EDISON

Paion

Filings pending

First filings later this year

Pharma & biotech

In December 2017 Paion granted Mundipharma an exclusive licence to develop and commercialise its ultra-short-acting sedative/anaesthetic remimazolam in Japan. Paion is on track to file for approval in both Japan (for general anaesthesia, GA, via Mundipharma) and the US (in procedural sedation via partner Cosmo Pharmaceuticals) within the next 12 months. It plans to initiate a GA Phase III trial in Europe in H218 and intends to self-commercialise remimazolam if it gains marketing approval in Europe. Anticipated filing milestones of €9.5m would extend the funding runway into H219 and beyond top-line data from the EU Phase III expected mid-2019. We increase our valuation to €269m or €4.40 per share, from €260m or €4.25 per share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
12/16	4.3	(25.1)	(37.8)	0.0	N/A	N/A
12/17	5.8	(15.9)	(20.5)	0.0	N/A	N/A
12/18e	3.1	(16.6)	(22.3)	0.0	N/A	N/A
12/19e	10.5	(6.4)	(6.6)	0.0	N/A	N/A

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

Commercialisation partner for Japan

The Mundipharma licence deal brings €1m upfront cash, regulatory and sales milestones of €25m and a tiered royalty starting in the low double digits to over 20% (we model average 16% royalty rate). Mundipharma will fund regulatory filing and commercialisation in Japan, and plans to file for market approval for GA in Japan in 2018. Paion expects to receive €2m in connection with filing in Japan.

Phase III for GA in Europe to commence H218

Based on a recent Phase I study and scientific advice from the European Medicines Agency (EMA), the company is planning to start a Phase III trial in GA in Europe in H218. The 450-500 patient trial would be similar in design to the successful Phase III trial in GA in Japan, but would target sicker and elderly patients who will gain the greatest benefit from the capacity of remimazolam to reduce the incidence of hypotension.

Cosmo plans US filing Q418 or Q119

Paion has completed clinical development of remimazolam for procedural sedation in the US, and is working to complete and deliver the data packages from the US development program to Cosmo. Cosmo plans to hold a pre-NDA meeting with the FDA shortly before filing, and expects to file for approval in Q418 or Q119.

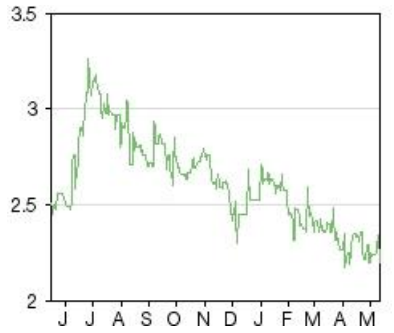
Valuation: Lifted to €269m

We increase our valuation to €269m, or €4.40 per share, from €260m or €4.25 per share. We have adopted self-commercialisation of remimazolam in Europe with a 30% operating profit margin in our base case model (previously modelled a 20% royalty), and increased probabilities of success in Japan, Europe and Canada. This has more than offset later remimazolam launch dates in most regions and adjusting commercial terms in Japan to align with the Mundipharma deal terms.

14 May 2018

Price	**€2.20**
Market cap	**€134m**
	US$1.10/€
Net cash (€m) at end March 2018	22.1
Shares in issue	61.1
Free float	75%
Code	PA8
Primary exchange	Frankfurt
Secondary exchange	Xetra

Share price performance



%	1m	3m	12m
Abs	(3.9)	(11.1)	(10.1)
Rel (local)	(9.2)	(17.2)	(12.1)
52-week high/low		€3.3	€2.2

Business description

Paion is an emerging specialty pharma company developing anaesthesia products. Lead product remimazolam is undergoing US Phase III trials and is partnered with Cosmo (US), Mundipharma (Japan), Yichang (China), Hana Pharma (South Korea), Pendopharm (Canada) and R-Pharm (CIS, Turkey, MENA).

Next events

Japan filing for GA by Mundipharma	2018
US filing for procedural sedation by Cosmo	Q418/Q119
Initiate GA Phase III in Europe	H218

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Investment summary

Company description: Anaesthesia and critical care

Paion is a Frankfurt-listed emerging specialty pharma company that develops products for anaesthesia and critical care. Its headquarters are in Aachen, Germany. Paion is focusing on lead programme remimazolam, which it acquired in 2008 through its purchase of CeNeS Pharma for €12m. Short-acting sedative/anaesthetic remimazolam has potential in three indications: procedural sedation, general anaesthesia and intensive care unit (ICU) sedation. Paion has completed a successful clinical development programme in procedural sedation in the US, including two pivotal Phase III studies, and plans to initiate a Phase III trial in GA in Europe in H218. It has raised over €120m since flotation in 2005, including €46m at the IPO. Paion has out-licensed rights to remimazolam to partners in the US, Japan and a number of other territories, but plans to establish its own sales force to self-commercialise remimazolam in some or all of the EU (if approved). Its partners expect to file for marketing approval for remimazolam in the US, Japan and Russia over the coming year.

