EDISON

BioPorto Diagnostics

Initiation of coverage

Altering the paradigm for kidney injury

Healthcare equipment & services

BioPorto is a commercial-stage diagnostic company with a portfolio of antibodies and other products sold for research and diagnostic purposes. However, its lead strategic goal is development of a test for acute kidney injury (AKI) using the biomarker NGAL. The test should provide superior results to the standard of care (serum creatinine, sCr) in two hours versus 24 hours or more. We initiate at DKK1,078m or DKK6.93 per share.

Year end	Revenue (DKKm)	PBT* (DKKm)	EPS* (DKK)	DPS (DKK)	P/E (x)	Yield (%)
12/16	20.7	(22.4)	(1.57)	0.0	N/A	N/A
12/17	25.2	(33.7)	(2.03)	0.0	N/A	N/A
12/18e	29.6	(33.3)	(1.87)	0.0	N/A	N/A
12/19e	52.7	(28.1)	(1.50)	0.0	N/A	N/A

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

The need for new technology

The standard of care for detecting AKI is measurement of sCr, a metabolite that is constantly produced by muscle and filtered from the blood. Because of this, the concentration of sCr may take 24 hours or more to build up after kidney function is compromised. By comparison, neutrophil gelatinase-associated lipocalin (NGAL) is released from the proximal tubules of the kidney and can be detected in plasma and urine within two hours of injury. This enables intervention to prevent further kidney damage and can improve hospital patient throughput.

NGAL has been heavily studied

NGAL has been examined in a large number of studies going back to 2003, with varying results. BioPorto previously submitted an application to the FDA that was rejected in 2016. The study showed 70-79% sensitivity and 73-77% specificity for stage 2-3 AKI, roughly consistent with earlier results. Following FDA feedback, the company completed an expanded trial with 17 sites and over 500 patients (results undisclosed), which was submitted to the FDA for approval in July 2018; a decision is expected before the end of 2018.

AKI detection is a major unmet need

AKI is a major complication associated with a range of serious medical conditions. Around 2% of hospital in-patients and 40% of intensive care unit (ICU) patients have AKI. We expect the ICU setting to be the first market targeted by the company with a label for risk assessment of AKI. We expect follow on indications to target the emergency department setting and following cardiothoracic surgery. The company has pre-existing distribution agreements with Roche and Siemens, through which we expect the product to be launched in the US.

Valuation: Initiated at DKK1,078m or DKK6.93/share

We arrive at an initial valuation of DKK1,078m or DKK6.93 per basic share, driven mostly by NGAL. The company had DKK25.2m in sales of its products in 2017 and has guided to sales of DKK30m in 2018. We expect it to require DKK60m in additional capital before profitability in 2020.

22 August 2018

Price	**DKK3.39**
Market cap	**DKK527m**
	DKK6.38/US$
Net cash (DKKm) at 31 June 2018	22.5
Shares in issue	155.5m
Free float	83.8%
Code	BIOPOR
Primary exchange	NASDAQ Copenhagen
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	1.2	5.8	14.0
Rel (local)	1.7	4.5	11.1
52-week high/low	DKK3.71	DKK2.99	

Business description

BioPorto is a diagnostic company focused on the development and marketing antibodies and other products for research and diagnostics. This includes a portfolio of products marketed for research use and The NGAL Test, which the company has submitted to the FDA for the prediction of acute kidney injury.

Next events

FDA decision on NGAL Test	H218
Launch of NGAL Test in US	Late 2018

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Edison profile page

BioPorto Diagnostics is a research client of Edison Investment Research Limited

Investment summary

Company description: Commercial-stage diagnostic developer

BioPorto is a diagnostics company focused on the development and commercialisation of antibody-based diagnostics. It has a portfolio of antibodies and other products that are commercially available for research use and are revenue generating, but its core commercial strategy is the launch of The NGAL Test, a diagnostic for the rapid prediction of AKI risk. NGAL is a biomarker for AKI that increases in plasma and urine concentrations in the hours following AKI, allowing intervention before substantial damage to kidneys has occurred. This is compared to the standard of care biomarker sCr, which can take one to several days to increase following AKI and only follows substantial loss in renal function. The company has completed clinical trials and has submitted a 510k application to the FDA for prediction of AKI risk. It is expecting a decision from before the end of 2018 and is targeting a US launch in late 2018.

Valuation: DKK1,078m or DKK6.93 per basic share

We arrive at an initial valuation of DKK1,078m or DKK6.93 per basic share. The immediate market following approval is the intensive care setting, which is our main value driver at DKK710m. We assign 50% probability of success for this approval and include the expansion of the test into both the emergency department setting and following cardiothoracic surgery, both at 30% probability of success. Sales of the test are expected to be primarily through the company's distribution partners Roche and Siemens, which also are the major providers of the clinical chemistry platforms on which The NGAL Test runs. Our valuation also includes the continued sales of The NGAL Test and the company's other products for research purposes.

Financials: Short path to NGAL commercialisation

The company is already revenue generating with sales of DKK25.2m in 2017 and guidance for DKK30m in sales in 2018. It has already completed the clinical trials needed for its current FDA application and future trials will largely be supportive of approval in additional indications. Because of this, future capital needs are limited and substantially offset by incoming revenue. We forecast that BioPorto will need DKK60m in additional capital to reach sustained profitability in 2020. We include this as illustrative debt in 2018.

Sensitivities: Risks of approval and adoption

The upcoming FDA approval decision is the biggest single determining factor for the success of BioPorto. The company has previously sought approval for The NGAL Test from the FDA and been rejected, and although it has been in communication with the agency regarding the improvements needed for the current clinical study, there is no guarantee this study will satisfy reviewers. The FDA has also rejected a previous application from Abbott for an NGAL-based test. The measurement of NGAL is potentially confounded by a number of other conditions, including sepsis, which is the leading cause of AKI in the ICU setting. In part, this can be used to explain the significant variability seen in studies of NGAL in the literature. A rejection from the FDA does not necessarily mean the test is dead, but it will necessitate additional clinical studies and delay approval. The company also faces the commercial hurdles associated with changing a longstanding clinical practice. sCr measurement is embedded into the diagnosis of AKI despite its limitations, and the company will need the widespread support of the physician community to change this practice. To this end, it is targeting inclusion into clinical guidelines, although this, like approval, will depend largely on the strength of the clinical data, which has not yet been published.

