VALUATIONLAB
FINANCIAL ANALYSIS

COSMO PHARMACEUTICALS

FOCUS AREA: GASTROINTESTINAL (DIGESTIVE SYSTEM) DISORDERS AND ENDOSCOPY (FOR COLON CANCER PREVENTION)

KEY DATA			SIX: COPN
MARKET CAPITALIZATION (CHF MN)	1,591	**PRICE ON MAY 31, 2019**	98
ENTERPRISE VALUE (CHF MN)	1,353	**RISK-ADJUSTED NPV PER SHARE** (CHF)	211
NET CASH (31 DECEMBER 2018) (CHF MN)	238	**UPSIDE/DOWNSIDE** (%)	117%
MONTHLY OPERATING EXPENSE (CHF MN)	6.3	**RISK PROFILE**	MEDIUM
CASH LIFE	SUSTAINABLE *	**SUCCESS PROBABILITY LEAD R&D PROJECT**	90%
BREAK-EVEN (YEAR)	2008	**EMPLOYEES**	275
FOUNDED (YEAR)	1997	**LISTED** (YEAR)	2007
KEY PRODUCTS:	**STATUS**	**MAJOR SHAREHOLDERS:**	**(%)**
- LIALDA/MEZAVANT (ULCERATIVE COLITIS)	LAUNCHED 2007	- COSMO HOLDING S.A.R.L.	37.1
- UCERIS/CORTIMENT (ULCERATIVE COLITIS)	LAUNCHED 2013	- HEINRICH HERZ AG / LOGISTABLE GROUP	8.3
- ELEVIEW (LESION RESECTION CUSHION)	LAUNCH	- DIEVINI HOPP BIOTECH HOLDING GMBH & CO. KG	5.2
- METHYLENEBLUE (LESION DETECTION)	PHASE III (US)/FILED (EU)	**- FREE FLOAT (EXCL. COSMO HOLDING S.A.R.L.)**	**63.0**
- AI SMART BOX (CB-17-08) (LESION DETECTION)	LAUNCH (EU)	- AVERAGE DAILY VOLUME (30-DAYS)	10,390
- AEMCOLO/RELAFALK (TRAVELERS' DIARRHEA/IBS-D**)	LAUNCH/PHASE II (IBS-D)		
- QOLOTAG (LESION DETECTION)	APPROVED (EU)		
- BYFAVO (REMIMAZOLAM) (PROCEDURAL SEDATION)	FILED (US)		
UPCOMING CATALYSTS:	**DATE**	**ANALYST(S):**	**BOB POOLER**
- AEMCOLO - US LAUNCH THROUGH ONLINE DTC MODEL	JUNE/JULY 2019		BP@VALUATIONLAB.COM
- AI SMART BOX (CB-17-08) - EU LAUNCH BY MEDTRONIC	MID 2019		+41 79 652 67 68
- METHYLENEBLUE - TRIAL DESIGN US 2ND PIVOTAL TRIAL	2019		

* TEMPORARILY LOSS IN 2017, 2018 & 2019 DUE TO BUILD UP ARIES PHARMA IN US; ** IBS-D = IRRITABLE BOWEL SYNDROME - DIARRHEA PREDOMINANT

ESTIMATES AS OF 3 JUNE, 2019 — SOURCE: VALUATIONLAB, COSMO PHARMACEUTICALS

Seeing is believing

AI-ing big profits with Medtronic

Cosmo Pharmaceuticals is focused on therapies for gastrointestinal (GI) disorders (ulcerative colitis, colon infections) and endoscopy (solutions to reduce the risk of colon cancer). Key value drivers for GI disorders include 1) Lialda/Mezavant (marketed by Shire, Giuliani and Nogra Pharma) and 2) Uceris/Cortiment (marketed by Bausch Health/Ferring) both for ulcerative colitis; and 3) Aemcolo/Relafalk (EU partner Dr. Falk) for travelers' diarrhea and IBS-D. Key value drivers for endoscopy include: 1) AI Smart Box, an artificial intelligence enhanced device for colonoscopy (global partner Medtronic), 2) Eleview, a lesion resection cushion (US partner Medtronic; Europe & Asia Fujifilm), 3) MethyleneBlue, a colonic lesion detection dye, and 4) Byfavo for procedural sedation. Cosmo's US commercial organization Aries Pharmaceuticals has been repositioned on an opportunity-by-opportunity basis. We derive a risk-adjusted NPV (rNPV) value of CHF 211 per share with a 90% success probability for lead project AI Smart Box. We consider Cosmo medium risk, as it has been profitable since 2008 with a strong balance sheet and four marketed products (Lialda, Uceris, Zacol NMX, Eleview). Cosmo is expected to return to profitability in 2020 now it has restructured Aries due to the US delay of MethyleneBlue.