Valuation: Filings in the US and Japan on track

Our sum-of-the-parts DCF valuation is €269m or €4.40 per share, increased from €260m in our November report. With a partner in place and a clinical development programme successfully completed in the US, we assume an 85% probability of success in that country, which we would likely increase to 90% on filing. We take a slightly more cautious view on Japan with an 80% likelihood of approval, in view of Ono's decision to return the rights in that country in 2014. In Europe, where a Phase III study is planned to commence in H218, we assume a 60% probability of success. We assume an average royalty rate of 20% in the US, with lower rates in other partnered territories. We assume a 30% operating profit margin for self-commercialisation in Europe.

Sensitivities: Filing and approval in the US and Japan

The main sensitivities for Paion are the success or failure of the pending marketing applications and clinical studies for the lead product remimazolam. There is already a substantial body of advanced clinical evidence for remimazolam showing it has a good safety and efficacy profile in comparison to the standard of care. This should support the product and the economic rationale, which will compete with established generic products. Other sensitivities include the usual regulatory, financial and partnering risks associated with a pharmaceutical company in the late stages of development and preparing for commercialisation.

Financials: Licensing deals have reduced funding risk

Paion reported revenues of €0.3m and a net loss of €3.1m for Q118 vs a loss of €2.2m in Q117. Operating cash outflow was €2.8m. R&D expenses declined by €0.7m to €3.4m due to lower costs for the Phase III studies in the US. Paion had €22.1m in net cash on 31 March 2018, which, when combined with €9.5m of milestone payments linked to anticipated filing in Japan and the US and €3m of UK income tax credits is expected to be sufficient to fund operations into H219. This will include preparations for filing in the US and Japan and conducting the Phase III GA trial in Europe. A further €15m funding would be required to support operations until filing in Europe, based on Paion's current planning. Depending on timing of approvals, these funds could potentially be provided by milestones payments for approval in the US (€15m) and Japan (we model €5m). Our end-2018 cash estimate is €11.2m.

Paion: Specialty pharma enters the home stretch

Paion is at an advanced stage in developing remimazolam, an ultra-short-acting intravenous (IV) benzodiazepine sedative/anaesthetic, which is on track for potential approvals in Japan in 2019 for GA and in the US in H219/H120 for procedural sedation. European studies in GA are planned to restart in H218. Paion has licenced US rights to Cosmo Pharmaceuticals and Japan rights to Mundipharma, and has a further four partners in other territories, as shown in Exhibit 1. The economic rationale for remimazolam focuses on an improved safety profile and faster induction and recovery from sedation allowing higher patient throughput compared to generic alternatives.

Exhibit 1: Summary of remimazolam's development status and global partners

Region/partner	Lead indication	Clinical status	Notes
US/Cosmo	Procedural sedation	Preparing to file	Clinical development programme successfully completed, including Phase III studies in colonoscopy and bronchoscopy and a safety study in higher-risk colonoscopy patients. Both pivotal Phase III studies were double-blind, placebo and midazolam controlled.
EU	General anaesthesia	New Phase III planned H218	Headline data from Phase II trial in cardiac surgery met the primary endpoint, efficacy as a general anaesthetic in 98% of pts in the two remimazolam groups vs 96% in the propofol group. Initial results indicate that both remimazolam groups experienced less cardiac depression. Randomised, Phase III study in general surgery patients planned to commence in H218. A previous Phase III in cardiac surgery patients was discontinued in February 2016 due to slow recruitment.
Japan/Mundipharma	General anaesthesia/ICU sedation	Preparing to file	Cardiovascular profile superior to standard-of-care propofol n=375. BP fell in 35.3%/34.7% of remimazolam pts vs 60% of propofol pts. Mundipharma is preparing for an NDA filing with Japanese regulator in 2018.
South Korea/Hana Pharma	Anaesthesia	Phase III	Phase III in GA initiated in March 2018. The Japanese filing document will be used as the basis for filing in South Korea.
China/Yichang Humanwell	Anaesthesia	Phase II in GA; Phase III in PS	Subject to the requirements of the SFDA. Has completed a Phase I study programme in China and is going to conduct a Phase III trial in procedural sedation and a Phase II study in GA.
CIS, Russia, Turkey, MENA/R-Pharm	Anaesthesia	Phase III in Russia underway	R-Pharm has a licence to develop, manufacture and commercialise remimazolam in these regions. It plans to file for approval in Russia in late 2018.
Canada/Pendopharm	Procedural sedation	Will file based on US dossier	Minimal additional development; intends to file after dossier has been submitted in the US.

Source: Paion, Edison Investment Research. Note: PS = procedural sedation; BP = blood pressure.

Remimazolam: Versatile, effective and safe sedation

Remimazolam has been shown to be a safer, faster alternative to approved sedatives and potentially carries a reduced risk of cardiac and respiratory depression, which is particularly significant for older and less healthy patients. Studies of remimazolam have shown it is suited for three indications requiring varying depths of sedation – general anaesthesia, procedural and ICU sedation – while maintaining the vital physiological and neurological functions of the patient.[1] The characteristics of remimazolam compared to standard sedatives are shown in Exhibit 2.