Company description: AKI front and centre

BioPorto was founded in 2000 in Copenhagen, and initially publicly listed on NASDAQ Copenhagen in 2004. The company was initially founded to commercialise intellectual property licensed from the Statens Serum Institut, although it has expanded its assets to include a number of important proprietary assets. The company has developed a generalizable point of care lateral flow device it has termed the generic rapid assay device (gRAD). However, the company's primary focus is the development and commercialisation of The NGAL Test for the prediction of AKI. NGAL is a biomarker secreted by the kidney shortly following injury and has been studied as a potential replacement for the standard of care, sCr. The benefit of NGAL is that it has the potential to deliver a more accurate assessment in a matter of hours, enabling interventions to preserve function, whereas sCr can take over 24 hours to reach detectable levels among other limitations. The test is commercially available in the US for research purposes and approved in Europe and some APAC countries, but the company's primary goal is approval in the US as a clinical diagnostic. It has completed clinical trials (although it has not released this data) and submitted an application to the FDA for approval for the prediction of AKI risk. We expect the product to initially be targeted to the intensive care setting. Potential future markets include the emergency department setting and continuous monitoring of AKI following surgery. The product is currently developed for use in high throughput systems, and the company has already established distribution contracts with the major commercial players in this space: Roche and Siemens.

Exhibit 1: The NGAL Test launch timing

Event	Date
Application submitted to FDA	July 2018
FDA approval decision	H218
Launch of NGAL test	Late 2018

Source: BioPorto

AKI: Desperate need for a diagnostic

AKI is a major risk to human health and wellbeing given the range of different causative factors and the potential for it to progress to long-term renal dysfunction. It is defined as the rapid deterioration in kidney function over hours or days. However, the damage associated with the condition is frequently reversible if the injury is identified quickly and patients are treated. There is therefore significant incentive to develop diagnostics that can quickly identify AKI in at-risk individuals.

There are a wide range of causes for AKI. The single largest contributing comorbidity to these rates of AKI is sepsis, which is responsible for 26% to 50% of all cases of AKI.[1] The aetiology of sepsis-induced AKI is complex and includes both direct damage to the kidneys as well as a reduction in blood flow (hypoperfusion). Hypoperfusion is a general causative factor for AKI and conditions or procedures that reduce blood flow to the kidney increases the risk of AKI. These include surgical procedures, in particular cardiac surgery, which is associated with exceptionally high rates. As many as 30% of patients undergoing cardiac surgery have complications associated with AKI.[2] AKI is responsible for a five-fold increase in mortality associated with these procedures. Due to the well understood and predictable nature of the risks in this population, these patients are routinely followed for AKI during their recovery period. Other major surgeries also carry a risk of AKI, albeit at lower rates. Other conditions that can cause a severe drop in blood pressure or fluid loss and thus

1 Alobaidi R, et al. (2015) Sepsis-Associated Acute Kidney Injury. *Semin Nephrol* 35, 2-11.

2 O'Neal JB, et al. (2016) Acute kidney injury following cardiac surgery: current understanding and future directions. *Crit Care* 20,187.

hypoperfusion can cause AKI, such as bleeding, diarrhoea, overdoses on NSAIDs, allergic reactions and shock associated with trauma, although this list is by no means exhaustive.

Given the range of conditions that can lead to AKI, the condition is relatively common. Based on measurement of sCr (more on this test below), the rate of AKI in the US is over 0.5% per year in the general population.[3] Approximately 2% of hospital inpatients and 40% of those in intensive care have AKI.[4] It is difficult to separate the prognosis of AKI from the underlying disorders, but AKI significantly increases the risk of death in a stage specific manner: odds ratio (OR) of 2.2 for stage 1, 6.1 for stage 2 and 8.6 for stage 3.[5] Among patients with AKI severe enough to require renal replacement, mortality has been observed as high as 60%.[6] Moreover, there is increasing evidence that even after resolution of AKI, that the event is correlated with increased risk of developing chronic kidney disease.[7]

Detection of AKI

AKI is classically diagnosed and staged based on the concentration of creatinine in serum and urine output. Both measurements are proxies for the glomerular filtration rate (GFR), or the rate at which the kidney can process liquid. Creatinine is the metabolic product of creatine degradation in muscle that is typically filtered from the blood by the kidney. Given that its production is relatively constant, an increase in serum levels can be indicative of renal dysfunction. The Kidney Disease International Global Organization (KDIGO) provides the criteria for staging AKI (Exhibit 2).

Exhibit 2: Staging of AKI based on KDIGO criteria

Stage	sCr	Urine output
1	1.5–1.9× baseline or ≥0.3 mg/dl above baseline	<0.5 ml/kg/hr for 6–12 hr
2	2.0–2.9× baseline	<0.5 ml/kg/hr for >12 hr
3	≥3.0× baseline, ≥4.0 mg/dl, or initiation of renal-replacement therapy	<0.3 ml/kg/hr for ≥24 hr or anuria for ≥12 hr

Source: Kidney Disease International Global Organization

Despite its widespread use, there are significant limitations in the use of sCr as a tool to diagnose AKI. The primary limitation is that changes in GFR are indicative of kidney damage, and therefore some injury and loss of function has already occurred by the time a change is measurable. This is exacerbated because creatinine must build up in the serum and it can take significant time for changes in GFR to manifest as measurable changes in creatinine. These measurements are typically taken over several days to provide adequate time to detect changes from baseline. This substantially increases the burden on providers and increases the probability that marginal cases of AKI will go undetected under a reasonable timeframe.

Baseline rates of creatinine can differ significantly between individuals and within the same individual due to a range of factors. Therefore, to be used as a biomarker, multiple measurements are required to establish a baseline and changes from this baseline. Patients of unknown status may already have elevated creatinine when they are initially tested, confounding the detection of issues. Moreover, the clearance of other substances such as medication can significantly impact the rate of creatinine clearance.

A problem in evaluating the utility of sCr as a diagnostic tool is that historically AKI has been defined in terms of sCr and little corroborative evidence has been available. One study, however, used

3 Hsu CY, et al. (2007) Community-based incidence of acute renal failure. *Kidney Int* 72, 208-212.

4 Bellomo R, et al. (2012) Acute kidney injury. *Lancet* 380, 756-766.

5 Thakar CD, et al. (2009) Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration study. *Crit Care Med* 37, 2552-2558.

