PAION AG

Germany / Biotechnology
Frankfurt Prime Standard
Bloomberg: PA8 GR
ISIN: DE000A0B65S3

Update

RATING	**BUY**
PRICE TARGET	**€ 4.10**
Return Potential	114.7%
Risk Rating	High

WORLDWIDE PRODUCT ROLLOUTS GATHERING PACE

So far this year PAION's partners have launched its ultra-short-acting sedative/anesthetic, remimazolam, in the US for procedural sedation and in South Korea for the indication general anaesthesia. These launches follow market introductions by partners last year in Japan for general anaesthesia and in China for procedural sedation. Furthermore in early 2021, PAION announced the acquisition of exclusive European commercialisation rights for the vasoconstrictor, giapreza, and the tetracycline-class antibiotic, xerava, from the US company, LaJolla Pharmaceutical. Both drugs are approved in the US and Europe. Giapreza is promising because it raises blood pressure in patients with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies. Xerava, which is indicated for complex intrabdominal infections, has a broader spectrum of action than recently approved cephalosporin- and carbapenem- beta-lactamase inhibitor antibiotic combinations. This acquisition is also important because with remimazolam it gives PAION the critical mass to justify setting up its own marketing apparatus in Europe. The EU and UK authorities have recently approved remimazolam for procedural sedation and approval for general anaesthesia is likely in 2022. PAION plans to launch giapreza, remimazolam and xerava in Germany, the UK, Netherlands and Denmark during H2 2021 and in further European markets in 2022. In our view PAION's 2026 target for revenue and EBITDA of €200m and €100m, respectively is realistic, especially given the wholesale pricing of remimazolam in the US for procedural sedation, which at USD39 per dose is over 60% above our previous expectation of USD24. Procedural sedation in the US is the single biggest market for remimazolam. We maintain our Buy recommendation but have lowered the price target to €4.10 (previously €4.90). The reduction in our price target mainly reflects a larger dilutive effect from future share issues than we had previously modelled. The additional capital is required to finance the build-up of the European marketing network ahead of projected cashflow breakeven in 2024. (p.t.o.)

FINANCIAL HISTORY & PROJECTIONS

	2017	2018	2019	2020	2021E	2022E
Revenue (€ m)	5.81	2.77	8.00	19.66	9.03	30.30
Y-o-y growth	36.4%	-52.4%	189.2%	145.7%	-54.1%	235.6%
EBIT (€ m)	-15.87	-12.46	-9.33	1.58	-18.96	-24.62
EBIT margin	-273.1%	-450.3%	-116.6%	8.1%	-210.0%	-81.2%
Net income (€ m)	-12.09	-9.94	-7.02	2.22	-20.07	-26.12
EPS (diluted) (€)	-0.20	-0.16	-0.11	0.03	-0.29	-0.34
DPS (€)	0.00	0.00	0.00	0.00	0.00	0.00
FCF (€m)	-17.75	-12.83	-2.86	0.89	-36.72	-29.31
Net gearing	-98.5%	-82.7%	-97.4%	-92.2%	111.5%	534.1%
Liquid assets (€ m)	24.84	17.23	18.79	19.67	10.01	10.71

RISKS

Risks to our price target include but are not limited to: acceptance of the conpany's products, financial, and regulatory risks.

COMPANY PROFILE

PAION is a specialty pharmaceutical company headquartered in Aachen (Germany). PAION's lead substance, remimazolam, is an intravenous ultra-short-acting benzodiazepine anaesthetic with multiple approvals in different regions and in different indications.

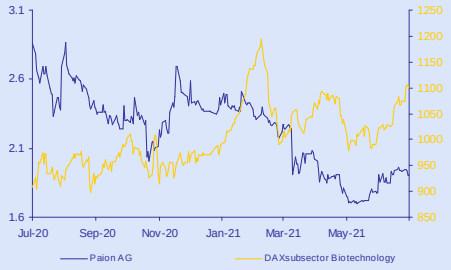
MARKET DATA

As of 09 Jul 2021

Closing Price	€ 1.91
Shares outstanding	71.30m
Market Capitalisation	€ 136.18m
52-week Range	€ 1.70 / 2.87
Avg. Volume (12 Months)	156,995

Multiples	2020	2021E	2022E
P/E	56.5	n.a.	n.a.
EV/Sales	6.9	14.9	4.5
EV/EBIT	85.2	n.a.	n.a.
Div. Yield	0.0%	0.0%	0.0%

STOCK OVERVIEW



COMPANY DATA

As of 31 Mar 2021

Liquid Assets	€ 13.90m
Current Assets	€ 20.90m
Intangible Assets	€ 20.04m
Total Assets	€ 41.84m
Current Liabilities	€ 10.75m
Shareholders' Equity	€ 17.56m

SHAREHOLDERS

Cosmo Pharmaceuticals	8.2%
Free Float	91.8%

Analyst: Simon Scholes, Tel. +49 (0)30 - 80 93 96 94

Figure 1: Q1/21 results

€ 000s	Q1 2021	Q1 2020	% chng.
Revenues	3,204	3,500	-8.5%
Cost of sales	-466	0	n.a.
R&D expenses	-1,337	-3,730	n.a.
S,G&A expenses	-3,831	-1,864	n.a.
EBIT	-2,558	-2,090	n.a.
Operating cashflow	321	-809	n.a.
Investing cashflow	-18,577	0	n.a.
Financing cashflow	12,488	-14	n.a.
Change in cash & equivs.	-5,762	-815	n.a.
Intangible assets	20,036	1,829	995.5%
Cash & equivs.	13,904	19,666	-29.3%
Equity	17,555	21,290	-17.5%
Current liabilities	10,754	6,845	57.1%
Non-current liabilities	13,535	15	90133%
Balance sheet total	41,844	28,150	48.6%

Source: PAION AG

Royalties from Japan for FY2020 and Q1/21 have still to be booked Q1/21 revenue of €3.2m (Q1/20: €3.5m) consisted of €2.6m in milestone payments and €0.6m from royalties and sales of the remimazolam active pharmaceutical ingredient to licensees. Cost of goods sold were €466k (Q1/20: €0k) and so it is likely that royalties were in the range €0.1m-€0.2m. Royalties stemmed from sales of remimazolam by PAION's partners in China and the US. PAION has not yet booked royalties from Japan for FY2020 (€0.2m) or Q1/21 because contract renegotiations with local partner Mundipharma were still ongoing as of 31 March. The amount outstanding for FY2020 and Q1/21 will be booked later this year.

R&D expenses fell by nearly two thirds to €1.3m (Q1/20: €3.7m) because of the completion of the EU Phase III study in general anaesthesia in 2020. General, administrative and selling expenses more than doubled to €3.8m (Q1/20: €1.9m) due to increased financing activities, the expansion of IT systems and infrastructure, and commercialisation and supply chain activities for remimazolam, giapreza and xerava in Europe.

PAION made an upfront payment of USD22.5m to acquire the European commercialisation rights to giapreza and xerava from La Jolla. La Jolla is also entitled to receive additional payments of up to USD109.5m dependent on the achievement of the sales milestones shown below. The contract with La Jolla also stipulates royalties on PAION's own net sales in Europe of 15% for xerava and 18%-24% for giapreza.

Milestone payments for giapreza:

- USD 5 million for annual sales > EUR 20 million
- USD 5 million for annual sales > EUR 50 million
- USD 15 million for annual sales > EUR 100 million
- USD 60 million for annual sales > EUR 250 million

Milestone payments for xerava:

- USD 2 million for annual sales > EUR 15 million
- USD 2.5 million upon EU approval of a second indication for xerava
- USD 5 million for annual sales > EUR 50 million
- USD 15 million for annual sales > EUR 100 million

Based on our forecasts, we expect additional payments to La Jolla of USD12.5m Given that we model peak sales of €70m and €30m for giapreza and xerava respectively, we forecast additional payments of USD12.5m.

Combined debt and equity financing of ca. €27m in H1/21 Cashflow from operating activities amounted to €0.3m in Q1/21 (Q1/20: €-0.8m). The upfront payment for the acquisition of the European marketing rights for giapreza and xerava accounted for most of the Q1/21 investing cash outflow of €18.6m (Q1/20: €0m). During Q1/21 PAION drew down the first two tranches (totalling €12.5m) of the EIB (European Investment Bank) loan agreement announced in June 2019. In Q2/21 the company drew down the third and final tranche of this loan (€7.5m) and also received gross proceeds of €7.8m through the issue of 5.1m new shares at €1.54. H1/21 combined debt and equity financing net proceeds of ca. €27m cover the outlay for the giapreza and xerava commercialisation rights and are also being used to prepare commercial launches of the product portfolio in selected European countries.