Exhibit 2: Summary of key features of remimazolam vs approved anaesthetics

Key feature	Remimazolam	Propofol	Midazolam	Dexmedetomidine
Rapid onset	Yes	Yes	No	Yes
Rapid offset	Yes	Yes	No	No
Low respiratory depression	Yes	No	No	Yes
Cardiovascular stability	Yes	No	No	No
Early recovery to full cognition	Yes	No	Yes	Yes
Reversal agent available	Yes	No	Yes	No
Need to adjust dose for body weight	No	Yes	Yes	Yes

Source: Edison Investment Research

1 American Society of Anesthiologists guidelines on the continuum of sedation.

Partner Mundipharma to file in Japan in H218

In December Paion licenced the Japanese rights to remimazolam to Mundipharma. Financial terms included €1m upfront, up to €25m of additional payments for achieving certain regulatory and commercial milestones in the three indications procedural sedation, general anaesthesia and ICU sedation. Paion will receive tiered royalties starting in the low single digits to over 20% of net sales (we model an average 16% royalty rate).

The licence agreement is a positive development for Paion. Mundipharma takes over responsibility for filing for approval for GA in Japan, and has the right and obligation to further develop remimazolam in all indications in Japan (including procedural sedation and ICU sedation). Mundipharma will bear all of the costs for market authorisation and distribution, and it plans to file for market approval in Japan in 2018. Paion expects to receive payments of €2m in connection with the Japan filing (this sum includes a payment from Hana Pharma, which has licenced rights in South Korea).

With a partner in place, we have increased the probability of success in Japan from 60% to 80%. We would likely further increase the probability to 85% when the marketing dossier is filed.

Paion had previously licenced Japan rights to Ono, which conducted a successful Phase II/III trial in GA. The 375-patient trial met its primary endpoint and showed remimazolam was 100% effective in inducing and maintaining general anaesthesia. There was a statistically significantly lower incidence of hypotension (low blood pressure) in the remimazolam groups than in the propofol arm (low blood pressure events observed in 35.3% and 34.7% of patients in the high-and low-dose remimazolam groups, vs 60% of patients in the propofol arm). The data are consistent with other studies that indicated remimazolam's good safety profile.

While the GA trial was very successful, in August 2013 Ono discontinued a separate Phase II dose-finding trial of remimazolam for sedation in ICUs. While all patients were sedated successfully and there were no significant unexpected adverse events, higher than expected plasma concentrations of remimazolam were observed in isolated cases after long-term treatment. The phenomenon of elevated remimazolam plasma concentrations could not be reproduced in preclinical studies or pharmacokinetic models. However, Ono subsequently terminated its licence agreement for remimazolam following a profit warning in October 2014. Anaesthesia is not a core business for Ono, and the anticipated delay in filing and the company's increased focus on oncology were likely important factors in its decision to return the rights to Paion.

Further analysis by Paion has shown that pharmacokinetic deviations are common for sedatives like midazolam and propofol in the ICU and are probably related to the underlying conditions of the patients in the ICU. Paion concluded that the maximum dose level has been identified for ICU sedation. Under the licence agreement, Mundipharma has an obligation to further develop remimazolam in ICU sedation and procedural sedation in Japan. Given the overall safety record of remimazolam, we do not expect the plasma levels seen in the ICU sedation trial to interfere with approvals in GA or procedural sedation.

Cosmo plans US filing Q418 or Q119

Paion granted Cosmo Pharmaceuticals an exclusive licence for the development and commercialisation of remimazolam in the US in June 2016, soon after it reported positive results for its first US-based Phase III study in procedural sedation in patients undergoing a colonoscopy. Since then, Paion has successfully completed a second Phase III study (in bronchoscopy patients), a further Phase III study in higher risk patients undergoing a colonoscopy, plus two Phase I studies to assess the abuse potential of remimazolam. It was advised by the FDA in November that these

studies provided all of the necessary data regarding the abuse potential in humans, so the clinical development programme for remimazolam in procedural sedation in the US is regarded as complete by Paion.

Paion is working to complete an integrated overall analysis of all clinical studies with remimazolam, and to complete and deliver the data packages from the US development programme to Cosmo. Cosmo plans to hold a pre-NDA meeting with the FDA shortly before filing.

The latest guidance from Cosmo is that it expects to file for approval in the US in Q418 or Q119. This represents slight slippage from previous guidance of filing in H218, although that target may yet be achieved. Paion has taken a conservative approach to timing and does not include filing milestones in its FY18 guidance. Given that filing may not occur until Q119, we have delayed our forecast US launch from 2019 to 2020.

We currently assume an 85% probability of approval, which we would increase to 90% when the marketing submission is filed.