6 Uchino S, et al. (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. *J Am Med Assoc* 294, 813-818.

7 Lakhnir S, et al. (2014) Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Eng J Med* 371,58-66.

biopsy data from deceased kidney donors to retrospectively evaluate the performance of sCr as a diagnostic.[8] Biopsies from these patients were examined for evidence of acute tubular injury (ATI) and compared to sCr measurements. It should be noted that ATI is a subtype of AKI and is the leading cause of AKI in a hospital setting (approximately 50%).[9] The results from this study suggest that sCr is a very poor indicator of ATI (Exhibit 3). The area under the curve (AUC) for sCr to identify any grade ATI was 0.52. This value increased marginally to 0.58 when the test was evaluated for the detection of severe ATI. AUC is a measure of the strength of a diagnostic irrespective of the particular cut-off value used for diagnosis, where 1.00 is a perfect test and 0.50 indicates no diagnostic value. So in this case sCr performed poorly.

Exhibit 3: Performance of sCr vs histology of ATI

	Severe ATI vs No ATI		Any ATI vs No ATI	
n	483		581	
AUC	0.58		0.52	
sCr criteria	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
Stage I AKI or higher	51%	61%	42%	61%
Stage II AKI or higher	26%	84%	20%	84%

Source: Moledina et al.**Error! Bookmark not defined.**

As an alternative to sCr, urine output can be used. However, monitoring of urine is unwieldy in clinical practice and is generally limited to patients with a catheter. Moreover, this measurement is rendered ineffective by diuretics. There are less clinical data to support urine output, because retrospective data are generally unavailable and clinical studies have had mixed results.[10]

NGAL to the rescue

Due to the limitations of sCr, there has been an effort to identify other biomarkers with improved performance. The most concerted effort has been focused on the investigation of NGAL. It was first identified as a marker for AKI in 2003 and has subsequently been the subject of multiple studies. Perhaps the clearest benefit of NGAL over sCr is evident in the time course of its elevation following kidney injury (Exhibit 4). NGAL is elevated within hours of the insult that results in AKI, as opposed to sCr, which requires a prolonged period of impaired GFR. Moreover, there is increasing evidence that patients that are identified by NGAL carry an increased risk for adverse events such as need for replacement therapy and death even when they are sCr negative.[11] NGAL is elevated before major loss of function, which should enable earlier intervention to halt progressive deterioration.

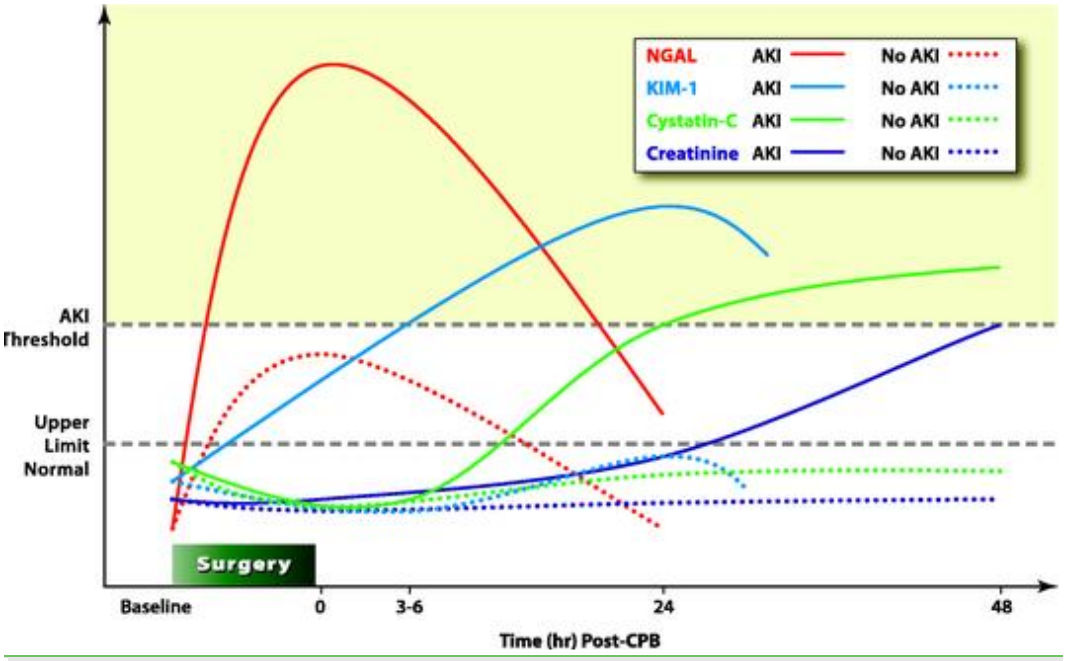
8 Moledina DG, et al. (2017) Performance of serum creatinine and kidney injury biomarkers for diagnosing histologic acute tubular injury. *Am J Kidney Dis* 70, 807-816.

9 Perazella MA, et al. (2010) Urine Microscopy Is Associated with Severity and Worsening of Acute Kidney Injury in Hospitalized Patients. *Clin J Am Soc Nephrol* 5, 402-408.

10 Cruz DN, et al. (2009) Clinical review: RIFLE and AKIN – time for reappraisal. *Crit Care* 13, 211.

11 Haase M, et al (2011) The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. *J Am Coll Cardiol* 57, 1752–1761.

Exhibit 4: Time course of biomarker elevation in AKI



Source: BioPorto

NGAL is a member of the lipocalin family, a class of proteins that bind hydrophobic molecules. It binds specifically to siderophores, proteins that bind to iron and aid in its metabolism. The protein was first discovered for its role in the innate immune system. Neutrophils secrete NGAL in response to the presence of bacteria, and the NGAL will then bind to bacterial siderophores to limit iron metabolism in the bacteria and limit their growth. However, expression of NGAL is not limited to the immune system. A range of different tissues, including but not limited to the kidney, secrete NGAL in response to cellular damage. Due to this, an increase in serum concentrations of the protein is associated with a range of indications including infection, inflammatory disorders, cancer and obesity. NGAL can be isolated from either the urine or plasma, with differing results. Urine NGAL provides a more direct readout of protein released in the kidney, but is affected by urine production and complicated by common conditions such as urinary tract infection. Plasma NGAL provides a less variable baseline but can be complicated by injury or inflammation in other tissues. Whether urine or plasma NGAL is better indicator is an unsettled question in the space, although BioPorto is advancing a plasma-based test, initially citing better reproducibility.

Two products have previously been developed for use as a NGAL test in the clinical setting, although neither was approved for in the US for diagnosis of AKI. Abbott developed a urine NGAL test for use with its Architect clinical chemistry platform. It was submitted to the FDA in 2010 but did not receive approval. Alere also developed a point-of-care plasma NGAL test for use with its Triage MeterPro platform. However, it was not submitted for FDA approval. Alere was subsequently purchased by Abbott in 2017, and as the Triage NGAL test was one of many products, it was likely not a motivating factor. BioPorto launched its first NGAL-based bioassay in 2006. This was the first commercially available NGAL ELISA kit available worldwide, albeit limited to research purposes. The company subsequently launched in 2010 a new version of the assay prepared for use in a high throughput clinical chemistry analyser branded The NGAL Test.