IN-LICENSING OF GIAPREZA AND XERAVA

In January PAION announced the acquisition of exclusive rights to commercialise giapreza and xerava in Europe from the US company La Jolla Pharmaceutical. Giapreza is synthetic human angiotensin II compound. Angiotensin II is a naturally occurring peptide hormone of the renin-angiotensin-aldosterone system that causes vasoconstriction and an increase in blood pressure. Giapreza is indicated for the treatment of hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies. Xerava is a tetracycline-class antibacterial indicated for the treatment of complicated intra-abdominal infections in adults.

GIAPREZA

Giapreza was approved by the FDA in December 2017 and by the European Commission in August 2019. In the US, where it is marketed by La Jolla, Q1/21 sales were flat at USD5.2m. In our view the flat sales development reflects difficulties in marketing the drug at a time when large numbers of medical personnel in the US were preoccupied with the COVID-19 pandemic.

Septic shock accounts for around 90% of all cases of septic or other distributive shock. Septic shock occurs when sepsis, which is organ injury or damage in response to infection, leads to dangerously low blood pressure. The standard components of treatment of sepsis/septic shock include antibiotics, fluid replenishment, and vasopressors to raise blood pressure.

Vasodilation leading to hypotension is the principal physiological abnormality in the cardiovascular response to sepsis. 1.7m adults become ill with sepsis in the US every year. Vasopressors are administered to about half these patients in order to raise their blood pressure. Three systems work together to regulate blood pressure in healthy individuals. These are the adrenal system, the vasopressin system and the renin-angiotensin-aldosterone system. Catecholamines are the first line vasopressor category of which the most widely used is norepinephrine, also known as noradrenaline. It acts to raise blood pressure by stimulating the a1 and a2 adrenergic receptors. About 40% of patients do not respond adequately to norepinephrine. The standard treatment administered to these patients is vasopressin. Vasopressin produces vasoconstriction through activation of V1 receptors on vascular smooth muscle cells. Ca. 40% of patients do not respond adequately to vasopressin. This is the target group for giapreza, which acts through the renin-angiotensin-aldosterone system.

We estimate the European target market for giapreza at 90,000 patients Given that sepsis is concentrated among older age groups, the number of 1.7m adults who become ill with sepsis each year in the US implies an annual incidence of ca. 0.5% of the population. Reliable, comprehensive figures for the incidence of sepsis in the EU and UK are hard to find. However, a German study from 2016 put the number of sepsis cases in Germany in 2013 at 279,530 which equates to an incidence rate of 0.35%. If we apply this incidence rate to the population of the European countries (Austria, France, Germany, Italy, Netherlands, Scandinavia, Switzerland, United Kingdom), which are likely to be among the initial targets for PAION's European marketing efforts, we arrive at an annual number of sepsis patients of 1.2m. Adjusting this figure for the over 90% of patients who can be satisfactorily treated with volume substitution, catecholamines or vasopressin, we arrive at an initial European target market for giapreza of ca. 90,000 patients annually.

Giapreza was approved by the European Commission on the basis of the ATHOS-phase 3 trial carried out between March 2015 and February 2017. The official title of the study was "A Phase 3, Placebo-Controlled, Randomized, Double-Blind, Multi-Center Study of LJPC-501 in Patients With Catecholamine-Resistant Hypotension". 321 adult participants were treated at nine study centres in Australia, Europe and North America. 62% of the participants were located in the US.

Patients with catecholamine-resistant hypotension were defined as requiring a total sum catecholamine dose of > 0.2 mcg/kg/min for a minimum of 6 hours and a maximum of 48 hours, to maintain a mean arterial pressure (MAP) between 55-70 mmHg.

The trial's primary outcome measure was increase in MAP defined as achievement of a day 1 MAP at three hours following the initiation of study drug of = 75 mmHg OR a 10 mmHg increase in baseline MAP.

Change in SOFA (sequential organ failure assessment) scores was a secondary objective and mortality was an exploratory objective of ATHOS-3. SOFA score is used to track a patient's status during the stay in the ICU to determine the extent of organ function or rate of failure. SOFA score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems.

Figure 2: Mean arterial pressure at Hour 3 (mITT population): Primary Efficacy Analysis (Logistic Regression)

Analysis	Placebo N = 158	LJPC-501 N = 163	Total N = 321
Number responding (n)	37	114	151
Percent responding	23.4%	69.9%	47.0%
95%[a]	17.1% - 30.8%	62.3% - 76.9%	41.5% - 52.7%
Primary analysis[b] Independent variable[b]	**Odds Ratio (95% CI)**		**p value**
Treatment, LJPC-501	7.95 (4.76 - 13.3)		2.54E-15
Baseline MAP, < 65mmHG	0.49 (0.28 - 0.86)		0.0122
Baseline APACHE II score	1.00 (0.97 - 1.03)		0.9218
Vasopressin during 6 h prior to randomisation	0.93 (0.53 - 1.62)		0.7938
Average NED in 6 h prior to randomisation	0.60 (0.29 - 1.26)		0.1803

Source: Committee for Medicinal Products for Human Use

Abbreviations: APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; mITT = modified intent-to-treat; NED = norepinephrine-equivalent dose.

[a] Exact binomial 95%

[b] Chi-square test from logistic regression model including LJPC-501 treatment (compared to placebo) adjusted by baseline MAP (<65 mmHG), baseline APACHE score, vasopressin use 6 hours prior to randomisation (yes/no) and mean norepinephrine-equivalent dose over the 6 hours prior to randomisation.

SOFA score ranges from 0 to 24. Observational studies indicate that a SOFA score of < 8, corresponds to mortality of <10%. A SOFA score of 8-11 implies mortality of around 20-30%. If the score is 12-14, mortality is 40-60%. For a score of >15 mortality is >80%.

As figure 2 shows, target MAP at hour 3 was obtained in 69.9% (95% CI: 62.3%-76.9%) of patients receiving LJPC-501 and in 23.4% (95% CI: 17.1%-30.8%) of patients receiving placebo. Angiotensin II was thus clearly superior to placebo in increasing blood pressure to MAP target 75 mmHg.

The p-value was very low at $2.5x10^{-15}$ and so the result was clearly statistically significant. The EMA's CHMP (Committee for Medicinal Products for Human Use) described the effect of angiotensin II in increasing MAP as "robust".

Total SOFA score at baseline was approximately 11.77 in the angiotensin group and 12.72 points in the placebo group. After 48 hours these figures were 12.69 and 13.76 respectively. The difference in change in SOFA score between the two groups of +1.05 for the angiotensin group and +1.04 for placebo was thus minimal. Mortality at day 28 was 46% in the angiotensin group and 54% in the placebo group. According to the CHMP's calculation the baseline imbalance in total SOFA score was statistically significant (angiotensin II SOFA score 11.77 points vs. placebo 12.72 points; Difference: -0.95; 95%CI: -1.63 to -0.27), suggesting that sicker patients were randomized to placebo. In its assessment report CHMP concluded that the "trend towards a lower mortality rate in the experimental group could be partly due to an imbalance in baseline characteristics regarding organ failure (more patients with organ failure in the placebo group)."

The CHMP's further comments on the primary outcome were: "Although the restoration of blood pressure is of main clinical relevance, there was uncertainty about whether this restoration conferred a clinical benefit, as there was a lack of improvement of total SOFA score over placebo and lack of significant improvement in the overall mortality at both Day 7 and Day 28 or any other objective assessment that would indicate clinical benefit other than increased blood pressure."

In addition, CHMP noted that angiotensin is associated with "ischemnic and thrombotic events." Thromboembolic events were reported in 13% of patients in the treatment arm (mainly deep-vein thrombosis) compared with 5% on placebo.

