EDISON

# Paion

Filings pending

## Filed for approval in US, Japan and China

Pharma & biotech

**Paion achieved a major milestone in April when partner Cosmo filed for approval of remimazolam in procedural sedation (PS) in the US. This adds to filings in Q418 by partners for general anaesthesia (GA) in Japan and for PS in China. Remimazolam is an ultra-short-acting sedative/anaesthetic that combines the best features of propofol and midazolam. We expect its rapid onset and offset of action combined with a favourable cardio-respiratory safety profile to drive market uptake, if approved. Paion intends to self-commercialise remimazolam for GA and PS in select countries in Europe if it gains approval. Additional partners are seeking approvals in other territories. We increase our valuation to €317m or €4.96 per share.**

| Year end | Revenue (€m) | PBT* (€m) | EPS* (c) | DPS (c) | P/E (x) | Yield (%) |
|---|---|---|---|---|---|---|
| 12/17 | 5.8 | (15.9) | (20.5) | 0.0 | N/A | N/A |
| 12/18 | 2.8 | (12.4) | (15.9) | 0.0 | N/A | N/A |
| 12/19e | 7.6 | (11.4) | (14.6) | 0.0 | N/A | N/A |
| 12/20e | 25.1 | 10.9 | 19.8 | 0.0 | 10.9 | N/A |

Note: *PBT and EPS are normalised, excluding exceptional items.

## Positive Phase III studies support approval prospects

Four Phase III studies of remimazolam in the US and Japan all met their primary endpoints and reported favourable safety data, so we believe the likelihood of approval is high. In the three US Phase III studies in PS, over 80% of subjects successfully completed the procedure with no need for additional doses or rescue medication, vs less than 4% with placebo. Open-label comparisons to midazolam were also favourable. In the Japanese Phase III in GA, 100% of subjects achieved the primary endpoint of successful anaesthesia with no need for rescue medication.

## Increased throughput and better patient experience

The US Phase III studies showed that induction of and recovery from sedation was ~ 20 minutes faster with remimazolam than market-leader midazolam. Patients also returned to feeling normal between 75 and 222 minutes faster. We expect the higher patient throughput achievable in procedures such as colonoscopy with remimazolam to be a key factor driving market uptake in preference to midazolam.

## Better safety to support uptake in GA

We expect improved safety to drive uptake of remimazolam in GA, especially in higher-risk patients. Patients anaesthetised with remimazolam were less likely to experience significant falls in blood pressure than those receiving propofol. They were also less likely to reach a deeper-than-targeted level of sedation. Remimazolam has the additional safety advantage that its sedation can be rapidly reversed by flumazenil.

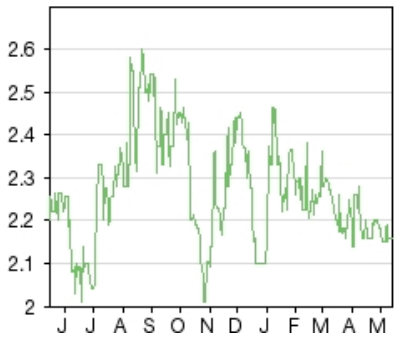
## Valuation: Lifted to €317m

We have modestly increased probabilities of success in the US and Japan following the recent filings, which lifts our valuation to €317m or €4.96/share, from €303m or €4.74/share. With the anticipated receipt of a €7.5m milestone for US filing, Paion is funded to mid-2020. A further €10m would be needed until filing in Europe (we model €23m of risk-adjusted milestone revenue from signed agreements in 2020).

**14 May 2019**

| | |
|---|---|
| **Price** | **€2.16** |
| **Market cap** | **€138m** |
| | US$1.10/€ |
| Net cash (€m) at end March 2019 | 15.6 |
| Shares in issue | 63.9m |
| Free float | 75% |
| Code | PA8 |
| Primary exchange | Frankfurt |
| Secondary exchange | Xetra |

### Share price performance




| % | 1m | 3m | 12m |
|---|---|---|---|
| Abs | 0.0 | (3.4) | (1.6) |
| Rel (local) | 1.0 | (9.1) | 7.7 |
| 52-week high/low | | €2.6 | €2.0 |

### Business description

Paion is an emerging specialty pharma company developing anaesthesia products. Lead product remimazolam has been filed for approval in the US, Japan and China and is partnered with Cosmo (US), Mundipharma (Japan), Yichang (China), Hana Pharma (South Korea), Pharmascience (Canada) and R-Pharm (CIS, Turkey, MENA).