Previous NGAL studies

NGAL has been investigated in a large number of clinical studies, both in urine and in plasma, and significant variability between results has been observed. A recent meta-analysis was performed that examined the capacity of biomarkers to predict the initiation of renal replacement therapy, an

intervention to limit the damage from AKI.[12] Urine NGAL was evaluated in 12 studies and showed a pooled AUC of 0.720, and plasma NGAL was evaluated in 16 studies with a pooled AUC of 0.787. AUCs in the meta-analysis for NGAL ranged from 0.260 to 0.884. A consistent factor that has been cited as a source of this variability has been the differing response of patients with sepsis. As mentioned above, sepsis is the most common cause of AKI in intensive care patients, but the systemic inflammation associated with the condition results in the release of NGAL from neutrophils. Although the test retains utility in sepsis patients, the AUC for predicting renal replacement therapy can drop significantly, 0.700 in one targeted study.[13] NGAL may be a better biomarker in patient populations outside the ICU with lower rates of confounding factors such as sepsis. For instance, one study using BioPorto's NGAL antibodies (although not performed by the company) that examined 635 patients presenting in an emergency department (instead of an ICU) showed dramatically better statistics: 90.0% sensitivity, 99.5% specificity and an AUC of 0.948.[14]

Another issue that has limited the interpretation of NGAL studies is that frequently the readout used to evaluate the test is the presence of AKI, as evaluated under the standard diagnostic criteria, ie sCr. This is a problem intrinsic to this field, and has been highlighted in research.[15] Even a perfect test (100% sensitivity and specificity) will have substantially lower apparent statistics when measured against an imperfect gold standard. The fact that NGAL can identify patients at increased risk of major intervention or death that are sCr negative is also supportive of this fact.[11]

A significant factor that can be difficult to capture in these statistical studies is the improvement in care NGAL can provide. In particular the ability to identify patients sooner and before significant loss of function can translate into improved outcomes and the associated reduction in costs. Even if NGAL were unable to provide a statistical improvement in AKI prediction rates, there are still significant benefits from earlier assessment. One study modelled these factors and estimated costs savings in the range of $408–522 per patient admitted to an emergency department.[16] The models in the study were using real world outcomes data from two emergency departments in New York tested for urine NGAL and sCr.

BioPorto's first clinical trial

BioPorto conducted its first US registration trial in 2014 and 2015 across four clinical centres. The purpose of the trial was to identify the correct parameters, such as NGAL thresholds for the clinical identification of AKI using both plasma and urine. It enrolled 245 patients from ICUs and AKI was determined using the KDIGO guidelines by a panel of physician adjudicators. The data reported by the investigators segregated the patents into two populations: those with stage 2 or 3 AKI, and those with stage 1 AKI or no AKI. Samples were taken from the patients daily.

Exhibit 5: The NGAL Test statistics for stage 2/3 AKI

Fluid	Sensitivity	Specificity	AUC
EDTA plasma	78.8%	73.0%	0.76
Heparin plasma	72.7%	73.8%	0.77
Urine	69.7%	76.8%	0.79

Source: Tecson et al.

12 Klein SJ, et al. (2018) Biomarkers for prediction of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. *Int Care Med* 44, 323-336.

13 Hjortrup PB, et al. (2015) Predictive value of NGAL for use of renal replacement therapy in patients with severe sepsis. *Acta Anaesthesiol Scand* 59, 25–34.

14 Nikolas TL, et al. (2008) Sensitivity and Specificity of a Single Emergency Department Measurement of Urinary Neutrophil Gelatinase–Associated Lipocalin for Diagnosing Acute Kidney Injury. *Ann Int Med* 148, 810-819.

15 Waikar SS, et al. (2012) Imperfect Gold Standards for Kidney Injury Biomarker Evaluation. *J Am Soc Nephrol* 23, 12-21.

16 Parikh A, et al. (2017) Does NGAL reduce costs? A cost analysis of urine NGAL (uNGAL) & serum creatinine (sCr) for acute kidney injury (AKI) diagnosis. *PLOS One* 12, e0178091.

The statistics from the study were positive. AUC measurements were 0.76 and above, and sensitivity and specificity measurements were approximately 70% or higher. These results are largely in line or better than those previously presented in the literature on NGAL, although it should be noted that they represent the identification of just stages 2 and 3 AKI. When the investigators examined patients with persistent stage 2/3 AKI, the results were further improved to a maximum AUC of 0.85 with the use of EDTA plasma.

The FDA rejected the company's application package including these data. There are limited details on the reason behind the FDA's decision in this case, although the company has stated that the rejection was "primarily because the dataset for mild cases of AKI did not support approval". When explaining the decision to exclude patients with stage 1 AKI from the primary end point, the investigators cited the observation from prior studies that many patients classified in this category are subject to transient sCr elevations without parenchymal AKI. In other words, the stated reason for this exclusion was aforementioned variability in the sCr gold standard.

Ongoing clinical programme and FDA registration

The company submitted a 510k application to the FDA for approval of The NGAL Test in July 2018. This application is made based on a clinical trial that the company initiated in 2017. The primary end point of the trial was the prediction of stage 2 or 3 AKI, with a secondary end point as an aid in the prediction of persistent (two days or more) grade 2 or 3 AKI. This clinical trial enrolled over 500 patients from intensive care patients across 17 clinical sites in the US and only enrolled hypotensive patients within the first 24 hours of their admission to the ICU. Four blood samples were collected from each patient and AKI was subsequently graded based on KDIGO guidelines by an independent adjudication panel. Results from the study have not been released, although they may be in the future at a medical conference or publication to support commercialisation. The company expects a response from the FDA regarding the application by the end of 2018. The purpose of the registration study was to test the clinical validity of the test, ie does The NGAL Test (specifically the 140ng/mL cut off) predict AKI outcomes. Although we have limited detail on the study, notable changes from the previous clinical trial are the increased enrolment and number of clinical sites, as well as the prospective diagnostic threshold. The previous clinical trial did not have a predefined cut-off for prediction of AKI risk, which is a statistically weaker approach that may have impacted the FDA assessment.