Cosmo has disclosed remimazolam milestones

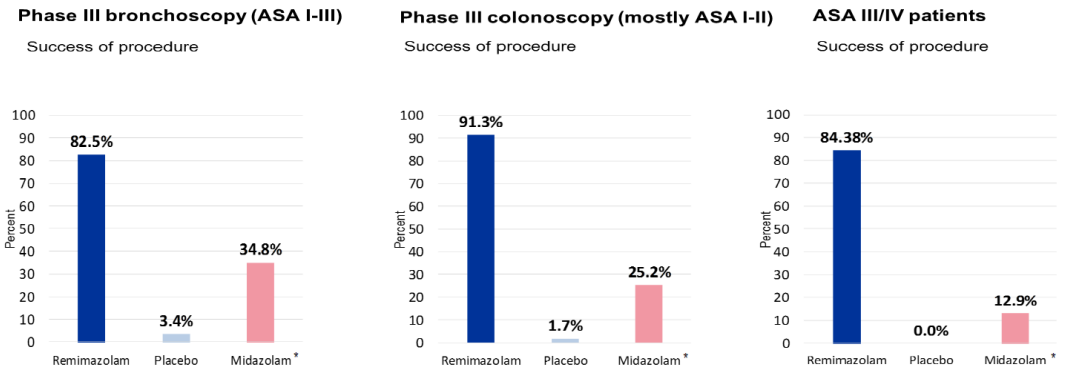
The Cosmo deal included €10m upfront, an equity injection of €10m, €42.5m in potential milestone payments, and a tiered royalty of 20-25% of sales. Cosmo's 2017 annual report disclosed that the potential milestone payments comprise €7.5m on filing, €15m on approval in procedural sedation, plus €10m on each of the second and third indication approvals. We have revised our forecasts to include the disclosed milestone schedule (we had previously modelled €4m for filing, €22.5m for the first approval and €16m of sales milestones).

Positive trial results support US approval and uptake

Based on the results of Paion's clinical development programme for procedural sedation, we believe there is a high likelihood that remimazolam will be granted marketing approval and capture a significant market share in the US. The US market opportunity represents approximately 50% of our valuation of remimazolam.

Remimazolam was highly successful in inducing sedation in the three US Phase III studies. Exhibit 3 shows that in each of the studies over 80% of patients achieved the primary efficacy endpoint, vs less than 5% of placebo-treated patients and less than 35% of those treated with midazolam. The primary outcome measure was a composite endpoint of no need for rescue medication, completion of the procedure and no more than five doses within any 15-minute window (no more than three doses in 12 minutes for midazolam).

Exhibit 3: Successful sedation with remimazolam in high proportion of patients in all three US trials

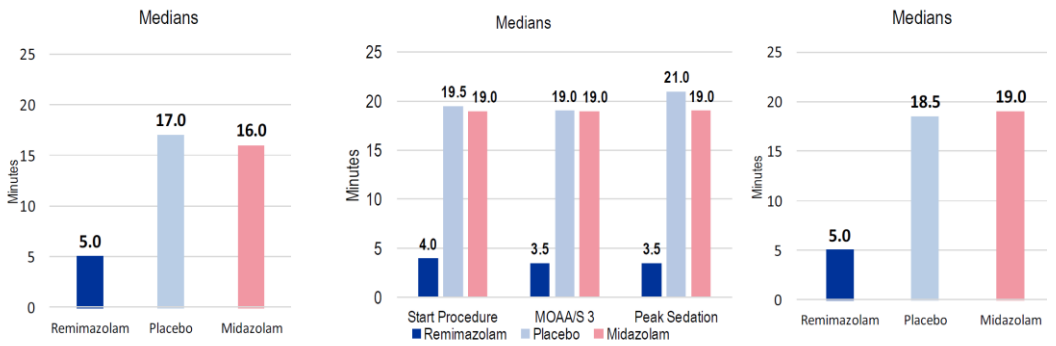


Source: Paion investor presentation. Note: ASA III/IV patients refers to the safety study in high-risk colonoscopy patients with severe systemic disease; *open label.

The patient populations in the three studies ranged from younger and mostly healthy individuals in the first Phase III colonoscopy study to a selected group of high-risk patients undergoing colonoscopy. These high-risk patients were classified as American Society of Anaesthesiologists (ASA) class III (patients with severe systemic disease) or class IV (patients with severe systemic disease that is a constant threat to life). The subjects in the bronchoscopy Phase III were intermediate between these two groups, with 38% ASA of subjects in class III compared to 7% in the colonoscopy Phase III trial.

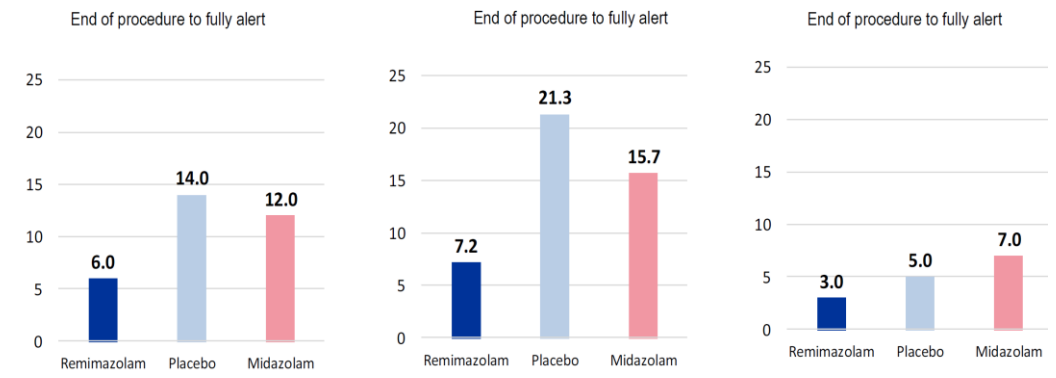
Exhibits 4 and 5 show that induction of and recovery from sedation was faster for remimazolam than midazolam in each of the three studies.

Exhibit 4: Shorter time to start of procedure for remimazolam



Source: Paion investor presentation. Note: ASA III/IV patients refers to the safety study in high-risk colonoscopy patients with severe systemic disease.