### Next events

| | |
|---|---|
| Update plans for file for PS in Europe | Q319 |
| Japan approval decision | Q419/H120 |
| Fully recruit GA Phase III in Europe | Q419 |

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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. 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 three Phase III studies and it initiated a Phase III trial in GA in Europe in July 2018. 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 salesforce to self-commercialise remimazolam in some or all of the EU (if approved). Its partners filed for marketing approval for remimazolam in the US, Japan and China over the past year.

## Valuation: Filed in the US, Japan and China

Our sum-of-the-parts DCF valuation is €317m or €4.96 per share, increased from €303m in our March report. With a partner in place, a clinical development programme successfully completed and a marketing application filed in the US, we assume a 90% probability of success in that country. We take a slightly more cautious view on Japan with an 85% 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 in GA is underway and the company is contemplating filing for approval in PS based on existing clinical data, we assume a 60% probability of success (based on GA as the main market opportunity in Europe). 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: Approval decisions in the US, Japan and China

The main sensitivities for Paion are the success or failure of marketing applications and clinical studies for the lead product remimazolam. There is 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: Approval milestones could cover funding needs

Paion reported a net loss of €3.2m for Q119 vs a loss of €3.1m in Q118. Reported operating cash outflow was €1.6m. R&D expenses, which mainly related to the ongoing EU Phase III study in GA, declined by €0.3m to €3.1m. Paion had €15.6m in net cash on 31 March 2019, which, when combined with €7.5m of milestone payments linked to the recent filing in the US and €2.5m cash inflow from UK income tax credits reported in 2018, is expected to be sufficient to fund operations to mid-2020. This will include completing and reporting the Phase III GA trial in Europe and includes an allowance of €1m for the cost of filing in PS in Europe. A further €10m funding would be required to support operations until filing in GA in Europe, based on Paion's current planning. Depending on timing of approvals, these funds could potentially be provided by milestone payments for approval in the US (€15m) and Japan (we model €5m). Additional funds will also be required in future years to support planned self-commercialisation in selected European markets. Our end 2019 cash estimate is €9.4m.

# Paion: Remimazolam enters the home stretch

Paion is approaching its first potential approvals of remimazolam, an ultra-short-acting intravenous (IV) benzodiazepine sedative/anaesthetic. Marketing approval applications have already been filed in the US (for PS), Japan (for GA) and China (for PS), with approval decisions in all three territories expected within the next 12 months. European studies in GA are underway and Paion is evaluating a potential filing for PS in Europe based on the existing clinical data in that indication (it considers GA to be the main market opportunity in Europe). 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 and a better patient experience compared to generic alternatives. Cosmo has an 8.2% shareholding in Paion.

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

| Region/partner | Lead indication | Clinical status | Notes |
|---|---|---|---|
| US/Cosmo | Procedural sedation | Filed April 2019 | 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 | Phase III ongoing | 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 ~500 general surgery patients commenced in July 2018 and is expected to complete recruitment by the end of 2019. |
| Japan/Mundipharma | General anaesthesia/ICU sedation | Filed December 2018 | 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 filed an NDA with the Japanese regulator in December 2018. |
| South Korea/Hana Pharma | Anaesthesia | Phase III | Phase III in GA fully recruited in October 2018. Hana Pharm plans to file for market approval in 2020, after it has established the production process for remimazolam in South Korea. |
| China/Yichang Humanwell | Anaesthesia | Filed in PS; Phase II in GA | Subject to the requirements of the SFDA. Filed for approval in procedural sedation in November 2018. |
| 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 completed a Phase III study in GA in Russia in November 2018 and plans to file for approval in Russia by the end of 2019. |
| Canada/ Pharmascience | Procedural sedation | Will file based on US dossier | Paion expects Pharmascience to file based on the US dossier. |