The current FDA application is for "risk use with AKI", as stated by the company. An important consideration for the FDA (as well as the eventual marketing of the test) is the test's positive and negative predictive value (PPV and NPV). The PPV measures the fraction of positive tests in which the patient truly has AKI, and conversely for NPV. Importantly, both of these statistics depend on the incidence rate of AKI in the particular setting in which they are measured. The company has stated that it hopes its application supports the use of The NGAL Test to "rule out AKI within 48 hours in ICU populations". Ruling out AKI is a proposition centred on the NPV of the test. The company may expand the approved indications for The NGAL Test through further clinical testing. These include approval for risk assessment in the emergency department setting and the monitoring of AKI risk following surgery. We will have better insight into the potential of these programmes following FDA approval and potentially upon the release of details of the most recent clinical trial.

Although the ultimate hope is that physicians will be able to intervene to prevent kidney damage, they were not provided with test results in this study to accurately assess the test's validity. The company may perform future clinical trials to measure if its use can alter outcomes, although it has not made any announcements to this effect.

The company is also studying the analytical performance of The NGAL Test in a series of 10 studies in the US, Denmark and Japan. These studies were performed in parallel with the

registration study and provided additional support for the safety, reproducibility and other parameters for the FDA application.

There is also a clinical trial that has been registered by Cincinnati Children's Hospital to examine The NGAL Test for paediatric AKI. Unlike in the registration trial, this study will specifically examine AKI as a result of nephrotoxic medications and it will use testing urine as opposed to plasma. The study is expected to be complete in early 2019.

Finally, FDA approval only represents the first milestone toward commercial adoption of the test. The company will have to alter clinical practice to achieve market share. We expect as part of this effort that the company will seek the inclusion of the test into medical guidelines published by physician organisations. The company has stated its intent to engage KDIGO for inclusion in its guidelines, and it has already had preliminary meetings with KDIGO officials ahead of FDA approval. But of course, the actual adoption of NGAL as a standard by KDIGO or any other organization will both take time and depend on the strength of the clinical data.

Sales, licensing and intellectual property

The NGAL Test is already commercially available for research purposes and had sales of DKK6.4m in 2017, with DKK2.5m in US sales. The company has global distribution agreements with both Roche and Siemens, as well as a small direct sales channel that provide the test. We expect these distributors to be the primary sales channels following FDA approval, although we expect the company to hire a small sales team dedicated to the promotion of The NGAL Test. The primary commercial hurdle will be altering the long standing clinical practice regarding the use of sCr for AKI, which will take physician outreach and education, which we expect the internal sales team to perform. Other aspects of the launch should be smooth considering it seamlessly integrates into existing workflow and is billable under existing DRG codes.

The company entered into an arrangement with Abbott in 2014 to cross-license their respective intellectual property. The company has also in-licensed additional patents from Columbia University regarding the NGAL technology. The company's proprietary and in-licensed patent families cover a range of aspects of the NGAL technology and its applications including the use of urine and plasma, the use of serial sampling, and the diagnostic threshold, among others. The test is not without some degree of intellectual property risk, for instance because some patents are still pending in the US, although this is not unusual or unique to The NGAL Test. Patents begin to expire in 2025, although we expect the portfolio as it stands to provide a decent commercial runway through approximately 2028.

Other testing methodologies

In addition to NGAL, a number of other biomarkers have been investigated as alternatives to sCr (Exhibit 6). The most prominent research (other than into NGAL) has been into KIM-1 (kidney injury molecule 1) and IL-18. KIM-1 is a protein that is upregulated in the kidney following reperfusion injury in renal tubules and is a direct measure of injury (although not as the name would suggest exclusively kidney injury). IL-18 on the other hand is a pro-inflammatory cytokine secreted by macrophages that are released in response to various inflammatory conditions, including AKI. The performance of these biomarkers has generally underperformed NGAL in the clinic (AUC of 0.68 and 0.63 respectively compared to 0.74 for NGAL in one study).[17] However, the performance of these markers tends to improve with more severe AKI, and one study demonstrated superior results

17 Hall IE, et al. (2011) Risk of poor outcomes with novel and traditional biomarkers at clinical AKI diagnosis. *Clin J Am Soc Nephrol* 6, 2740-2749.

for the use in combination: AUC of 0.93 for KIM-1 + IL-18 compared to 0.89 for NGAL + sCr for the ability to predict stage 3 AKI or death.[18]

Exhibit 6: Selection of alternative AKI biomarkers

Marker	Name	Notes
NGAL	Neutrophil gelatinase-associated lipocalin	Component of the innate immune system, secreted by neutrophils and the kidney and other tissues following injury.
L-FABP	Liver-type fatty acid-binding protein	Long chain fatty acid transporter, elevated in response to tissue damage of multiple types.
IL-18	Interleukin 18	Proinflammatory cytokine produce from macrophages, associated with ischemic injury.
KIM-1	Kidney injury molecule 1	Protein specific to the kidney, upregulated following ischemia.
Cys C	Cystatin C	Protease inhibitor, ubiquitously expressed, clearance rate associated with GFR like sCr.
TIMP-2 + IGFBP-7	NephroCheck	Only branded proprietary AKI test available for the identification if imminent stage 2/3 AKI.

Source: Various

The only commercially available alternative test is NephroCheck, marketed by Astute Medical. Astute Medical was a private healthcare company that was recently acquired by BioMérieux in April 2018 for approximately $90m. NephroCheck and associated systems are its sole products, but we have limited visibility on sales.

The test combines readouts of two biomarkers TIMP-2 and IGFBP-7 in the company's proprietary linear flow devices to be used in a dedicated testing platform (the Astute140 device). These proteins were discovered in a longitudinal study of 300 biomarkers in 2013, and thus have a shorter history of study compared to other biomarkers.[19] The test is intended for use in patients following major cardiac or pulmonary events for AKI monitoring. NephroCheck was evaluated in two clinical studies. The first clinical study enrolled 408 patients and found a sensitivity of 90–93% and a specificity of 45–49% (with values varying based on the laboratory used). However, in the second clinical study of 126 patients, sensitivity dropped significantly to 76% with a specificity of 51%. This implies a negative predictive value of only 88% in the second study, meaning that 12% of patients that were ruled as AKI free in the study really had kidney injury. However, in spite of these limitations, given the low bar set by sCr, the test has been shown to improve outcomes following cardiac surgery,[20, 21] and the test (or more accurately TIMP-2 and IGFBP-7 testing) was recently included in the consensus guidelines from the ERAS Cardiac Surgery group presented to the American Association for Thoracic Surgery (moderate level of recommendation).