Exhibit 5: Recovery faster with remimazolam in all three pivotal studies*



Source: Paion investor presentation. Note: ASA III/IV patients refers to the safety study in high-risk colonoscopy patients with severe systemic disease; * median times shown for bronchoscopy and ASA III/IV patient trials, mean times shown for Phase III colonoscopy trial.

Exhibit 6 summarises the sedation and recovery times for remimazolam and midazolam in the three studies. In each study the total induction and recovery times were between 17 and 20.3 minutes shorter for remimazolam than for midazolam (average 18.4 minutes).

As we previously noted in our report dated 21 November 2016, in the clinical setting midazolam is often administered at higher initial doses and with shorter intervals between top-ups than is

recommended on the label. However, our review of published studies found that while this led to faster induction of sedation (six minutes) the average recovery times were significantly longer (30 minutes), so the total induction and recovery time in the published studies averaged 36 minutes, slightly longer than the 32 minutes total for midazolam in Paion's Phase III colonoscopy study. It is possible that the more rapid administration of midazolam results in higher total doses leading to slower recovery from sedation.

Exhibit 6: Induction and recovery times for the three pivotal studies*

	Bronchoscopy Phase III		Colonoscopy Phase III		High-risk colonoscopy	
	Remimazolam	Midazolam	Remimazolam	Midazolam	Remimazolam	Midazolam
Time to start of procedure (min)	5.0	16.0	4.1	15.9	5.0	19.0
End of procedure to fully alert (min)	6.0	12.0	7.2	15.7	3.0	7.0
Total induction plus recovery time	11.0	28.0	11.3	31.6	8.0	26.0
Time saving with remimazolam	**17.0**		**20.3**		**18.0**	

Source: Edison Investment Research. Note: *Median times shown for bronchoscopy and high-risk colonoscopy trials, mean times shown for Phase III colonoscopy trial.

With the average time savings with remimazolam being almost 20 minutes and the average duration of the colonoscopy examination itself being less than 20 minutes,[2] the results demonstrate that centres could significantly increase throughput by switching from midazolam to remimazolam. We expect this improved throughput to drive significant uptake of remimazolam in the addressable market of 35m procedures per year in the US.[3]

Paion to start GA Phase III in Europe in H218

Paion plans to initiate a Phase III trial in GA in Europe in H218. After successfully completing an additional GA Phase I trial in 2017 and receiving scientific advice from the EMA in January 2018, it assumes that 450-500 patients will be required for the Phase III, which is in line with our previous expectations.

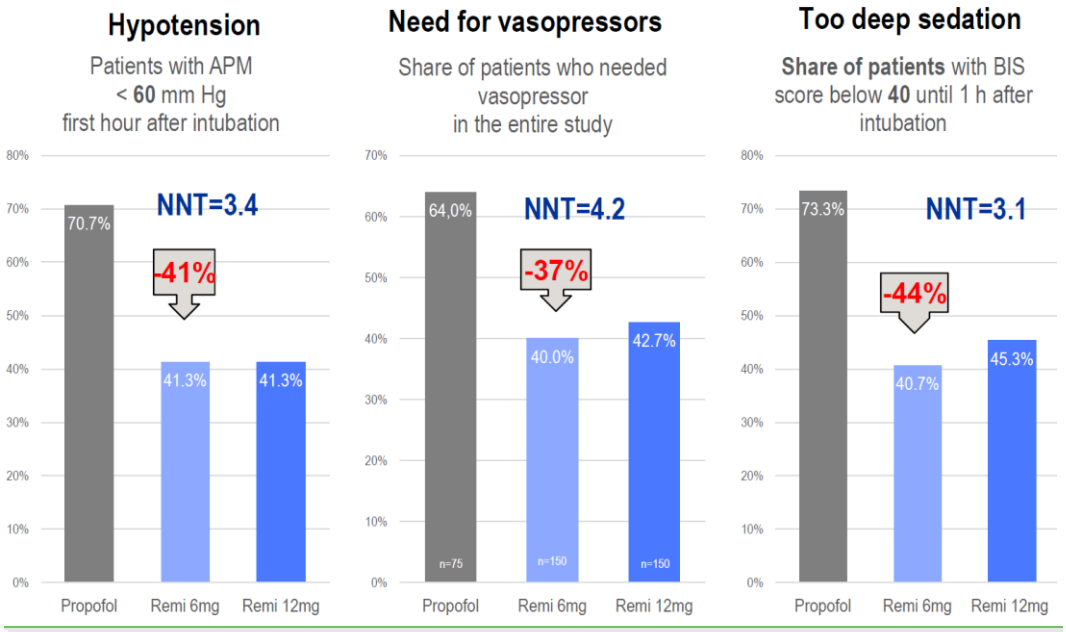
The Phase III study will compare remimazolam to propofol in general surgery patients. The study design will be similar to the successful Phase III programme in GA in Japan, but will recruit sicker patients where the capacity of remimazolam to lead to reduced hypotensive events, as shown in Exhibit 7, is of greater benefit.