Approval granted on basis that in increase in MAP is likely to be correlated with increase in survival Despite these reservations, CHMP granted marketing authorisation to giapreza. In our view the following passage from the assessment report explains why:

"Looking at subgroup analyses, the treatment effect of LJPC-501 in raising and then supporting MAP when added to SOC vasopressors was particularly high in the group of patients in whom SOC vasopressors are ineffective, as evidenced by a failure to achieve the international consensus minimum target MAP of 65 mmHg. In this group, LJPC-501 was found to be nearly 3 times more effective in achieving a MAP > 65 mmHg when compared with placebo, with both arms receiving SOC vasopressors. A correlation has also been found from the literature and from exploratory analysis between achieving a MAP > 65 mmHg and survival benefit. Therefore, although the ATHOS-3 trial was not powered for mortality, the effect in raising MAP is likely to be correlated to a positive effect in survival."

CHMP requires post-authorisation efficacy study However, CHMP did require La Jolla to perform a post-authorisation efficacy study in a subpopulation at high risk of morbidity/mortality events in order to "confirm the potential clinical benefit imparted via improved haemodynamics." The deadline for submission of this study is 30 June 2024.

XERAVA

La Jolla added xerava to its product portfolio through the July 2020 acquisition of Tetraphase Pharmaceuticals. Tetraphase developed xerava as an intravenous (IV) antibiotic with the potential to become a first-line empiric monotherapy for the treatment of multidrug-resistant (MDR) bacterial infections. It usually takes 24 to 72 hours from the time a specimen is received in the laboratory to definitively diagnose a particular bacterial infection. Empiric treatment refers to treatment before diagnosis of the bacterial infection and therefore requires antibiotics effective against a broad range of bacteria.

Xerava was approved by the FDA and the European Commission in August and September 2018 respectively for treatment of complicated intra-abdominal infections (cIAIs). La Jolla's Q1/21 sales of the drug in the US rose 6% to USD1.8m (Q1/20: USD1.7m). As with giapreza, we believe that sales development was adversely affected by the impact of the COVID-19 pandemic.

Intra-abdominal infections are classified as uncomplicated or complicated based on the extent of the infection. cIAIs extend into the peritoneal space (the space between the two membranes that separate the organs in the abdominal cavity from the abdominal wall) as a result of perforation or other damage to the gastrointestinal tract. There are two broad categories of bacteria - gram-positive and gram-negative. Gram-positive bacteria take up the violet stain used in the gram stain test which classifies bacteria into gram-positive or gram-negative according to their type of cell wall. Gram-negative bacteria do not retain the violet stain. Bacterial pathogens responsible for cIAIs include gram-negative and gram-positive aerobic bacteria, and anaerobic bacteria, some of which are gram-negative and some gram-positive. Figure 3 below shows the types of bacteria which are most common in cIAIs.

Figure 3: Types of bacteria most common in cIAIs

Gram-positive	Gram-negative	Anaerobes
Streptococcus spp.	Escherichia coli	Bacterioides spp.
Enterococcus spp.	Enterobacter spp.	Anaerobe cocci
Staphylococcus spp.	Pseudomonas spp.	
	Klebsiella spp.	
	Proteus spp.	
	Acinetobacter spp.	

Source: CHMP - xerava assessment report (2018)

Overuse of existing antibiotics and lack of new therapies have resulted in a rapid increase in bacterial infections which are resistant to antibacterial agents. According to The Review on Antimicrobial Resistance, an analysis commissioned by the U.K. government in 2016, global microbial resistance, including bacteria, viruses and fungi, now results in the death of at least 700,000 people each year. Further, in a 2019 report, the CDC (Centers for Disease Control and Prevention) estimated that every year in the United States, more than 2.8 million people acquire serious infections that are resistant to one or more of the antibiotics designed to treat those infections, with at least 35,000 dying as a result, and many more dying from other conditions that are complicated by the occurrence of an antibiotic-resistant infection.

At the end of the 20th century the problem of antimicrobial resistance was concentrated on gram-positive bacteria including MRSA (methicillin-resistant staphlyococcus aureus) and vancomycin resistant enterococci (VRE). During the 21st century a shift towards a higher frequency of resistant gram-negative bacteria has occurred. In recent years there has been an increase in antibiotics that target resistant gram-negative bacteria, but there still remain limited therapeutic options for resistant gram-negative infections.

The key issue in the field of MDR gram-negative bacteria is the emergence of beta-lactamases. Beta-lactamases are enzymes produced by bacteria which provide multi-resistance to beta-lactam antibiotics such as penicillins, cephalosporins and carbapenems.

Figure 4 shows the most prevalent beta-lactamases among common bacterial species and the antimicrobial agents (substrates) to which they are resistant. As figure 4 shows, there are four molecular classes of beta-lactamases. Class A has two subcategories. Extended-spectrum beta-lactamases (ESBLs) confer resistance to cephalosporins and klebsiella-pneumoniae-carbapenemases (KPC) are resistant to cephalosporins and all carbapenems. Class B (metallo-beta-lactamases) confers resistance to all carbapenems. Class C (for example AmpC) can lead to resistance to cephalosporins and class D (for example OXAs) confers resistance mostly to carbapenems.

Figure 4: Prevalent B-lactamases among pathogens with extended drug resistance

Classification	Mechanism	Common bacterial species	Examples	Substrate
B-lactamase Ambler class A	Extended spectrum beta-lactamases	Enterobacteriacae, pseudomonas aeruginosa, acinetobacter spp.	SHV-like, CTX-like, KLUG-like	Penicillins, cephalosporins (except cefamycins), aztreonam
B-lactamase Ambler class A	Serine carbapenemases Acquisition of a mobile genetic element	Klebsiella spp.	KPC-like, IMI-like	Penicillins, cephalosporins, aztreonam, carbapenems
B-lactamase Ambler class B	Metallo-β-lactamases, carbapenemases, acquisition of a mobile genetic element	Pseudomonas aeruginosa, bacterioides fragilis acinetobacter baumannii	VIM-like, IMP-like, NDM-like GIM,SPM,SIM	Penicillins, cephalosporins, and carbapenems Monobactams are stable
B-lactamase Ambler class C	Extended spectrum, cephalosporinases Mainly Chromosomal	Enterobacter spp., klebsiella spp. proteus spp., citrobacter spp., e. coli	AmpC, P99, ACT-like CMY-like, MIR-like	-
B-lactamase Ambler class D	Carbapenemases	A. Baumannii, p. aeruginosa, e. coli	OXA-like (OXA-51,OXA-23)	Penicillins, aztreonam, and carbapenems

Source: Karaiskos I. et al (2019). The Old and the New Antibiotics for MDR Gram-Negative Pathogens: For Whom, When, and How

Figure 5 shows the prevalence of MDR bacteria in the EU/EAA as of 2019 together with the frequency of resistance to each antimicrobial agent.

Figure 5: Resistance levels of MDR bacteria to antimicrobial agents in the EU/EAA 2019

Bacterial species	No. of isolates with complete susceptibility information	% total isolates	Anitimicrobial group	Anitimicrobial agents	% resistance
			aminopenicillins	amoxicillin,ampicillin	57.10%
Escherichia coli	118,399	44.7%	third gen. cephalosporins	cefotaxime, ceftriaxone, ceftazidime	15.10%
			carbapenems	imipenem, meropenem	0.30%
Staphylococcus aureus	53,377	20.1%	MRSA	cefoxatin, oxacillin or molecular MRSA confirmation tests	15.5%
Klebsiella	39,025	14.7%	third gen. cephalosporins	cefotaxime, ceftriaxone, ceftazidime	31.30%
pneumoniae			carbapenems	imipenem,meropenem	7.90%
Pseudomonas	18,416	6.9%	piperacillin + tazobactam	piperacillin + tazobactam	16.90%
aeruginosa			ceftazidime	ceftazidime	14.30%
			carbapenems	imipenem, meropenem	16.50%
Enterococcus faecium	16,432	6.2%	vancomycin	vancomycin	18.30%
Enterococcus faecalis	13,638	5.1%	high-level aminoglycoside resistance	gentamicin high-level resistance	26.6%
Acinetobacter	5,696	2.1%	carbapenems	imipenem, meropenem	32.60%
Total isolates	264,983	100.0%			

Source: European Antimicrobial Resistance Surveillance Network (EARS-Net)

The past five years have seen the approval in both the US and Europe of several new antibiotics, including xerava, with activity against MDR gram-negative bacteria.

Approved in US and EU on basis of IGNITE1 and IGNITE4 trials Xerava was approved by the European Commission on the basis of the successful IGNITE1 (Investigating Gram-Negative Infections Treated with Eravacycline) and IGNITE4 phase 3 trials. IGNITE1 and IGNITE4 were designed as non-inferiority trials of xerava in comparison with the carbapenems, ertapenem and meropenem, respectively.