The antibody portfolio

Although the company's primary focus is the FDA approval of The NGAL Test and commercialisation in the US, it has an extensive portfolio of antibodies that generate recurring revenue through sales for research (Exhibit 7). In addition to the antibodies and ELISA kits derived from them, the company sells a small number of proteins (predominantly NGAL standards) and sera for research use. The company had sales of DKK25.2m in 2017 (including NGAL products).

18 Arthur JM, et al. (2014) Evaluation of 32 urine biomarkers to predict the progression of acute kidney injury after cardiac surgery. *Kidney Int* 85, 431-438.

19 Kashani K, et al. (2013) Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care* 17, R25.

20 Göcze I, et al. (2017) Biomarker-guided intervention to prevent acute kidney injury after major surgery: the prospective randomized BigpAK Study. *Ann Surg* 267, 1013-1020.

21 Meersch M, et al. (2017) Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med* 43, 1551-1561.

Exhibit 7: Classes of antibodies provided by BioPorto

Category	Examples	Notes
Animal NGAL tests	Mouse, rat, dog, pig, monkey	For use in drug development to assess renal toxicity
Allergy	Human IgE, gliadin	Only commercially available human monoclonal IgE
Appetite hormones	GLP-1, Exendin, Peptide YY	Useful for diabetes and obesity research
Compliment system	MBL, C1s, C9	Used for study of infectious disease and immunodeficiency
Autoimmune disease	Gc-Globulin, P1CP	Applications for the study of Hashimoto's, Graves', Crohn's
Infectious disease	poliovirus, influenza B, tuberculosis	Useful in testing, histology, laboratory diagnostics
Coagulation	Facor IX, antithrombin, D dimer	Study of common and rare clotting disorders

Source: BioPorto

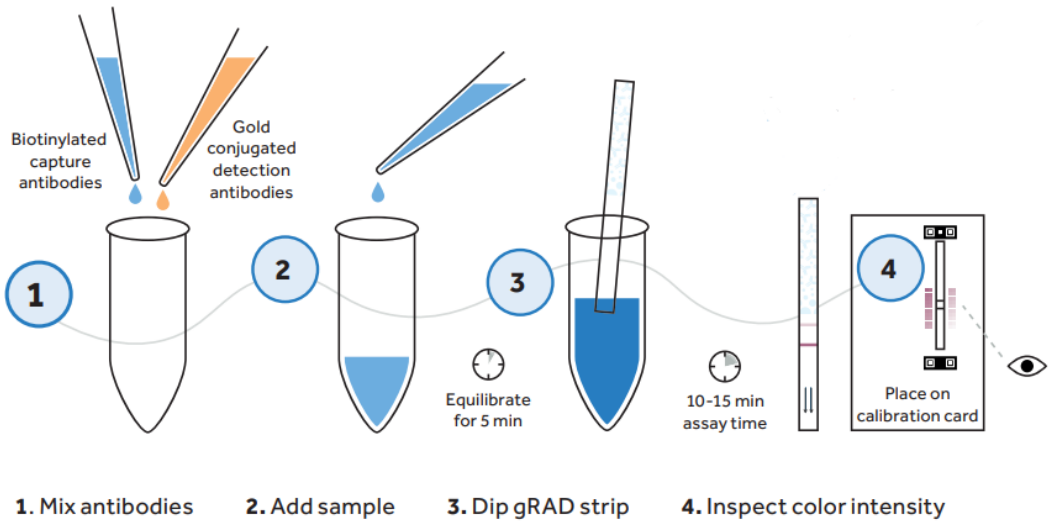
One highlight of this portfolio includes the animal NGAL tests. The company provides antibodies and standards for a range of non-human mammalian species. These may provide a more sensitive measure of kidney injury for use in the detection for renal toxicity in preclinical drug development. The company is also the only provider of monoclonal human IgE, an antibody of naturally low abundance in the body that is the primary mediator of allergic reaction. In addition to antibodies and ELISA kits, the company also sells test for mannan binding lectin (MBL) in a clinical chemistry format similar to The NGAL Test. MBL is a protein important for the innate immune system, and low levels are indicative of a compromised immune system. The expansion of the MBL test into a clinical diagnostic along the same lines of The NGAL Test is a potential future avenue of development, although we currently do not include it in our models.

The company's customers for the antibody portfolio span the healthcare space and include virtually every large pharma company, such as Pfizer, Eli Lilly, Merck, GSK, etc. Additionally, it counts large academic institutions and research institutes as clients, such as the Karolinska Institutet and the La Jolla Institute. The company has guided to continued expansion of the portfolio of one to two new products per year and minimum 19% top-line growth in 2018.

The gRAD: Generic rapid assay device

Aside from BioPorto's biologic products, it has also developed a generalisable lateral flow device called the generic rapid assay device (gRAD) (Exhibit 8). The device consists of a paper test strip similar to that used for at home diagnostics such as urine glucose strips, ovulation tests, etc. However, unlike these products, the gRAD does not come pre-loaded with detection antibodies. Instead, it can be arbitrarily used in any detection system consisting of a biotinylated antibody and a gold conjugated antibody. The strip contains a biotin binding region (presumably with some type of avidin) that captures the biotinylated antibody and immobilises the analyte, which is subsequently detected by the gold conjugated antibody. The product can therefore be used to assay biomarkers that otherwise lack a point of care test, without the need for high-cost capital equipment such as clinical chemistry instruments. The product has potential in segments of healthcare where capital equipment is unavailable, such as in field work, at the bedside and in the office of general practitioners. The gRAD was launched in 2015, but it only constitutes a small portion of the company's revenues to date. The product could potentially be used as a platform to develop tests using the company's antibodies for the point-of-care setting, although this would require additional clinical studies and is hypothetical at this stage.

Exhibit 8: Schematic of gRAD testing protocol



Source: BioPorto

Sensitivities

The biggest hurdle faced by BioPorto is the regulatory risk associated with the upcoming FDA decision on The NGAL Test. NGAL is heavily studied and, despite variability in the reported results, there is substantial benefit over the sCr standard of care even in the worst-case scenario. The barrier in this case is in communicating these benefits to the FDA and satisfying their internal standards. We have limited insight into what criteria will be used to evaluate The NGAL Test, but we can say that previous evaluations of this technology have been stringent. The FDA has previously rejected all applications for NGAL products, including from BioPorto. The company has had numerous discussions with the agency regarding a pathway to approval, but these are by no means a guarantee. However, the recent approval of NephroCheck indicates the agency recognises the need for innovation in this area. The event of an FDA dismissal does not necessarily mean the product is unapprovable, but it will likely necessitate additional clinical studies and delay the product's commercialisation. And finally, if the company does receive FDA approval, we expect it to continue to perform clinical trials in additional clinical settings to expand the market for the product, each of which will carry its individual clinical and regulatory risk.