The fact that the planned Phase III will be targeting general surgery patients distinguishes it from the company's previous European Phase III GA trial which recruited cardiac surgery patients. That study began in August 2015 but was terminated in February 2016 because recruitment proved difficult due to the complex study design. In contrast, Paion expects to complete the new study within 12 months and report results in mid-2019.

2 Singh H et al. Propofol for sedation during colonoscopy. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD006268. DOI: 10.1002/14651858.CD006268.pub2.

3 CDC procedural stats.

Exhibit 7: Less hypotension during GA with remimazolam in Japan Phase III



Source: Paion. Note: NNT= number needed to treat; APM = arterial pressure mean; BIS = bispectral index; Remi = remimazolam.

Targeting self-commercialisation in Europe

With its financial position strengthened by recent licence agreements in the US and Japan, Paion's target is now to commercialise remimazolam on its own in the EU (or in certain markets within the EU) to maximise potential returns on sales. We have changed our modelling assumptions for Europe and now assume self-commercialisation in Europe delivering 30% operating profit margin on net sales as our base case vs prior assumption of a 20% royalty.

With Paion intending to establish its own sales force to market remimazolam in some or all of the EU if approved (we model a launch in Europe on 2022), the company will seek to expand its portfolio to include additional products that it can market to anaesthesiologists and critical care physicians. Its intention is to target small opportunities that are not attractive to big pharma. This is a longer-term strategy that is not likely to be pursued until after remimazolam marketing applications have been filed in the US and Japan.

Partners progressing remimazolam in a range of countries

Paion has adopted a regional partnering strategy to accelerate remimazolam's global development and provide marketing partners in each region. The US and Japanese filing dossiers will be bridged to data from each region and could abbreviate clinical studies of remimazolam in these individual geographies. This strategy advances remimazolam's global clinical status and market potential in a cost-effective way. Paion received upfront payments for each of its regional partners and is eligible to receive up to €88.8m of further milestone payments (Exhibit 8) plus royalties. These partners will commercialise remimazolam in the respective regions.

In August 2017 Paion announced that its partner R-Pharm had started a Phase III GA study in Russia in 150 general surgery patients, and plans to file for approval at the end of 2018. R-Pharm is also managing development in Turkey and the MENA region, where it will file based on the US or Japanese dossiers.

In March Hana Pharm initiated a Phase III study in 198 patients undergoing GA.

Yichang Humanwell has completed a Phase I study programme in China and is going to conduct a Phase III trial in procedural sedation and a Phase II study in GA.

Exhibit 8: Summary of upfront/milestone/royalties from remimazolam regional partners

Partner	Total received or upfront payment	Total outstanding
Yichang, China	€3m	Up to €4m
Hana Pharma, Korea	€1m	€2m
R-Pharm, CIS	€1m	€3m
R-Pharm, Turkey	€1m	€3m
R-Pharm, MENA	€1.5m	€5.5m
Pendopharm, Canada	€0.4m	~€3.8
Cosmo, US	€20m*	€42.5m
Mundipharma, Japan	€1m	€25m
Total		**~€88.8m**

Source: Paion. Note: *Comprises €10m upfront payment and €10m received via a private placement in June 2016.

Developing Remimazolam in ICU sedation is a longer term goal

As we outlined on page 3 of this report, following a detailed examination of the pharmacokinetics of Remimazolam, Paion is confident that the drug can be successfully developed for sedating patients while they are treated in an ICU.

Under their licensing agreements, partners Cosmo and Mundipharma are responsible for developing remimazolam for ICU sedation in the US and Japan, respectively, while Paion would be responsible for development in this indication in Europe. Paion envisages a collaborative development program, wherein each party is responsible for development in its own territory, but the parties also work together on some aspects of the program.

ICU sedation is a longer term opportunity, and is not part of Paion's near-term clinical program, which is focused on its Phase III trial of remimazolam in GA in Europe.

Paion estimates that there are ~14m ICU patient days requiring ICU sedation in the US and EU each year, which represents a significant commercial opportunity. We do not currently include the ICU sedation in our sales forecasts for remimazolam, so successful development for this indication would represent upside to our valuation. Development for ICU sedation would require additional funds which are not considered in our current forecasts.

Sensitivities

The key sensitivity is the successful filing of marketing applications and subsequent regulatory approval decisions for remimazolam in the US and Japan. The successful execution and outcome of the planned European Phase III in GA is another key risk.

Paion has indicated that it intends to self-commercialise remimazolam in some or all of the EU (if approved). This strategy offers greater potential returns but higher risk than appointing a partner. Paion expects current cash of €24.8m plus tax credits and milestone payments associated with anticipated filings in Japan and the US to provide a funding runway into H219 and likely reporting of top-line data from the EU Phase III. A further €15m would be required to support operations until filing for market approval in the EU. While we model this funding being provided by further milestone payments, depending on the timing of income and expenditure, additional dilutive funds may be required.