According to their US labels both ertapenem and meropenem are indicated for cIAIs. However the Infectious Disease Society of America recommends ertapenem for treatment of community-acquired intra-abdominal infections of mild-to-moderate severity and meropenem for high-risk community-acquired abdominal infections and for abdominal infections that are hospital-acquired. Tetraphase announced in December 2014 that Xerava had met the primary endpoint of statistical non-inferiority compared to ertapenem in IGNITE1 and in July 2017 that it had met the primary endpoint of statistical non-inferiority compared to meropenem in IGNITE4. In IGNITE 1 primary analysis was conducted using a 10% non-inferiority margin under FDA guidance and 12.5% non-inferiority margin under EMA guidance. Both agencies used a 12.5% non-inferiority margin to evaluate the results of IGNITE4.

Xerava failed to reach primary endpoint in cUTI trial Tetraphase also carried out the IGNITE2 and IGNITE3 phase 3 trials which studied xerava in complicated urinary tract infections. IGNITE2 and IGNITE3 were designed as non-inferiority trials of xerava in comparison with levofloxacin and ertapenem, respectively. Xerava failed to achieve the primary endpoint of a 10% non-inferiority margin in both trials.

In its 2020 10K report, La Jolla states that xerava competes with a number of antibiotics which are currently marketed for the treatment of cIAI and other multidrug resistant infections. These include merrem, recarbrio, tienam, tygacil, vaborem, zavicefta and zerbaxa. Figure 6 shows xerava and competing antibiotics ordered from left to right according to their date of approval in the EU.

Figure 6: Xerava and competing antibiotics

Brandname	Tienam	Tazocin	Merrem	Tygacil	Zavicefta	Zerbaxa	Vaborem	Xerava	Recarbrio
International non-propretiary name	imipenem/ cilastatin	piperacillin/ tazobactam	meropenem	tigecycline	ceftazidime/ avibactam	ceftolozane/ tazobactam	meropenem/ vaborbactam	eravacycline	imipenem/cilastatin/ relebactam
EU approval date	from 1985	1990s	1990s	2006	2015	2015	2018	2018	2020
EU approval for cIAI	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
EU approval for cUTI	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No
Generic/non-generic	generic	generic	generic	generic	non-generic	non-generic	non-generic	non-generic	non-generic
Sales USDm	248	69	24	182	211	56	10	8	n.a.
Region	ex-US	ex-US	Europe	ex-US	ex-US	ex-US	global	US	n.a.
Reporting company	Merck & Co.	Pfizer	Astra Zeneca	Pfizer	Pfizer	Merck & Co.	Melinta	LaJolla	n.a.
Year	2020	2019	2015	2019	2020	2020	2018/19	2020	n.a.
MIC breakpoints (S≤, R>; mg/L)* **									
Gram-negative micro-organisms including:									
Escherichia coli	2-4	8-8	2-8	0.5-0.5	8-8	2-2	8-8	0.5-0.5	2-2
Klebsiella pneumoniae	2-4	8-8	2-8	0.5-0.5	8-8	2-2	8-8	0.5-0.5	2-2
Pseudomonas aeruginosa	0.001-4	0.001-16	2-8	R	8-8	4-4	8-8	R	2-2
Enterobacter cloacae	2-4	8-8	2-8	0.5-0.5	8-8	2-2	8-8	0.5-0.5	2-2
Acinetobacter species	2-4	IE	2-8	IE	R	R	IE	IE	2-2
Gram-positive micro-organisms including:									
MS Staphylococcus aureus	0.001-4	R	R	0.5-0.5	R	R	R	0.25-0.25	0.001-4
MR Staphylococcus aureus	0.001-4	R	R	0.5-0.5	R	R	R	0.25-0.25	0.001-4
Enterococcus species	0.001-4	S	R	0.25-0.25	R	R	R	0.125-0.125	IE
Streptococcus groups A,B,C and G	S	S	S	0.125-0.125	R	IE	S	IE	S
Streptococcus pneumoniae	2-2	S	0.25-0.25	IE	R	R	S	IE	S
Streptococcus viridans	2-2	S	2-2	IE	R	IE	S	0.125-0.125	2-2
Anaerobes micro-organisms including:									
Anaerobe cocci	2-4	8-16	2-8	IE	R	IE	S	R	2-2
Bacteroides species	2-4	8-16	2-8	IE	R	IE	S	S	2-2
Clostridium species. ex clostridium difficile	2-4	8-16	2-8	IE	R	IE	S	S	2-2

MIC = Minimum Inhibitory Concentration
*S = susceptible, R = resistant
**IE = insufficient evidence

Source: European Medicines Agency, companies, European Committee on Antimicrobial Susceptibility Testing

Tienam is a combination of the carbapenem, imipenem, and cilastatin. Cilastatin has no antibiotic activity. It is a dehydropeptidase-I (DHP-I) inhibitor that prevents inactivation of imipenem by renal DHP-I thereby prolonging its antibiotic effect. Although Tienam has been available in the EU since the mid-1980s, and is now a generic, its non-US sales are among the highest generated by a xerava competitor. The USD248m sales shown in figure 6 only represents sales by Merck & Co. Fresnenius Kabi and Hexal, among others, market generic versions of tienam in the EU. Tienam's high sales, despite its generic status, are attributable to its broad spectrum coverage in bacterial infections where carbapenemases are not present.

Tazocin was first approved in the EU in the 1990s and is now available as a generic. It is a combination medication containing the penicillin-antibiotic, piperacillin and the beta-lactamase inhibitor, tazobactam. Tazobactam was invented in the early 1990s. It inhibits ESBLs, but not AmpC, KPC, MBL, or OXA-48.

Merrem is a member of the carbapenem class of antibiotics. It was first approved for use in the US in 1996 and is now available as a generic. Carbapenems are the empiric drug of choice against ESBLs but are not effective against carbapenemases.

Like Xerava, **Tygacil** is a tetracycline-class antibiotic. Tetracyclines are broad-spectrum antibacterial agents which were first introduced into human clinical use in the 1940s. However, their widespread use in human and veterinary medicine as well as in agriculture has led to the development of substantial bacterial resistance and decreased utility in indications such as cIAI. The primary mechanisms responsible for resistance to tetracyclines are efflux pumps and ribosomal protection proteins which are present in both gram-positive and gram-negative bacteria. Tygacil, which was developed using semisynthetic methods, marked a major advance for the tetracycline class as it retains broad-spectrum activity against both gram-positive and gram-negative bacteria including isolates expressing tetracycline efflux pump and ribosomal protection resistance mechanisms as well as carbapenem-resistant, ESBL-producing and MDR Enterobacteriaceae. Tygacil was approved by the FDA in June 2005 and by the European Commission in April 2006. However, the FDA issued a black box warning for tygacil in September 2010, citing an increased risk of death compared to other appropriate treatment (cause is unknown). The FDA updated the black box warning in 2013. The FDA recommends that tygacil be reserved for situations in which alternative treatment is not suitable.

Zavicefta is a fixed-dose combination of ceftazidime, a cephalosporin antibiotic and the beta-lactamase inhibitor avibactam. Cephalosporins were discovered in 1945 and first sold in 1964. Ceftazidime is a third generation cephalosporin with antipseudomonal activity. It was originally patented in 1978 and came into commercial use as a monotherapy in 1984.
Zavicefta is active against ESBLs, carbapenem-nonsusceptible enterobacterales and Pseudomonas aeruginosa as long as it is not due to metallo-beta-lactamase (MBL) genes. There is only limited data on the susceptibility of acinetobacter Baumannii to zavicefta.

Zerbaxa is a combination antibiotic consisting of the fifth generation cephalosporin, ceftolozane, and the beta-lactamase inhibitor, tazobactam. Zerbaxa is the most potent antibiotic in clinical use against pseudomonas aeruginosa, a moderately common cause of hospital-acquired infections. It is also very effective against escherichia coli but poor activity is observed against ESBL-expressing klebsiella pneumoniae for which the MIC90 (minimum inhibitory concentration at which 90% of isolates are inhibited) is 32µg/ml. It also has limited activity against carbapenem-nonsusceptible acinetobacter spp. and enterobacterales.