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: Paion, Edison Investment Research

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

## Cosmo filed for FDA approval in April 2019

Paion granted Cosmo Pharmaceuticals an exclusive licence for the development and commercialisation of remimazolam in the US in June 2016. Cosmo filed for marketing approval of the use of remimazolam in procedural sedation on 8 April 2019. The FDA has not yet formally accepted the submission for review, so it has not yet set a target date for completing its review of the marketing application (the FDA has 60 days to decide whether to accept the submission for review). However, if the review proceeds as anticipated, we would expect the FDA to decide whether to approve remimazolam around the end of Q120.

We previously modelled an 85% probability of approval; we increase the probability of a US market launch in 2020 to 90%, now the marketing submission has been filed.

The Cosmo licence deal included a €10m upfront payment, an equity injection of €10m, €42.5m in potential milestone payments, and a tiered royalty of 20–25% of sales. Paion qualified for a €7.5m milestone payment for the recent filing and would become eligible for a milestone payment of €15m on FDA approval in procedural sedation. It would also earn €10m on the approval of remimazolam in a second indication and a further €10m on approval in a third indication.

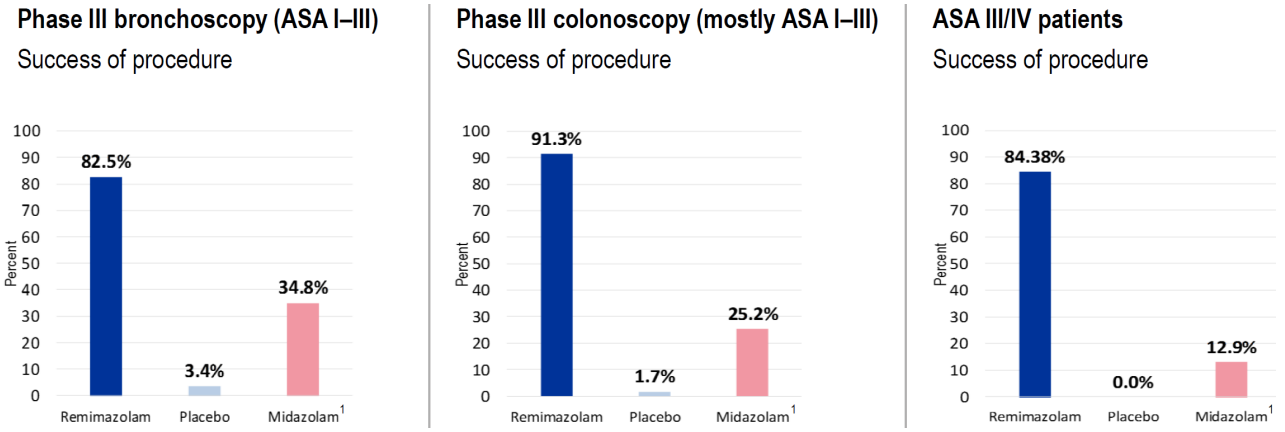
## Positive trial results support US approval and uptake

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 over 50% of our valuation of remimazolam.

Paion has completed three US-based Phase III studies of remimazolam compared to placebo with midazolam rescue in procedural sedation. This includes studies in patients undergoing colonoscopy and bronchoscopy procedures, plus a further Phase III study in higher-risk patients undergoing a colonoscopy. It has also completed two Phase I studies to assess the abuse potential 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, versus less than 4% 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). Failure of a patient to achieve the composite endpoint usually meant that one or more additional doses of midazolam as a rescue medicine were required to achieve adequate sedation and complete the procedure.

**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; [1]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 Anesthesiologists (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.

## Shorter procedure times, better patient experience

We expect shorter procedure times and a better patient experience with remimazolam compared to midazolam to be important drivers of market uptake for Paion's drug.