Valuation

Our sum-of-the-parts DCF valuation is increased to €269m, or €4.40 per share, from €260m, or €4.25 per share. This is based on the assumption that Paion self-commercialises remimazolam in the EU with a 30% operating profit margin and forms post-approval commercialisation deals for remimazolam which yield a royalty rate of 20% in other unpartnered regions. The summary of changes to our assumptions includes:

- increasing the likelihood of success in Europe and RoW markets from 50% to 60% now that Paion has committed to commencing a Phase III trial in Europe in H218 and has the funding in place to complete the study and report top-line data;
- changing the commercialisation model in the EU from out-licensing to self-commercialisation with an operating profit margin of 30% of net sales;
- reducing the average royalty rate for Japan from 20% to 16% (Mundipharma tiered royalties starting in the low double digits to over 20%);
- increasing the likelihood of success in Japan from 60% to 80% now that licensee Mundipharma has taken over responsibility for obtaining regulatory approval and commercialising remimazolam Japan;
- reducing the modelled upfront and milestone payments for Japan from €50m to €26m to align with the terms of the Mundipharma licence deal;
- increasing the likelihood of success in Canada from 60% to 85%, in line with the US;
- pushing back the timeline for launch by 12 months in all territories except for Canada to allow for later assumed filing dates.

In the US, our cost per procedure assumption for remimazolam is $40 and our peak sales estimate is $280m for the lead indication procedural sedation, assuming an addressable market of 35m procedures a year.[4] In Canada, our peak sales assumption is $42m, for seven million procedures at a revenue per procedure of $30, and we use a market penetration estimate of 22% in the US and Canada, with time savings over midazolam seen in the colonoscopy and bronchoscopy Phase III trials expected to support market uptake.

Our peak sales assumption in Europe for the lead general anaesthesia indication is $175m, assuming a price of $25 per procedure and 35 million high-risk or class III/IV discharges in the OECD region per year. In Japan, our peak sales assumption is $75m at an average price of $25 and 20 million procedures a year (in general anaesthesia). We assume a 20% market penetration in Europe and 15% in Japan.

Exhibit 9: Valuation assumptions for pipeline

	Launch date	Peak sales (US$m)	Risk adjustment (%)	Market penetration (%)	Royalty/ profit margin (%)
Remimazolam EU	2022	175	60	20	30*
Remimazolam US	2020	280	85	22	20
Remimazolam Japan	2020	75	80	15	17
Remimazolam RoW	2021	165	60	12	12
Remimazolam Canada	2020	42	85	22	15

Source: Edison Investment Research Note *operating margin

The key catalysts in 2018 include anticipated filings in Japan and potentially also in the US and Russia, initiation of the Phase III trial in Europe, as well as clinical development progress in other markets, including China and South Korea. Progress on these matters would likely lead us to increase our assumed likelihood of success in the affected territories.

4 CDC procedural stats.

Exhibit 10: Summary valuation

	Value (€m)	Value per share (€)
Remimazolam EU	73.0	1.19
Remimazolam US	171.9	2.81
Remimazolam Japan	31.5	0.52
Remimazolam RoW	23.9	0.39
Remimazolam Canada	16.6	0.27
Risk adjusted milestones	40.3	0.66
Expenses	-29.7	-0.49
Tax	-69.6	-1.14
net cash FY18e	11.2	0.18
Total	**269.1**	**4.40**

Source: Edison Investment Research

Financials

Paion reported revenues of €0.3m and a net loss of €3.1m for Q118 vs a loss of €2.2m in Q117. Operating cash outflow was €2.8m. R&D expenses declined by €0.7m to €3.4m due to lower costs for the Phase III studies in the US.

Paion had €22.1m in net cash on 31 March 2018, which, when combined with €9.5m of milestone payments linked to anticipated filing in Japan and the US and €3m of UK income tax credits, is expected to be sufficient to fund operations into H219 including preparations for filing in the US and Japan and the conduct of the Phase III GA trial in Europe. A further €15m funding would be required to support operations until filing in Europe, based on Paion's current planning. Depending on timing of approvals, this could potentially be provided by milestones payments for approval in the US (€15m) and Japan (we model €5m).

We have revised our forecasts for 2018, which are broadly in line with Paion's financial outlook guidance, as shown in Exhibits 11 and 12. Our end-2018 cash estimate is €11.2m.

Exhibit 11: Main changes to our financial forecasts

€m	2018 Old	2018 New	% Change
Revenue	3.5	3.1	-11%
Research and development	(13.0)	(16.0)	+23%
Selling, general and administration	(3.9)	(3.8)	-2%
Profit/(loss) before tax (reported)	(13.3)	(16.6)	+25%
Profit/(loss) after tax (reported)	(11.2)	(13.6)	+22%

Source: Edison Investment Research

Exhibit 12: Paion's 2018 outlook versus our estimates

	2018 targets		2018
€m	Low	High	Estimates
Revenue	3.0	N/A	3.1
Research and development	(15.0)	(17.0)	(16.0)
Income tax credits	3.0	N/A	3.0
Selling, general and administration	(3.5)	(4.0)	(3.8)
Profit/(loss) after tax (reported)	(12.5)	(15.0)	(13.6)