The company's commercial strategy is to leverage its existing relationships with distributers supported by a small internal sales team. This will allow it to achieve substantial commercial reach with limited overheads, but it does leave the company at the mercy of these distributers. We believe this arrangement is optimal, given that Roche and Siemens are major suppliers of the capital equipment needed to run the test and have existing relationships with the hospital customer base. However, there is the unavoidable risk these companies will not act in the best interests of The NGAL Test or BioPorto.

BioPorto is a commercial-stage company with growing revenue streams, which significantly reduces the financial burden of its development programmes. However, we do expect the company to require additional capital to bring The NGAL Test to market, which carries associated risks. However, given the potential near term approval and commercialisation in the US, we expect this amount to be limited. We forecast the company will need DKK60m in additional capital to reach profitability in 2020, contingent upon FDA approval having been received.

Valuation

We arrive at an initial valuation of DKK1,078m or DKK6.93 per basic share. Our valuation is based on a series of assumptions about the company's products and their commercialisation. We have modelled three target markets for The NGAL Test:

- ICU patients: we believe this market is supported by the current FDA application, which is estimated as 4.6 million people in the US per year.[22] All of these patients of unknown AKI status are a potential market. We model four tests per patient in this setting as we expect continued evaluation for development of AKI. We model a peak penetration of 30%.
- Emergency department (ED) patients: we believe the company will need to perform an additional clinical study (modelled for 2019) to support approval in 2020 for this indication. As a potential market we model the population of patients that would normally receive creatinine testing (approximately 7%) of the 140 million annual ED admissions in the US.[23] We estimate one test per patient and 30% peak penetration.
- Monitoring following cardiothoracic surgery: an additional study is needed in 2019 to support approval in 2020. This population has been heavily studied in the literature and has a clear medical need, so we estimate 50% peak penetration with an average of four tests per patient. An estimated 530,000 cardiothoracic surgeries were performed in 2010 in the US and this is estimated to increase to 850,000 by 2035.[24]

This list of potential indications is not exhaustive. However, we believe expansion beyond this will be predicated on success in these areas first, although we may add other indications if the company is successful in these areas. We assign a 50% probability of success for the ICU market given the advanced nature of the programme, the results released to date, and the applicability to this patient population. We are also encouraged by the FDA's recent approval of NephroCheck, which signals an openness to innovation in this area. Consequently, ED and post-surgery markets have lower probabilities of success at 30%. We expect each of these indications will require new clinical studies, which we model costing approximately DKK13m each. The company is engaged in a study of paediatric AKI patients following nephrotoxic medications, which we do not explicitly include in our valuation as we expect the sales to be incremental. However, we do believe that expansion into the paediatric market will provide goodwill surrounding the test that can potentially boost other indications.

We model commercialisation in both the US (strategically the main focus) and Europe for these clinical populations. The US market is more attractive given that we expect adoption to be quicker following FDA approval, with first sales expected in 2019. The product is already CE marked and commercially available in Europe. However, widespread adoption in the clinical setting will need published clinical studies to support marketing. Additionally, we expect adoption in Europe to be slower than the US because of the greater control of central regulators over the implementation of new clinical methodologies. Our costs of selling are limited (modelled as 10% of revenue), because we expect most sales to go through distributor channels, and for the company's internal salesforce to be small. We expect COGS, including royalties, to be small at approximately 5% of the list price.

Our valuations are based on a $20 list price per assay for The NGAL Test. This corresponds to approximately $2,000 for a 100-assay kit, which is in line with current pricing, although we forecast a modest 2% increase in price per year. We model the price to distributors at approximately 50% the list price ($10 per assay). Our valuation for the pre-commercial indications is based on a risk adjusted NPV model at a 12.5% discount rate (our standard for pre-commercial products). We do

22 Healthcare Cost and Utilization Project.

23 National Hospital Ambulatory Medical Care Survey, CDC.

24 American Associated for Thoracic Surgery.

not expect significant tail on revenue after the company's IP expires in 2028, as we expect it to be replaced in distributor channels.

We model the company's research products (including The NGAL Test for the research market) using a DCF model at a 10% discount rate (our standard for commercial products) and a -5% terminal growth rate. We conservatively assume the products are at peak growth right now and this trend will stabilise in the coming years. We expect growth to be driven by both new products and expanding market share of existing products. We do not include the gRAD in our valuation, but we may at a later point if the product is more widely adopted. Unallocated costs in our model include administrative costs and exploratory research.

The major inflection point for the valuation will be with the FDA approval decision, expected in H218. We may adjust our valuation if data from the registration trial are released because the statistics from this study should illuminate the potential of the product in future indications. And finally, we may adjust our valuation following feedback on The NGAL Test form medical associations, which will provide a barometer for physician perceptions and rates of adoption. The inclusion of the test into any medical guidelines such as KDIGOs will represent a best-case scenario.

Exhibit 9: Valuation of BioPorto

Program	Market	Prob. of success	Peak revenue ($m)	Valuation (DKKm)
The NGAL Test	ICU	50%	188.1	732.3
	ED	30%	179.0	341.0
	Post-surgery	30%	57.3	101.6
	Research	100%	2.6	21.8
Other products	Research	100%	3.9	33.1
Unallocated costs				-174.1
Total				1055.7
Net cash and equivalents (Q218) (DKKm)				22.5
Total firm value (DKKm)				1078.3
Total shares (m)				155.51
Value per share (DKK)				6.93
Dilutive warrants (m)				11.6
Total diluted shares (m)				167.1
Value per diluted share (DKK)				6.68

Source: BioPorto reports, Edison Investment Research

Financials

BioPorto has generated consistent revenue from the sale of its research products. The company reported sales of DKK25.2m in 2017. H118 revenue was DKK11.8m, 5% lower than in the previous year (DKK12.4m in H117). This decrease was driven by delays in deliveries of antibody products and prioritisation of The NGAL Test inventory for the clinical trial. The company has a backlog of NGAL test orders to be filled later in the year and in 2019 and has guided to revenue of DKK30m for 2018. This corresponds to an expected 19% annual growth rate, which the company expects will be driven by an increase in use of The NGAL Test for research in the US. We expect the company to reach sustained profitability in 2020 as sales from The NGAL Test ramp in the US. The company ended Q218 with DKK22.5m, and we expect it to require at least DKK60m in additional capital to reach profitability. We include this financing as illustrative debt in our model in 2018, although it may be met in whole or in part through equity or licensing agreements.