Exhibit 4 summarises the sedation and recovery times for remimazolam and midazolam in the three Phase III 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).

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 although 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 4: Induction and recovery times for the three Phase III 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 (min) | 11.0 | 28.0 | 11.3 | 31.6 | 8.0 | 26.0 |
| **Time saving with remimazolam (min)** | **17.0** | | **20.3** | | **18.0** | |

Source: Paion, 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

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.

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]

Exhibit 5 shows that, in addition to becoming fully alert more quickly, patients reported they felt they were back to normal more quickly with remimazolam than with midazolam. This indicates that patients had a better overall experience with remimazolam, which could help improve compliance to recommendations for regular colonoscopy screening.

**Exhibit 5: Back-to-normal times for the bronchoscopy and colonoscopy pivotal studies**

| | Bronchoscopy Phase III | | Colonoscopy Phase III | |
|---|---|---|---|---|
| | Remimazolam | Midazolam | Remimazolam | Midazolam |
| Patient's self-evaluation of 'back-to-normal' (min) | 404 | 479 | 331 | 553 |
| **Improvement with remimazolam (min)** | **75** | | **222** | |

Source: Paion, Edison Investment Research.

## Mundipharma filed for GA approval in Japan

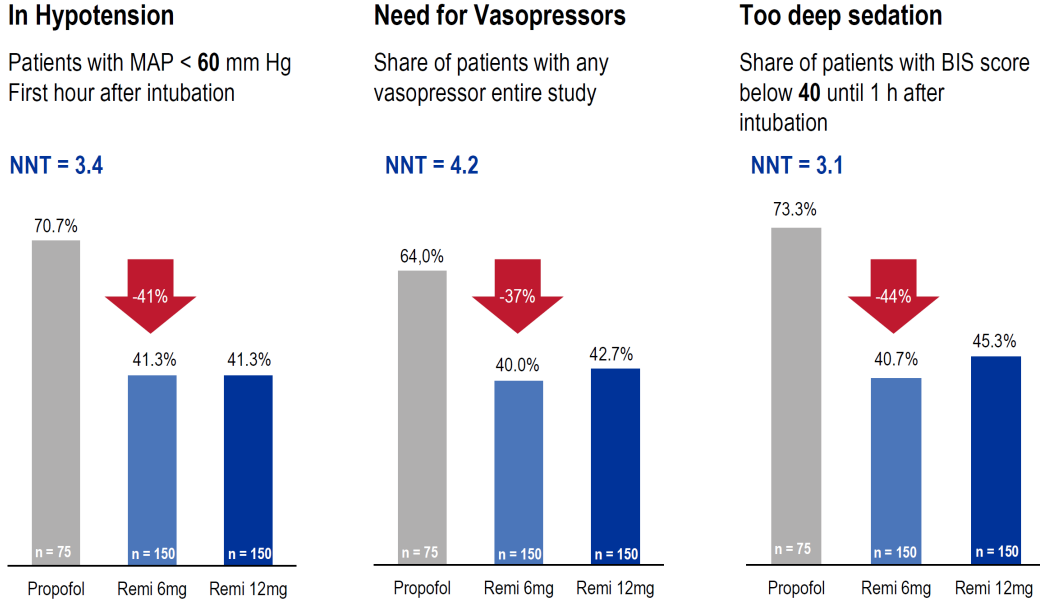
In December 2017 Paion licenced the Japanese rights to remimazolam to Mundipharma. Mundipharma assumed responsibility for filing for approval for GA in Japan and has the right and obligation to further develop remimazolam in all indications in Japan (including procedural sedation and ICU sedation).

Mundipharma filed for market approval in Japan in December 2018. Paion expects to receive payments of ~€2m in connection with the Japan filing (this includes a payment from Hana Pharma, which has licenced rights in South Korea).

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. The study results reported in November 2013 showed 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). Exhibit 6 illustrates the results from Paion's post hoc analysis of the haemodynamic data from the study, which showed that in addition to the lower incidence of hypotension, subjects anaesthetised with remimazolam required less use of vasopressors to support their blood pressure and were less likely to experience sedation that was too deep. The data are consistent with other studies that indicated remimazolam has a good safety profile.

