of concept (before partnering). In hindsight, NeuroVive made the right decision to fill its war chest before it was known how the CiPRICS study would turn out. This means that the company is not in an immediate need to raise more cash, something that would have negatively affected many shareholders (should this have been the case when the share tanked). Judging from NeuroVive's current share price, CEO Erik Kinnman has clearly regained some confidence among the company's investors. NeuroVive seems to have gained traction and hopefully the completion of the ongoing human and experimental trials in TBI will further reinforce this momentum. A much anticipated milestone this year, will be the announcement of new results from the NV556-program in NASH. If there is positive news, Erik Kinnman will be able to test the new business model by initiating out-licensing discussion already this year. Later this year, a lead candidate from the energy regulation (NVP015) project will be announced. Lead candidate selection within HCC is expected next year and, based on the market reaction of previous HCC news, this is certainly a track many investors are watching closely.

Arguably the new business model spreads risk – however – it is by no means easy to out-license early assets. A perceived risk for investors is therefore that the market expects that the deal process will be quick and deliver short-term revenues soon. This may lead to impatience in waiting for the deal process to take its due time. For the same reason, it will be difficult for management to communicate when it expects to close a NASH deal. Another obvious short-term risk is that the TBI results do not live up to expectations. However, since the CHIC trial is designed as a PK and safety study, investors should bear in mind that a clinical phase 2b study will need to be run before we will know more about NeuroSTAT's effects in humans. Overall, we believe that NeuroVive is currently regaining its position among investors as a leader in mitochondrial medicine and that the new business model is an interesting move - which could prove ingenious, if it works.

### *Important catalysts for investors to watch:*

- Results from the CHIC phase 1/2 trial in TBI. Expected in H1 2017.
- Results from the experimental study in TBI. Expected in H1 2017.
- Results from confirming NASH and fibrosis studies with NV556. Lead candidate selection in the second NASH program NVP022. Expected in H1 2018.
- NVP015 lead candidate selection within energy regulation. Expected in H2 2017.
- Lead candidate selection within HCC program. Expected in H1 2018.



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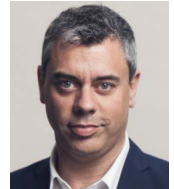
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