Vaborem is another combination antibiotic consisting of the carbapenem meropenem and the beta-lactamase inhibitor, vaborbactam. Like avibactam and tazobactam, vaborbactam protects its beta-lactam from degradation through enzymes produced by multidrug-resistant gram negative bacteria. The addition of vaborbactam improves activity against carbapenem-nonsusceptible enterobacterales including those with klebsiella pneumoniae carbapenamase but not against acinetobacter Baumannii or pseudomonas aeruginosa. Vaborem shows limited activity against isolates with MBL and OXA.

Semisynthetic processes enabled the development of tygacil but they also limited the number of chemical modifications possible at the tetracycline core. Tetraphase overcame this limitation through the development of a total synthesis method which was used to generate xerava. **Xerava** is structurally similar to tygacil but with two modifications to the D-ring of its tetracycline core. Xerava shows broad-spectrum antimicrobial activity against gram-positive, gram-negative, and anaerobic bacteria with the exception of pseudomonas aeruginosa. The structural modifications facilitated by the total synthesis method mean that xerava is two- to fourfold more potent than tygacil versus gram-positive cocci and two-to eightfold more potent than tygacil versus gram-negative bacilli. The European Committee on Antimicrobial Susceptibility Testing see insufficient evidence of xerava's activity against acinetobacter Baumannii (see figure 6). However, a recent study by Seifert H. et al – "In-vitro activity of the novel fluorocycline eravacycline against carbapenem non-susceptible acinetobacter Baumannii" (2018) compared xerava and commonly used antibiotics against a collection of 284 carbapenem-resistant acinetobacter Baumannii isolates possessing an acquired OXA or a metallo-beta-lactamase, or expressing an up-regulated intrinsic OXA-51-like enzyme. Xerava was found to be the most potent in vitro agent vs. all comparators (beta-lactams, aminoglycosides, colistin, tetracyclines, sulbactam and fluoroquinolones).

Figure 7: Possible applications of new antibiotics against gram- bacteria based on resistant mechanisms

	ESBL and AmpC	KPC	OXA-48	MBL	Carbapenem-Nonsusceptible A. baumanni	Carbapenem Nonsusceptible P. aeruginsoa
Xerava	++	++	++	+[a]	++	-
Zavicefta	++	++	++	-	-	+/-
Zerbaxa	++	-	-	-	-	+/-[b]
Vaborem	++	++	-	-	?	?
Recarbrio	++	++	-	-	-	+/-[c]

[a] 70% susceptible isolates

[b] good activity against isolates with elevated efflux, derepressed AmpC or loss of OprD, but not when the underlying mechanism is MBL production

[c] not for isolates with class B or D carbapenamase activity

Source: Yusuf E. et al (2021). An Update on Eight "New" Antibiotics against MDR gram- Bacteria

As figure 7 shows, xerava has a wider spectrum of activity against resistant gram-negative bacteria than any of the antibiotics identified by La Jolla as competitors. This, coupled with a good level of activity against gram-positive and anaerobic microorganisms (see figure 6), suggests to us that xerava is very competitive.

Recarbrio is a combination of three molecules - imipenem, cilastatin and relebactam. It is active against enterobacterales (including ESBL and AmpC isolates) and pseudomonas aeruginosa but not against acinetobacter spp. The beta-lactamase inhibitor relebactam restores imipenem's activity against klebsiella pneumoniae carbapenamase isolates and decreases the MIC values of imipenem against pseudomonas aeruginosa isolates fourfold. Recarbrio is not active against OXAs.

OUTLOOK AND VALUATION

Figure 8 below shows PAION's FY2021 guidance. Overall revenue guidance of €8.5m-€9.5m includes €5m to €6m from royalties and the sale of the remimazolam active pharmaceutical ingredient (API). We gather that PAION is supplying the API to its licensees outside Europe at a small mark-up to cost. Given that cost of revenues relates to the API, this suggests royalties on licensee sales of €2m. The small figure of €0.5m from own commercialisation of remimazolam, giapreza and Europe reflects the fact that the roll-out in Europe will only begin in H2/21 and will start in the UK, Netherlands and Nordics. Planned 2022 launches in Austria, France, Germany and Italy will be confirmed towards the end of this year.

Figure 8: 2021 revenue and profit guidance

	FY2020A	Guidance FY2021	Comments
Revenues	€19.7m	€8m-€9.5m	€7.5m to €9m from licensees - €5m to €6m from royalties and sale of remimazolam API - €2.5m to €3m from milestones €0.5m from own commercialisation of remimazolam, giapreza and xerava in parts of Europe
Cost of revenues	-	€3.5m- €4m	
R&D	€10.3m	€4.5m- €5.5m	Ongoing R&D expenses mainly in connection with market approval applications in the EU
S,G&A	€7.5m	€18m- €20m	Increase due to commercial build-up and launches ca. 10% non-cash (amortisation)
EBIT	€1.6m	€-16.5m - €-21.5m	Negative EBIT expected

Source: PAION AG

Figure 9 below shows changes to our forecasts since our last report of 9 December 2020. The changes to our 2021 numbers incorporate management guidance given at the time of the publication of the FY20 results in March. Our 2022 forecasts reflect the first full year of sales of giapreza, remimazolam and xerava in Europe.

Figure 9: Changes to forecasts

	2021E			2022E
in EURm	Old	New	Δ	New
Revenues	7.54	6.53	-13.4%	28.30
Other operating income	3.00	2.50	-16.7%	2.00
Total revenues	10.54	9.03	-14.3%	30.30
Cost of goods sold	3.31	3.99	-	16.58
% revenues	43.9%	61.1%	-	58.6%
SG&A	20.28	19.00	-	33.33
% revenues	269.0%	291.0%	-	117.8%
R&D	8.00	5.00	-	5.00
% revenues	75.9%	76.6%	-	17.7%
EBIT	-21.05	-18.96	n.a.	-24.62
% total revenues	*-199.7%*	*-210.0%*	-	*-81.2%*
Net income	-17.44	-20.07	n.a.	-26.12
% total revenues	*-165.5%*	*-222.3%*	-	*-86.2%*
EPS (dil., in EUR)	-0.27	-0.29	n.a.	-0.34

Source: First Berlin Equity Research estimates

Accelerating worldwide launch activity prompted PAION's management to give medium-term sale and EBITDA guidance in its FY2020 results presentation as shown below.

- Potential Peak Revenues with the existing portfolio of >€300m ca. 2028
  - Remimazolam EU Peak Sales c€150m
  - Remimazolam Royalties ex-EU c€60m
  - Giapreza EU Peak Sales c€70m
  - Xerava EU peak sales c€30m
  - Enables Revenues & EBITDA to potentially reach >€150m &>€75m in 2025 respectively - and then rising >€200m &>€100m in 2026

We think these numbers are realistic, especially given PAION's early 2021 announcement that the wholesale price of remimazolam in the US for procedural sedation is USD39 per dose. This is over 60% above our previous expectation of USD24. Procedural sedation in the US is the single biggest market for remimazolam.

Buy recommendation maintained but price target lowered from €4.90 to €4.10 We maintain our Buy recommendation but have lowered the price target from €4.90 to €4.10 (see figures 10 and 11 below). The reduction in our price target mainly reflects a larger dilutive effect from future share issues than we had previously modelled. The additional capital is required to finance the build-up of the European marketing network ahead of projected cashflow breakeven in 2024.