3 CDC procedural stats.

**Exhibit 6: Less hypotension during GA with remimazolam in Japan Phase III (post hoc)**




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

Although 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, soon after it released a profit warning, Ono terminated its licence agreement for remimazolam in October 2014 (anaesthesia is not a core business for Ono).

Further analysis by Paion has shown that pharmacokinetic deviations are common for sedatives such as midazolam and propofol in the ICU and are probably related to the underlying disease conditions of the patients. Paion concluded that the maximum dose level has been identified for ICU sedation. Under the licence agreement signed in December 2017, 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.

With the marketing dossier filed, we have increased the probability of success in Japan from 80% to 85%. Market approval (if successful) could be granted at the end of 2019 or in H120.

## European GA Phase III to fully recruit by end-2019

Paion initiated a 500-patient Phase III trial in GA in Europe in July 2018. The Phase III study is comparing remimazolam to propofol in general surgery patients. The study design is similar to the successful Phase III programme in GA in Japan, but it is recruiting higher-risk ASA III/IV patients where the capacity of remimazolam to lead to reduced hypotensive events is of greater benefit. Paion expects to fully recruit the study by the end of 2019.

## Paion considering an EU filing for procedural sedation

Paion is evaluating the opportunity to file for approval in PS in Europe. Following a productive pre-submission meeting with the European Medicines Agency (EMA), Paion assumes the existing data package is sufficient to be able to file for approval of remimazolam in PS in the EU (ie no extra trials will be needed). It will meet with an EMA rapporteur who would lead the evaluation of the marketing application, and anticipates updating the market as to potential timing with the H1 report. If Paion decides to proceed, it has indicated that it may be possible to file a marketing application for PS in the EU before the end of the year.

Unlike in the US, where in most states an anaesthesiologist needs to be present if propofol is used as the sedating agent, in a number of jurisdictions in Europe propofol-induced sedation of low-risk patients can be administered by appropriately trained staff who are not anaesthesia specialists. This is likely to make it more challenging to drive market uptake of remimazolam in PS in Europe than in the US. Paion chose GA as the lead indication in Europe because it believes it will be able to gain market share in this indication if its Phase III study demonstrates that remimazolam is safer than propofol.

In our view, a filing in PS would be an excellent opportunity to familiarise regulators, anaesthesiologists and other clinicians with remimazolam. It could also bring an early start to the important process of getting remimazolam listed on hospital formularies. These factors should lead to a faster uptake in GA (if approved).

## Targeting self-commercialisation in Europe

Paion's target is to commercialise remimazolam on its own in selected markets within the EU to maximise potential returns on sales.

With Paion intending to establish its own salesforce to market remimazolam in some or all of the EU if approved (we model a launch in Europe in 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 Paion has filed remimazolam marketing applications in Europe.

## 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 €76.1m of further milestone payments (Exhibit 7) plus royalties. These partners will commercialise remimazolam in their respective regions.

In November 2018 Paion announced that its partner R-Pharm had successfully completed a Phase III GA study in 150 patients in Russia. R-Pharm plans to file for approval in Russia by the end of 2019. It is also managing development in Turkey and the MENA region, where it will file based on the US or Japanese dossiers.

Yichang Humanwell filed for approval in PS in China in November 2018. Marketing approval could be granted at the end of 2019 at the earliest.

In October 2018 Hana Pharm successfully completed a Phase III study in 198 patients undergoing GA. It intends to file for approval in 2020, once it has established the remimazolam production process in South Korea.

**Exhibit 7: Summary of upfront/milestone/royalties from remimazolam regional partners**

| Partner | Total received or upfront payment | Maximum outstanding amount |
|---|---|---|
| Yichang, China | €3.5m | Up to €0.5m |
| Hana Pharma, Korea | €1.5m | €1.5m |
| R-Pharm, CIS | €1m | €3m |
| R-Pharm, Turkey | €1m | €3m |
| R-Pharm, MENA | €1.5m | €5.5m |
| Pharmascience, Canada | €0.4m | ~€3.6 |
| Cosmo, US | €27.5m* | €35m |
| Mundipharma, Japan | €2m | €24m |
| Total | | **~€76.1m** |

Source: Paion. Note: *Comprises €10m upfront payment, €10m received via a private placement in June 2016, and €7.5m earned for the US filing.