Source: Edison Investment Research, Paion

Exhibit 13: Financial summary

€'000s	2015	2016	2017	2018e	2019e
Year end 31 December					
PROFIT & LOSS					
Revenue	61	4,262	5,811	3,100	10,475
Cost of sales	0	0	0	0	0
Gross profit	61	4,262	5,811	3,100	10,475
R&D expenditure	(29,385)	(23,408)	(17,854)	(16,000)	(13,000)
General, administrative & selling	(5,729)	(5,129)	(3,828)	(3,820)	(3,935)
Other	965	(807)	(2)	51	51
Operating profit	(34,088)	(25,841)	(16,219)	(17,069)	(6,709)
Depreciation and amortisation	0	(759)	(347)	(400)	(300)
Share-based payments	0	0	0	0	0
Exceptionals	0	0	0	0	0
EBITDA	(34,088)	(25,082)	(15,872)	(16,669)	(6,409)
Operating profit (before GW and except)	(34,088)	(25,082)	(15,872)	(16,669)	(6,409)
Net interest	42	21	20	20	20
Profit before tax (norm)	(34,046)	(25,061)	(15,852)	(16,649)	(6,389)
Profit before tax (reported)	(34,046)	(25,061)	(15,852)	(16,649)	(6,389)
Tax	5,834	4,944	3,759	3,040	2,340
Profit after tax (norm)	(28,212)	(20,118)	(12,093)	(13,609)	(4,049)
Profit after tax (reported)	(28,212)	(20,118)	(12,093)	(13,609)	(4,049)
Average number of shares outstanding (m)	50.7	53.2	59.1	61.1	61.1
EPS - normalised (c)	(55.7)	(37.8)	(20.5)	(22.3)	(6.6)
EPS - reported (c)	(55.7)	(37.8)	(20.5)	(22.3)	(6.6)
Dividend per share (c)	0.0	0.0	0.0	0.0	0.0
Gross margin (%)	NA	NA	NA	NA	NA
EBITDA margin (%)	NA	NA	NA	NA	NA
Operating margin (before GW and except.) (%)	NA	NA	NA	NA	NA
BALANCE SHEET					
Fixed assets	3,417	2,855	2,529	2,529	2,529
Intangible assets	3,362	2,688	2,415	2,415	2,415
Tangible assets	56	167	114	114	114
Refund from assumption of dev costs	0	0	0	0	0
Other	0	0	0	0	0
Current assets	40,051	35,128	29,357	15,748	11,699
Stocks	0	0	0	0	0
Debtors	0	0	37	25	25
Cash	32,680	30,111	24,839	11,242	7,193
Other	7,371	5,017	4,481	4,481	4,481
Current liabilities	(7,901)	(13,040)	(6,656)	(6,656)	(6,656)
Trade payables	(7,332)	(6,353)	(5,921)	(5,921)	(5,921)
Short-term borrowings	0	0	0	0	0
Provisions	(224)	(555)	(391)	(391)	(391)
Finance lease liabilities	0	0	0	0	0
Other current liabilities	(305)	(359)	(325)	(325)	(325)
Current deferred income	(39)	(5,774)	(19)	(19)	(19)
Long-term liabilities	(6)	0	0	0	0
Long-term borrowings	0	0	0	0	0
Provisions	0	0	0	0	0
Long-term deferred income	(6)	0	0	0	0
Deferred taxes	0	0	0	0	0
Other long-term liabilities	0	0	0	0	0
Net assets	35,562	24,943	25,229	11,620	7,572
CASH FLOW					
Operating cash flow	(28,212)	(17,135)	(22,318)	(16,657)	(6,409)
Net interest	43	19	20	20	20
Tax	2,575	5,529	4,577	3,040	2,340
Capex	0	7	0	0	0
Purchase of intangibles	(33)	0	0	0	0
Acquisitions/disposals	0	(199)	(25)	0	0
Equity Financing	22	9,212	12,494	0	0
Dividends	0	0	0	0	0
Other	0	0	0	0	0
Net cash flow	(25,605)	(2,567)	(5,251)	(13,597)	(4,049)
Opening net debt/(cash)	(58,912)	(32,680)	(30,111)	(24,839)	(11,242)
Effect of exchange rate changes	(66)	(2)	(22)	0	0
Other	(560)	0	0	0	0
Closing net debt/(cash)	(32,680)	(30,111)	(24,839)	(11,242)	(7,193)

Source: Edison Investment Research, company accounts

Contact details	Revenue by geography
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Management team

CEO: Dr Wolfgang Söhngen	CDO: Dr Jürgen Beck
Dr Söhngen co-founded Paion in 2000 and became CEO in 2004. Previously, he founded Virtuality, a consulting firm in 1997 and from 1987 worked in clinical development, project management, corporate development and strategic planning at Grünenthal. Before this, he was a pharmaceutical representative at Pfizer.	Dr Beck has over 25 years of experience in the European pharma business, with positions held in various drug development projects. He has held various senior management positions at Synthélabo, was managing director of the CRO Monitoring Force, senior vice president of Medical Affairs at Epigenomics and vice president of clinical operations Europe at InterMune Internationa.
Chairman of the supervisory board: Dr Jörg Spiekerkötter	**CFO: Abdelghani Omari**
Dr Spiekerkötter has been a board member since 2008. He worked as CFO of Schering and Organon Biosciences, and until December 2010 was CFO of Conergy.	Prior to joining Paion, Mr Omari held various positions at KPMG, Cologne in auditing and advisory. He studied at the University of Aachen and has a diploma in business administration.

Principal shareholders	(%)
Cosmo Pharmaceuticals	9.1
TIAA Cref	3.0

Companies named in this report

Cosmo Pharmaceuticals, Ono, Pendopharm, Mundipharma

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