Figure 10: Valuation model

Compound	Project (1)	Present Value	Patient Pop	Treatment Cost	Market Size	Market Share	Peak Sales	PACME Margin (2)	Discount Factor	Patent Life (3)	Time to Market
Remimazolam	PS EU	€67.6M	15,144K	€14	€208.6M	25%	€68.1M	30%	12%	12	-
Remimazolam	PS US	€126.8M	22,000K	€33	€715.0M	25%	€226.7M	20%	12%	11	-
Remimazolam	PS CHN	€7.6M	33,260K	€10	€346.5M	10%	€45.7M	5%	15%	11	-
Remimazolam	PS CAN	€4.9M	1,056K	€20	€21.1M	50%	€13.4M	18%	15%	9	2 Years
Remimazolam	PS TWN	€9.6M	708K	€30	€21.2M	50%	€13.5M	30%	15%	9	2 Years
Remimazolam	GA EU	€87.5M	15,144K	€60	€908.6M	10%	€119.9M	30%	15%	11	1 Year
Remimazolam	GA US	€79.9M	23,925K	€90	€2,153.3M	10%	€273.1M	20%	15%	7	3 Years
Remimazolam	GA CHN	€14.1M	51,000K	€28	€1,405.0M	10%	€185.4M	5%	15%	8	3 Years
Remimazolam	GA JAP	€80.8M	10,000K	€90	€900.0M	12%	€142.5M	16%	12%	13	-
Remimazolam	GA KOR	€21.5M	2,585K	€75	€193.9M	25%	€64.0M	10%	12%	11	-
Remimazolam	GA TWN	€22.8M	3,750K	€33	€103.3M	25%	€34.1M	30%	15%	9	2 Years
Remimazolam	GA CIS/MENA/TUR	€38.4M	55,247K	€28	€1,566.6M	10%	€206.7M	12%	15%	9	2 Years
Remimazolam	ICU US	€14.9M	1,561K	€250	€390.2M	25%	€123.7M	20%	15%	5	5 Years
Remimazolam	ICU EU	€29.2M	2,439K	€167	€406.5M	25%	€136.8M	30%	15%	8	4 Years
Remimazolam	ICU Japan	€3.5M	606K	€167	€101.0M	25%	€33.3M	16%	15%	7	5 Years
Giapreza	DS EU	€59.3M	90K	€1,413	€127.2M	50%	€70.4M	21%	12%	13	-
Xerava	CIAI EU	€17.9M	690K	€464	€320.0M	10%	€30.6M	30%	12%	12	-
PACME PV		€686.3M									
Costs PV (4)		€363.6M									
NPV		€322.7M									
Milestones PV		€14.9M									
Pro forma net cash		€23.3M									
Fair Value		€360.9M									
Pro forma share count		88,076K									
Price Target		€4.10									

1) A project typically refers to a specific indication or, where necessary or relevant, a combination between indication and geographic market

PS EU = Procedural Sedation in the EU
PS US = Procedural Sedation in the US
PS CHN = Procedural Sedation in China
PS CAN = Procedural Sedation in Canada
PS TWN = Procedural Sedation in Taiwan
GA EU = General Anaesthesia in the EU
GA US = General Anaesthesia in the US
GA CHN = General Anaesthesia in China
GA JAP = General Anaesthesia in Japan
GA KOR = General Anaesthesia in South Korea
GA TWN = General Anaesthesia in Taiwan
GA CIS/MENA/TUR = General Anaesthesia in the Commonwealth of Independent States, Middle East & North Africa, and Turkey
ICU US = General Anaesthesia in Intensive Care Units in the US
ICU EU = General Anaesthesia in Intensive Care Units in the EU
ICU Japan = General Anaesthesia in Intensive Care Units in Japan
DS EU = Distributive Shock in the EU
CIAI EU = Complicated Intra-abdominal Infections in the EU

2) PACME (Profit After Costs and Marketing Expenses) reflects the company's profit share on future revenues. This share may be derived in the form of royalties (outsourced marketing/manufacturing) or operating EBITDA margin (in-house model), or some mix of both (depending on the specific parameters of partnership agreements)

3) Remaining patent life in years after the point of approval

4) Includes company-level R&D, G&A, Financing Costs, CapEx and working capital; COGS and S&M are factored into the PACME margin for each project

Source: First Berlin Equity Research estimates

Figure 11: Changes to our pipeline valuation model

	Old	New	Delta
NPV	**€276.1M**	**€322.7M**	**16.9%**
Milestones PV	€23.6M	€14.9M	-36.7%
Pro Forma Net Cash	€24.5M	€23.3M	-5.0%
Fair Value	€324.2M	€360.9M	11.3%
Diluted Share Count	66.2M	88.1M	33.0%
Fair Value Per Share	**€4.90**	**€4.10**	**-16.4%**

Source: First Berlin Equity Research estimates

INCOME STATEMENT

All figures in EUR '000	2017	2018	2019	2020	2021E	2022E
Net revenues	**0**	**0**	**0**	**100**	**6,530**	**28,301**
Other op. inc. (including milestones)	**5,811**	**2,766**	**8,000**	**19,555**	**2,500**	**2,000**
Total revenue	**5,811**	**2,766**	**8,000**	**19,655**	**9,030**	**30,301**
Cost of goods sold	0	0	0	0	3,989	16,584
Gross profit	**5,811**	**2,766**	**8,000**	**19,655**	**5,041**	**13,716**
S,G&A	3,828	3,408	5,023	7,523	19,000	33,333
R&D	17,854	12,167	13,099	10,288	5,000	5,000
Other operating income (expense)	-2	354	796	-261	0	0
Operating income (EBIT)	**-15,872**	**-12,455**	**-9,326**	**1,583**	**-18,959**	**-24,616**
Net financial result	20	8	-122	-152	-1,615	-2,000
Pre-tax income (EBT)	**-15,852**	**-12,447**	**-9,448**	**1,430**	**-20,574**	**-26,616**
Income taxes	3,759	2,510	2,432	792	500	500
Net income / loss	**-12,093**	**-9,937**	**-7,016**	**2,222**	**-20,074**	**-26,116**
Diluted EPS	**-0.20**	**-0.16**	**-0.11**	**0.03**	**-0.29**	**-0.34**
EBITDA	**-15,626**	**-12,265**	**-9,085**	**1,811**	**-17,374**	**-23,029**
Ratios						
EBIT margin	n.m.	n.m.	n.m.	8.1%	-210.0%	-81.2%
EBITDA margin	n.m.	n.m.	n.m.	9.2%	-192.4%	-76.0%
Net margin	n.m.	n.m.	n.m.	11.3%	-222.3%	-86.2%
Cash Coverage of Expenses						
Cash / G&A	6.5x	5.1x	3.7x	2.6x	0.5x	0.3x
Cash / R&D	1.4x	1.4x	1.4x	1.9x	2.0x	2.1x
Y-Y Growth						
Total revenue	36.4%	-52.4%	189.2%	145.7%	-54.1%	235.6%
Operating income	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.
Net income/ loss	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.

BALANCE SHEET

All figures in EUR '000	2017	2018	2019	2020	2021E	2022E
Assets						
Current assets, total	**29,357**	**22,037**	**22,650**	**26,278**	**13,836**	**27,487**
Cash and cash equivalents	24,839	17,227	18,787	19,666	10,015	10,710
Receivables	37	1,500	500	500	964	5,822
Inventories	0	0	0	1,774	1,607	9,704
Other current assets	4,481	3,311	3,363	4,337	1,250	1,250
Non-current assets, total	**2,529**	**2,286**	**2,262**	**1,872**	**18,929**	**17,397**
Property, plant & equipment	114	74	46	16	20	23
Right-of-use assets	0	0	79	26	30	35
Goodwill & other intangibles	2,415	2,212	2,137	1,829	18,879	17,339
Total assets	**31,885**	**24,323**	**24,912**	**28,150**	**32,766**	**44,884**
Shareholders' equity & debt						
Current Liabilities, Total	**6,656**	**3,501**	**10,154**	**6,845**	**3,763**	**11,246**
Convertible bond	0	0	4,354	0	0	0
Accounts payable	5,921	2,218	4,843	3,907	1,607	9,704
Provisions	391	630	270	2,206	1,500	750
Lease liabilities	0	0	55	11	13	15
Other current liabilities	344	654	632	720	643	776
Longterm liabilities, total	**0**	**0**	**26**	**15**	**20,018**	**30,020**
Long-term debt	0	0	0	0	20,000	30,000
Lease liabilities	0	0	26	15	18	20
Shareholders' equity	**25,229**	**20,822**	**14,732**	**21,290**	**8,984**	**3,618**
Total consolidated equity and debt	**31,885**	**24,323**	**24,912**	**28,150**	**32,766**	**44,884**
Ratios						
Current ratio (x)	4.41	6.29	2.23	3.84	3.68	2.44
Quick ratio (x)	4.41	6.29	2.23	3.58	3.25	1.58
Net gearing	-98.5%	-82.7%	-97.4%	-92.2%	111.5%	534.1%
Book value per share (€)	0.41	0.33	0.23	0.32	0.13	0.04
Return on equity (ROE)	-48.2%	-43.2%	-39.5%	12.3%	-132.6%	-414.5%