## Developing Remimazolam in ICU sedation remains a longer-term goal

Following a detailed examination of the pharmacokinetics of remimazolam, Paion is confident 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 programme, wherein each party is responsible for development in its own territory, but the parties also work together on some aspects.

The treatment of severely ill ICU patients would be expected to be associated with a higher risk of side effects. For this reason ICU sedation is a longer-term opportunity and is not part of Paion's near-term clinical programme, which is focused on its Phase III trial of remimazolam in GA in Europe.

Paion estimates there are ~14m ICU patient days requiring ICU sedation in the US and EU each year, which represents a significant commercial opportunity that could eventually rival sales in GA or PS. We do not 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 that are not considered in our current forecasts.

## Sensitivities

The key sensitivity is the regulatory decisions regarding potential approval of remimazolam in the US, Japan and China. The successful execution and outcome of the European Phase III in GA and submission of marketing applications in additional territories are other key risks.

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 is higher risk than appointing a partner. We expect current cash of €15.6m, plus tax credits and a €7.5m milestone for US filing to provide a funding runway to mid-2020 and beyond expected reporting of top-line data from the EU Phase III. A further €10m would be required to support operations until filing for market approval in the GA

indication in the EU. While we model this funding being provided by €23m of risk-adjusted milestone payments associated with regulatory approval decisions in the US, Japan and other territories, depending on the timing of income and expenditure, additional dilutive funds may be required. Additional funds will also be required in future years to support planned self-commercialisation in selected European markets.

# Valuation

Following the recent filings, we have increased our probabilities of success in the US to 90% (from 85%) and in Japan to 85% (from 80%) and have rolled forward our model in time. The positive impact of these changes has been partly offset by deferring the assumed €5m Japan approval milestone to 2020. Our sum-of-the-parts DCF valuation is increased to €317m, or €4.96 per share, from €303m, or €4.74 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 that yield a royalty rate of 20% in other unpartnered regions.

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 35m 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 20m procedures a year (in general anaesthesia). We assume a 20% market penetration in Europe and 15% in Japan.

**Exhibit 8: 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 | 90 | 22 | 20 |
| Remimazolam Japan | 2020 | 75 | 85 | 15 | 17 |
| Remimazolam RoW | 2021 | 165 | 60 | 12 | 12 |
| Remimazolam Canada | 2020 | 42 | 85 | 22 | 15 |

Source: Edison Investment Research. Note *Operating margin.

**Exhibit 9: Summary valuation**

| | Value (€m) | Value per share (€) |
|---|---|---|
| Remimazolam EU | 83.1 | 1.30 |
| Remimazolam US | 205.4 | 3.22 |
| Remimazolam Japan | 37.8 | 0.59 |
| Remimazolam RoW | 27.0 | 0.42 |
| Remimazolam Canada | 18.8 | 0.29 |
| Risk adjusted milestones | 41.2 | 0.64 |
| Expenses | -22.8 | -0.36 |
| Tax | -83.2 | -1.30 |
| Net cash FY19e | 9.4 | 0.15 |
| **Total** | **316.8** | **4.96** |

Source: Edison Investment Research

4 CDC procedural stats.

# Financials

Paion reported a net loss of €3.2m for Q119 vs a loss of €3.1m in Q118. Reported operating cash outflow was €1.6m. R&D expenses, which mainly related to the ongoing EU Phase III study in GA, declined by €0.3m to €3.1m.