Exhibit 10: Financial summary

DKK000s	2016	2017	2018e	2019e
31-December	IFRS	IFRS	IFRS	IFRS
INCOME STATEMENT				
Revenue	20,720	25,155	29,561	52,707
Cost of Sales	(5,027)	(6,907)	(8,095)	(11,295)
Gross Profit	15,693	18,248	21,466	41,412
Sales	(18,041)	(18,545)	(19,033)	(21,409)
R&D	(9,669)	(21,930)	(23,705)	(35,479)
Administrative	(13,030)	(14,267)	(15,923)	(16,719)
EBITDA	(22,596)	(33,134)	(33,804)	(28,803)
Normalised operating profit	(22,596)	(33,134)	(33,804)	(28,803)
Amortisation of acquired intangibles	(182)	(329)	(329)	(329)
Exceptionals	0	0	0	0
Share-based payments	(2,061)	(2,856)	(2,856)	(2,856)
Reported operating profit	(24,839)	(36,319)	(36,989)	(31,988)
Net Interest	148	(570)	462	741
Joint ventures & associates (post tax)	0	0	0	0
Exceptionals	0	0	0	0
Profit Before Tax (norm)	(22,448)	(33,704)	(33,342)	(28,061)
Profit Before Tax (reported)	(24,691)	(36,889)	(36,527)	(31,246)
Reported tax	2,099	4,821	3,767	3,226
Profit After Tax (norm)	(20,538)	(29,297)	(29,901)	(25,162)
Profit After Tax (reported)	(22,592)	(32,068)	(32,759)	(28,021)
Minority interests	0	0	0	0
Discontinued operations	0	0	0	0
Net income (normalised)	(20,538)	(29,297)	(29,901)	(25,162)
Net income (reported)	(22,592)	(32,068)	(32,759)	(28,021)
Basic average number of shares outstanding (m)	131	145	160	168
EPS - basic normalised (ore)	(157)	(203)	(187)	(150)
EPS - diluted normalised (ore)	(157)	(203)	(187)	(150)
EBITDA Margin (%)	-109.1	-131.7	-114.4	-54.6
Normalised Operating Margin	-109.1	-131.7	-114.4	-54.6
BALANCE SHEET				
Fixed Assets	3,069	2,623	3,158	2,622
Intangible Assets	1,959	1,629	1,223	894
Tangible Assets	400	263	1,204	997
Investments & other	710	731	731	731
Current Assets	47,572	62,981	93,224	69,880
Stocks	3,941	3,434	2,661	3,713
Debtors	4,662	6,380	7,289	12,996
Cash & cash equivalents	35,641	47,080	75,532	45,429
Other	3,328	6,087	7,741	7,741
Current Liabilities	(5,146)	(8,653)	(9,436)	(10,927)
Creditors	(1,169)	(3,412)	(5,208)	(6,699)
Tax and social security	(242)	(182)	0	0
Short term borrowings	0	0	0	0
Other	(3,735)	(5,059)	(4,228)	(4,228)
Long Term Liabilities	(1,204)	(883)	(61,040)	(61,040)
Long term borrowings	0	0	(60,000)	(60,000)
Other long term liabilities	(1,204)	(883)	(1,040)	(1,040)
Net Assets	44,291	56,068	25,906	534
Minority interests	0	0	0	0
Shareholders' equity	44,291	56,068	25,906	534
CASH FLOW				
Op Cash Flow before WC and tax	(22,596)	(33,134)	(33,804)	(28,803)
Working capital	839	2,325	604	(5,268)
Exceptional & other	(239)	(595)	462	741
Tax	2,336	2,005	2,495	3,226
Net operating cash flow	(19,660)	(29,399)	(30,243)	(30,103)
Capex	(357)	(38)	(1,148)	0
Acquisitions/disposals	0	0	0	0
Net interest	0	0	0	0
Equity financing	20,858	40,921	0	0
Dividends	0	0	0	0
Other	(67)	(45)	(157)	0
Net Cash Flow	774	11,439	(31,548)	(30,103)
Opening net debt/(cash)	(34,867)	(35,641)	(47,080)	(15,532)
FX	0	0	0	0
Other non-cash movements	0	0	0	0
Closing net debt/(cash)	(35,641)	(47,080)	(15,532)	14,571

Source: BioPorto reports, Edison Investment Research

Contact details	Revenue by geography
Tuborg Havnevej 15, st. 2900 Hellerup Denmark +45 45 29 00 00 www.bioporto.com	N/A

Management team

CEO: Peter Mørch Eriksen	COO: Jan Kuhlmann Andersen
Peter Mørch Eriksen was appointed CEO of BioPorto in July 2013. Peter Mørch Eriksen has more than 15 years of experience within medtech/life science in Denmark and abroad. Prior to joining BioPorto, Peter Mørch Eriksen was CEO of Sense and before this, he held positions as vice president of Medtronic in both the US and Denmark. In addition to being CEO of BioPorto, Peter Mørch Eriksen chairs the board of MTIC, is a board member at Nervex, member of Lund University Advisory Board, and director of PMEconsult ApS.	Jan Kuhlmann Andersen was appointed COO of BioPorto in August 2016. Jan Kuhlmann Andersen is a very experienced executive having worked with sales within the life sciences area, mostly in US-owned companies such as FMC, Cambrex, Fisher Scientific and Thermo Fisher Scientific since 1995. From 2007 and until joining BioPorto, Jan Kuhlmann Andersen was Vice President, sales & marketing, in the Animal Health & Nutrition division in Chr. Hansen.
CFO: Ole Larsen	**Chairman: Thomas Magnussen**
Ole Larsen was appointed CFO of BioPorto in June 2018. Most recently from Bavarian Nordic, a NASDAQ-listed Danish biotechnology company focused on cancer immunotherapies and vaccines for infectious diseases. Since 2008, Ole Larsen served as executive vice president and CFO and was responsible for Finance, IR and IT. Prior to this, Ole Larsen held CFO positions at two of the largest Danish and Nordic media groups, Nordisk Film and Berlingske Tidende.	Thomas Magnussen is chairman and co-founder and partner in QuantumWise and Zylinc, respectively, as well as an entrepreneur in the high-tech space, engaging in start-up companies with global business scope. Thomas Magnussen has experience in commercialization strategies and from industries including nanotechnology, ICT and medtech.

Principal shareholders	(%)
Ejendomsselskabet Jano	11.40
Media-Invest Danmark	8.06

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