CASH FLOW STATEMENT

All figures in EUR '000	2017	2018	2019	2020	2021E	2022E
Net result	**-12,093**	**-9,939**	**-7,016**	**2,222**	**-20,074**	**-26,116**
Depreciation and amortization	347	255	118	343	1,585	1,587
Changes in working capital	-911	-4,647	3,516	-1,232	413	-4,725
Milestone	-5,730	0	0	0	0	0
Net taxes received	838	1,219	3	-792	0	0
Other items	-170	299	532	365	0	0
Operating cash flow	**-17,720**	**-12,813**	**-2,847**	**906**	**-18,076**	**-29,254**
CAPEX	-25	-13	-14	-14	-18,642	-55
Free cash flow	**-17,745**	**-12,826**	**-2,861**	**892**	**-36,718**	**-29,309**
Debt financing, net	**0**	**0**	**0**	**0**	**20,000**	**10,000**
Convertible bond financing, net	**0**	**0**	**4,472**	**0**	**0**	**0**
Lease financing, net	**0**	**0**	**-52**	**-51**	**4**	**5**
Equity financing, net	**12,494**	**5,214**	**0**	**26**	**7,062**	**20,000**
Other changes in cash	**-22**	**0**	**1**	**11**	**0**	**0**
Net cash flows	**-5,273**	**-7,612**	**1,560**	**878**	**-9,651**	**695**
Cash, start of the year	30,111	24,839	17,227	18,787	19,666	10,015
Cash, end of the year	**24,839**	**17,227**	**18,787**	**19,666**	**10,015**	**10,710**

Y-Y Growth						
Operating cash flow	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.
Free cash flow	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.
EBITDA/share	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.

Imprint / Disclaimer

First Berlin Equity Research

First Berlin Equity Research GmbH ist ein von der BaFin betreffend die Einhaltung der Pflichten des §85 Abs. 1 S. 1 WpHG, des Art. 20 Abs. 1 Marktmissbrauchsverordnung (MAR) und der Markets Financial Instruments Directive (MiFID) II, Markets in Financial Instruments Directive (MiFID) II Durchführungsverordnung und der Markets in Financial Instruments Regulations (MiFIR) beaufsichtigtes Unternehmen.

First Berlin Equity Research GmbH is one of the companies monitored by BaFin with regard to its compliance with the requirements of Section 85 (1) sentence 1 of the German Securities Trading Act [WpHG], art. 20 (1) Market Abuse Regulation (MAR) and Markets in Financial Instruments Directive (MiFID) II, Markets in Financial Instruments Directive (MiFID) II Commission Delegated Regulation and Markets in Financial Instruments Regulations (MiFIR).

Anschrift:
First Berlin Equity Research GmbH
Mohrenstr. 34
10117 Berlin
Germany

Vertreten durch den Geschäftsführer: Martin Bailey

Telefon: +49 (0) 30-80 93 9 680
Fax: +49 (0) 30-80 93 9 687
E-Mail: info@firstberlin.com

Amtsgericht Berlin Charlottenburg HR B 103329 B
UST-Id.: 251601797
Ggf. Inhaltlich Verantwortlicher gem. § 6 MDStV
First Berlin Equity Research GmbH

Authored by: Simon Scholes, Analyst
All publications of the last 12 months were authored by Simon Scholes.

Company responsible for preparation: First Berlin Equity Research GmbH, Mohrenstraße 34, 10117 Berlin

The production of this recommendation was completed on 12 July 2021 at 12:33

Person responsible for forwarding or distributing this financial analysis: Martin Bailey

INFORMATION PURSUANT TO SECTION 85 (1) SENTENCE 1 OF THE GERMAN SECURITIES TRADING ACT [WPHG], TO ART. 20 (1) OF REGULATION (EU) NO 596/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF APRIL 16, 2014, ON MARKET ABUSE (MARKET ABUSE REGULATION) AND TO ART. 37 OF COMMISSION DELEGATED REGULATION (EU) NO 2017/565 (MIFID) II.

First Berlin Equity Research GmbH (hereinafter referred to as: "First Berlin") prepares financial analyses while taking the relevant regulatory provisions, in particular section 85 (1) sentence 1 of the German Securities Trading Act [WpHG], art. 20 (1) of Regulation (EU) No 596/2014 of the European Parliament and of the Council of April 16, 2014, on market abuse (market abuse regulation) and art. 37 of Commission Delegated Regulation (EU) no. 2017/565 (MiFID II) into consideration. In the following First Berlin provides investors with information about the statutory provisions that are to be observed in the preparation of financial analyses.

CONFLICTS OF INTEREST

In accordance with art. 37 (1) of Commission Delegated Regulation (EU) no. 2017/565 (MiFID) II and art. 20 (1) of Regulation (EU) No 596/2014 of the European Parliament and of the Council of April 16, 2014, on market abuse (market abuse regulation) investment firms which produce, or arrange for the production of, investment research that is intended or likely to be subsequently disseminated to clients of the firm or to the public, under their own responsibility or that of a member of their group, shall ensure the implementation of all the measures set forth in accordance with Article 34 (2) lit. (b) of Regulation (EU) 2017/565 in relation to the financial analysts involved in the production of the investment research and other relevant persons whose responsibilities or business interests may conflict with the interests of the persons to whom the investment research is disseminated. In accordance with art. 34 (3) of Regulation (EU) 2017/565 the procedures and measures referred to in paragraph 2 lit. (b) of such article shall be designed to ensure that relevant persons engaged in different business activities involving a conflict of interests carry on those activities at a level of independence appropriate to the size and activities of the investment firm and of the group to which it belongs, and to the risk of damage to the interests of clients.

In addition, First Berlin shall pursuant to Article 5 of the Commission Delegated Regulation (EU) 2016/958 disclose in their recommendations all relationships and circumstances that may reasonably be expected to impair the objectivity of the financial analyses, including interests or conflicts of interest, on their part or on the part of any natural or legal person working for them under a contract, including a contract of employment, or otherwise, who was involved in producing financial analyses, concerning any financial instrument or the issuer to which the recommendation directly or indirectly relates.

With regard to the financial analyses of PAION AG the following relationships and circumstances exist which may reasonably be expected to impair the objectivity of the financial analyses: The author, First Berlin, or a company associated with First Berlin reached an agreement with the PAION AG for preparation of a financial analysis for which remuneration is owed.

Furthermore, First Berlin offers a range of services that go beyond the preparation of financial analyses. Although First Berlin strives to avoid conflicts of interest wherever possible, First Berlin may maintain the following relations with the analysed company, which in particular may constitute a potential conflict of interest:

- The author, First Berlin, or a company associated with First Berlin owns a net long or short position exceeding the threshold of 0,5 % of the total issued share capital of the analysed company;
- The author, First Berlin, or a company associated with First Berlin holds an interest of more than five percent in the share capital of the analysed company;

- The author, First Berlin, or a company associated with First Berlin provided investment banking or consulting services for the analysed company within the past twelve months for which remuneration was or was to be paid;
- The author, First Berlin, or a company associated with First Berlin reached an agreement with the analysed company for preparation of a financial analysis for which remuneration is owed;
- The author, First Berlin, or a company associated with First Berlin has other significant financial interests in the analysed company;

With regard to the financial analyses of PAION AG the following of the aforementioned potential conflicts of interests or the potential conflicts of interest mentioned in Article 6 paragraph 1 of the Commission Delegated Regulation (EU) 2016/958 exist: The author, First Berlin, or a company associated with First Berlin reached an agreement with the PAION AG for preparation of a financial analysis for which remuneration is owed.

In order to avoid and, if necessary, manage possible conflicts of interest both the author of the financial analysis and First Berlin shall be obliged to neither hold nor in any way trade the securities of the company analyzed. The remuneration of the author of the financial analysis stands in no direct or indirect connection with the recommendations or opinions represented in the financial analysis. Furthermore, the remuneration of the author of the financial analysis is neither coupled directly to financial transactions nor to stock exchange trading volume or asset management fees.

INFORMATION PURSUANT TO SECTION 64 OF THE GERMAN SECURITIES TRADING ACT [WPHG], DIRECTIVE 2014/65/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 15 MAY 2014 ON MARKETS IN FINANCIAL INSTRUMENTS AND AMENDING DIRECTIVE 2002/92/EC AND DIRECTIVE 2011/61/EU, ACCOMPANIED BY THE MARKETS IN FINANCIAL INSTRUMENTS REGULATION (MIFIR, REG. EU NO. 600/2014).

First Berlin notes that is has concluded a contract with the issuer to prepare financial analyses and is paid for that by the issuer. First Berlin makes the financial analysis simultaneously available for all interested security financial services companies. First Berlin thus believes that it fulfils the requirements of section 64 WpHG for minor non-monetary benefits.