Paion had €15.6m in net cash on 31 March 2019, which, when combined with €7.5m of milestone payments linked to the recent filing in the US and €2.5m cash inflow from UK income tax credits reported in 2018 is expected to be sufficient to fund operations until mid-2020. This will include completing and reporting the Phase III GA trial in Europe and includes an allowance of €1m for the cost of filing in PS in Europe. A further €10m funding would be required to support operations until filing in GA in Europe, based on Paion's current planning. Depending on timing of approvals, these funds could potentially be provided by milestone payments for approval in the US (€15m) and Japan (we model €5m).

We have decreased forecast revenue in 2019 and increased 2020 revenue due to the full recognition of the €7.5m filing milestone from Cosmo (previously 85% or €6.8m), and the increase to 90% of the likelihood of receiving approval milestones in the US and to 85% in Japan, offset by the deferral of an estimated €5m Japan approval milestone into 2020. Our revised forecasts for 2019, which are broadly in line with Paion's financial outlook guidance, are shown in Exhibits 10 and 11. Our end-2019 cash estimate is €9.4m.

**Exhibit 10: Main changes to our financial forecasts**

| | 2019 | 2019 | | 2020 | 2020 | |
|---|---|---|---|---|---|---|
| €m | Old | New | % Change | Old | New | % Change |
| Revenue | 10.5 | 7.6 | -27% | 20.0 | 25.1 | +25% |
| Research and development | (14.5) | (14.5) | +0% | (9.5) | (9.5) | +0% |
| Selling, general and administration | (4.6) | (4.6) | +0% | (4.7) | (4.7) | +0% |
| Profit/(loss) before tax (reported) | (8.6) | (11.4) | +34% | 5.8 | 10.9 | +87% |
| Profit/(loss) after tax (reported) | (5.9) | (9.3) | +57% | 7.5 | 12.6 | +68% |

Source: Edison Investment Research

**Exhibit 11: Paion's 2019 outlook versus our estimates**

| | 2019 targets | | 2019 |
|---|---|---|---|
| €m | Low | High | Estimates |
| Revenue | 8.0 | N/A | 7.6 |
| Research and development | (13.0) | (15.0) | (14.5) |
| Income tax credits | 2.0 | N/A | 2.1 |
| Selling, general and administration | (4.0) | (5.0) | (4.6) |
| Profit/(loss) after tax (reported) | (7.0) | (10.0) | (9.3) |

Source: Edison Investment Research, Paion

**Exhibit 12: Financial summary**

| €'000s | 2016 | 2017 | 2018 | 2019e | 2020e |
|---|---|---|---|---|---|
| Year end 31 December | | | | | |
| **PROFIT & LOSS** | | | | | |
| Revenue | 4,262 | 5,811 | 2,766 | 7,600 | 25,103 |
| Cost of sales | 0 | 0 | 0 | 0 | 0 |
| Gross profit | 4,262 | 5,811 | 2,766 | 7,600 | 25,103 |
| R&D expenditure | (23,408) | (17,854) | (12,167) | (14,500) | (9,500) |
| General, administrative & selling | (5,129) | (3,828) | (3,408) | (4,601) | (4,739) |
| Other | (807) | (2) | 354 | 51 | 51 |
| Operating profit | (25,841) | (16,219) | (12,711) | (11,750) | 10,615 |
| Depreciation and amortisation | (759) | (347) | (256) | (300) | (300) |
| Share-based payments | 0 | 0 | 0 | 0 | 0 |
| Exceptionals | 0 | 0 | 0 | 0 | 0 |
| EBITDA | (25,082) | (15,872) | (12,455) | (11,450) | 10,915 |
| Operating profit (before GW and except) | (25,082) | (15,872) | (12,455) | (11,450) | 10,915 |
| Net interest | 21 | 20 | 6 | 20 | 20 |
| Profit before tax (norm) | (25,061) | (15,852) | (12,449) | (11,430) | 10,935 |
| Profit before tax (reported) | (25,061) | (15,852) | (12,449) | (11,430) | 10,935 |
| Tax | 4,944 | 3,759 | 2,510 | 2,100 | 1,710 |
| Profit after tax (norm) | (20,118) | (12,093) | (9,939) | (9,330) | 12,645 |
| Profit after tax (reported) | (20,118) | (12,093) | (9,939) | (9,330) | 12,645 |
| Average number of shares outstanding (m) | 53.2 | 59.1 | 62.5 | 63.9 | 63.9 |
| EPS - normalised (c) | (37.8) | (20.5) | (15.9) | (14.6) | 19.8 |
| EPS - reported (c) | (37.8) | (20.5) | (15.9) | (14.6) | 19.8 |
| 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 | 2,855 | 2,529 | 2,286 | 2,286 | 2,286 |
| Intangible assets | 2,688 | 2,415 | 2,212 | 2,212 | 2,212 |
| Tangible assets | 167 | 114 | 74 | 74 | 74 |
| Refund from assumption of dev costs | 0 | 0 | 0 | 0 | 0 |
| Other | 0 | 0 | 0 | 0 | 0 |
| Current assets | 35,128 | 29,357 | 22,037 | 12,708 | 25,353 |
| Stocks | 0 | 0 | 0 | 0 | 0 |
| Debtors | 0 | 37 | 1,500 | 25 | 25 |
| Cash | 30,111 | 24,839 | 17,227 | 9,372 | 22,017 |
| Other | 5,017 | 4,481 | 3,311 | 3,311 | 3,311 |
| Current liabilities | (13,040) | (6,656) | (3,501) | (3,501) | (3,501) |
| Trade payables | (6,353) | (5,921) | (2,218) | (2,218) | (2,218) |
| Short-term borrowings | 0 | 0 | 0 | 0 | 0 |
| Provisions | (555) | (391) | (630) | (630) | (630) |
| Finance lease liabilities | 0 | 0 | 0 | 0 | 0 |
| Other current liabilities | (359) | (325) | (654) | (654) | (654) |
| Current deferred income | (5,774) | (19) | 0 | 0 | 0 |
| Long-term liabilities | 0 | 0 | 0 | 0 | 0 |
| Long-term borrowings | 0 | 0 | 0 | 0 | 0 |
| Provisions | 0 | 0 | 0 | 0 | 0 |
| Long-term deferred income | 0 | 0 | 0 | 0 | 0 |
| Deferred taxes | 0 | 0 | 0 | 0 | 0 |
| Other long-term liabilities | 0 | 0 | 0 | 0 | 0 |
| Net assets | 24,943 | 25,229 | 20,822 | 11,493 | 24,138 |
| **CASH FLOW** | | | | | |
| Operating cash flow before interest and tax | (17,135) | (22,318) | (16,547) | (9,975) | 10,915 |
| Net interest | 19 | 20 | 5 | 20 | 20 |
| Tax | 5,529 | 4,577 | 3,729 | 2,100 | 1,710 |
| Capex | 7 | 0 | 0 | 0 | 0 |
| Purchase of intangibles | 0 | 0 | 0 | 0 | 0 |
| Acquisitions/disposals | (199) | (25) | (13) | 0 | 0 |
| Equity Financing | 9,212 | 12,494 | 5,214 | 0 | 0 |
| Dividends | 0 | 0 | 0 | 0 | 0 |
| Other | 0 | 0 | 0 | 0 | 0 |
| Net cash flow | (2,567) | (5,251) | (7,612) | (7,855) | 12,645 |
| Opening net debt/(cash) | (32,680) | (30,111) | (24,839) | (17,227) | (9,372) |
| Effect of exchange rate changes | (2) | (22) | (0) | 0 | 0 |
| Other | 0 | 0 | 0 | 0 | 0 |
| Closing net debt/(cash) | (30,111) | (24,839) | (17,227) | (9,372) | (22,017) |

Source: Edison Investment Research, company accounts

| Contact details | Revenue by geography |
|---|---|
| Martinstraße 10-12<br>52062 Aachen<br>Germany<br>+49 241 4453 152<br>www.paion.com | N/A |

**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. | Before 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 | 8.2 |
| TIAA Cref | 3.0 |

| Companies named in this report |
|---|
| Cosmo Pharmaceuticals, Ono, Pharmascience, Mundipharma |

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