PRICE TARGET DATES

Unless otherwise indicated, current prices refer to the closing prices of the previous trading day.

AGREEMENT WITH THE ANALYSED COMPANY AND MAINTENANCE OF OBJECTIVITY

The present financial analysis is based on the author's own knowledge and research. The author prepared this study without any direct or indirect influence exerted on the part of the analysed company. Parts of the financial analysis were possibly provided to the analysed company prior to publication in order to avoid inaccuracies in the representation of facts. However, no substantial changes were made at the request of the analysed company following any such provision.

ASSET VALUATION SYSTEM

First Berlin's system for asset valuation is divided into an asset recommendation and a risk assessment.

ASSET RECOMMENDATION

The recommendations determined in accordance with the share price trend anticipated by First Berlin in the respectively indicated investment period are as follows:

Category		1	2
Current market capitalisation (in €)		0 - 2 billion	> 2 billion
Strong Buy[1]	An expected favourable price trend of:	> 50%	> 30%
Buy	An expected favourable price trend of:	> 25%	> 15%
Add	An expected favourable price trend of:	0% to 25%	0% to 15%
Reduce	An expected negative price trend of:	0% to -15%	0% to -10%
Sell	An expected negative price trend of:	< -15%	< -10%

[1] The expected price trend is in combination with sizable confidence in the quality and forecast security of management.

Our recommendation system places each company into one of two market capitalisation categories. Category 1 companies have a market capitalisation of €0 – €2 billion, and Category 2 companies have a market capitalisation of > €2 billion. The expected return thresholds underlying our recommendation system are lower for Category 2 companies than for Category 1 companies. This reflects the generally lower level of risk associated with higher market capitalisation companies.

RISK ASSESSMENT

The First Berlin categories for risk assessment are low, average, high and speculative. They are determined by ten factors: Corporate governance, quality of earnings, management strength, balance sheet and financial risk, competitive position, standard of financial disclosure, regulatory and political uncertainty, strength of brandname, market capitalisation and free float. These risk factors are incorporated into the First Berlin valuation models and are thus included in the target prices. First Berlin customers may request the models.

RECOMMENDATION & PRICE TARGET HISTORY

Report No.:	Date of publication	Previous day closing price	Recommendation	Price target
Initial Report	2 April 2012	€0.79	Buy	€2.00
2...38	↓	↓	↓	↓
39	28 March 2019	€2.17	Buy	€4.10
40	21 August 2019	€2.26	Buy	€4.20
41	19 February 2020	€2.22	Buy	€3.80
42	23 April 2020	€1.74	Buy	€3.60
43	9 July 2020	€2.93	Buy	€4.90
44	17 August 2020	€2.69	Buy	€4.90
45	9 December 2020	€2.45	Buy	€4.90
47	Today	€1.91	Buy	€4.10

INVESTMENT HORIZON

Unless otherwise stated in the financial analysis, the ratings refer to an investment period of twelve months.

UPDATES

At the time of publication of this financial analysis it is not certain whether, when and on what occasion an update will be provided. In general First Berlin strives to review the financial analysis for its topicality and, if required, to update it in a very timely manner in connection with the reporting obligations of the analysed company or on the occasion of ad hoc notifications.

SUBJECT TO CHANGE

The opinions contained in the financial analysis reflect the assessment of the author on the day of publication of the financial analysis. The author of the financial analysis reserves the right to change such opinion without prior notification.

Legally required information regarding

- **key sources of information in the preparation of this research report**
- **valuation methods and principles**
- **sensitivity of valuation parameters**

can be accessed through the following internet link: https://firstberlin.com/disclaimer-english-link/

SUPERVISORY AUTHORITY: Bundesanstalt für Finanzdienstleistungsaufsicht (German Federal Financial Supervisory Authority) [BaFin], Graurheindorferstraße 108, 53117 Bonn and Marie-Curie-Straße 24-28, 60439 Frankfurt am Main

EXCLUSION OF LIABILITY (DISCLAIMER)

RELIABILITY OF INFORMATION AND SOURCES OF INFORMATION

The information contained in this study is based on sources considered by the author to be reliable. Comprehensive verification of the accuracy and completeness of information and the reliability of sources of information has neither been carried out by the author nor by First Berlin. As a result no warranty of any kind whatsoever shall be assumed for the accuracy and completeness of information and the reliability of sources of information, and neither the author nor First Berlin, nor the person responsible for passing on or distributing the financial analysis shall be liable for any direct or indirect damage incurred through reliance on the accuracy and completeness of information and the reliability of sources of information.

RELIABILITY OF ESTIMATES AND FORECASTS

The author of the financial analysis made estimates and forecasts to the best of the author's knowledge. These estimates and forecasts reflect the author's personal opinion and judgement. The premises for estimates and forecasts as well as the author's perspective on such premises are subject to constant change. Expectations with regard to the future performance of a financial instrument are the result of a measurement at a single point in time and may change at any time. The result of a financial analysis always describes only one possible future development – the one that is most probable from the perspective of the author – of a number of possible future developments.

Any and all market values or target prices indicated for the company analysed in this financial analysis may not be achieved due to various risk factors, including but not limited to market volatility, sector volatility, the actions of the analysed company, economic climate, failure to achieve earnings and/or sales forecasts, unavailability of complete and precise information and/or a subsequently occurring event which affects the underlying assumptions of the author and/or other sources on which the author relies in this document. Past performance is not an indicator of future results; past values cannot be carried over into the future.

Consequently, no warranty of any kind whatsoever shall be assumed for the accuracy of estimates and forecasts, and neither the author nor First Berlin, nor the person responsible for passing on or distributing the financial analysis shall be liable for any direct or indirect damage incurred through reliance on the correctness of estimates and forecasts.

INFORMATION PURPOSES, NO RECOMMENDATION, SOLICITATION, NO OFFER FOR THE PURCHASE OF SECURITIES

The present financial analysis serves information purposes. It is intended to support institutional investors in making their own investment decisions; however in no way provide the investor with investment advice. Neither the author, nor First Berlin, nor the person responsible for passing on or distributing the financial analysis shall be considered to be acting as an investment advisor or portfolio manager vis-à-vis an investor. Each investor must form his own independent opinion with regard to the suitability of an investment in view of his own investment objectives, experience, tax situation, financial position and other circumstances.

The financial analysis does not represent a recommendation or solicitation and is not an offer for the purchase of the security specified in this financial analysis. Consequently, neither the author nor First Berlin, nor the person responsible for passing on or distributing the financial analysis shall as a result be liable for losses incurred through direct or indirect employment or use of any kind whatsoever of information or statements arising out of this financial analysis.

A decision concerning an investment in securities should take place on the basis of independent investment analyses and procedures as well as other studies including, but not limited to, information memoranda, sales or issuing prospectuses and not on the basis of this document.

NO ESTABLISHMENT OF CONTRACTUAL OBLIGATIONS

By taking note of this financial analysis the recipient neither becomes a customer of First Berlin, nor does First Berlin incur any contractual, quasi-contractual or pre-contractual obligations and/or responsibilities toward the recipient. In particular no information contract shall be established between First Berlin and the recipient of this information.

NO OBLIGATION TO UPDATE

First Berlin, the author and/or the person responsible for passing on or distributing the financial analysis shall not be obliged to update the financial analysis. Investors must keep themselves informed about the current course of business and any changes in the current course of business of the analysed company.

DUPLICATION

Dispatch or duplication of this document is not permitted without the prior written consent of First Berlin.

SEVERABILITY

Should any provision of this disclaimer prove to be illegal, invalid or unenforceable under the respectively applicable law, then such provision shall be treated as if it were not an integral component of this disclaimer; in no way shall it affect the legality, validity or enforceability of the remaining provisions.

APPLICABLE LAW, PLACE OF JURISDICTION

The preparation of this financial analysis shall be subject to the law obtaining in the Federal Republic of Germany. The place of jurisdiction for any disputes shall be Berlin (Germany).

NOTICE OF DISCLAIMER

By taking note of this financial analysis the recipient confirms the binding nature of the above explanations.

By using this document or relying on it in any manner whatsoever the recipient accepts the above restrictions as binding for the recipient.

QUALIFIED INSTITUTIONAL INVESTORS

First Berlin financial analyses are intended exclusively for qualified institutional investors.

This report is not intended for distribution in the USA and/or Canada.