Key catalysts:

1) **Activity started for 2nd confirmatory phase III trial MethyleneBlue (2019):** with Cosmo to present a new clinical trial plan with different endpoints to the FDA.
2) **AI Smart Box (CB-17-08) European launch (mid 2019):** marks the first commercial launch of a revolutionary artificial intelligence enhanced lesion detection system in colonoscopy marketed by global commercialization partner Medtronic.
3) **US launch Aemcolo (June/July 2019):** through a novel online DTC business model directly targeting the 46 mn yearly US travelers, which if successful provides substantial upside to our conservative forecasts in travelers' diarrhea.

Recent Developments

Since our latest Cosmo Valuation Report in December 2018, the company has made great strides in reducing its US cost structure caused by the unexpected delay of MethyleneBlue in the US, has started activity for a second confirmatory phase III trial for MethyleneBlue after a second appeal at the FDA was turned downed, filed MethyleneBlue for EU approval in colonoscopy, and filed remimazolam (branded Byfavo) for US approval in procedural sedation.

At the 2019 R&D Day, Cosmo revealed the AI Smart Box (CB-17-08), a revolutionary artificial intelligence enhanced device for colonoscopy alongside a global distribution agreement with Medtronic; a novel marketing approach for recently approved Aemcolo directly targeting travelers through DTC advertising and social media; a new exclusive agreement for Eleview with Medtronic in the US, China and South America replacing the existing agreement with Olympus; and last but not least, announced a new proprietary compound CB-03-10, a novel androgen receptor that will start phase I development in Q4 2019 and on positive results will be partnered to a strong oncology player in return for upfront, development, regulatory and sales milestones and royalties on sales.

Cosmo reiterated its 2019 outlook with savings of approximately EUR 20 mn (EUR 5 mn more than initially targeted at the FY 2018 release) following the restructuring of the Aries US sales organization. In 2019, a net loss of around EUR 12 mn is expected with the company returning to profitability in 2020. Net cash of EUR 348 mn (6 May 2019) will be used to strengthen the pipeline when external opportunities present.

We have included forecasts for the AI Smart Box with conservative peak sales of EUR 540 mn (booked by Medtronic) with a net margin for Cosmo expected above 20%, while conservatively reducing our peak sales forecasts for MethyleneBlue to EUR 500 mn from EUR 750 mn on potentially lower pricing affected by the additional fee for the AI Smart Box. Consequently, our risk-adjusted NPV increases by ~13% to CHF 211 per share, pointing to considerable equity upside from current share price levels.

May 8 – AI Smart Box a game changer in colonoscopy revealed at R&D Day
Prior to the 2019 R&D Day event in the afternoon, Cosmo announced in the morning a new exclusive agreement for Eleview (lesion resection cushion in colonoscopy) with Medtronic in the US, China and South America, effectively replacing the existing distribution agreement with Olympus, which was terminated by mutual consent. No financial terms were announced.

AI Smart Box (CB-17-08) artificial intelligence enhanced colonoscopy
The highlight of the event was the reveal of the pre-announced in-house developed AI (artificial intelligence) colonoscopy device (CB-17-08). For simplicity we dub it the “AI Smart Box”. We believe this is the first commercial AI system in colonoscopy that combined with the global marketing muscle of Medtronic will become a game changer in colonoscopy with a high adoption rate. In real-time, the AI Smart Box can automatically detect lesions with high accuracy and project a dynamic green box around the lesion on the screen similar to face or eye detection in digital cameras. The AI device works as a “second set of expert eyes” to avoid the

colonoscopist missing pre-cancerous lesions such as adenomas and ultimately improve the overall adenoma detection rate (ADR). The reported miss rates range between 20% and 40% due to both polyp and operator characteristics. A 1% increase in the ADR is associated with a 3% decrease in the risk of colorectal cancer occurring before the next colonoscopy examination.

Cosmo signed a global distribution agreement with Medtronic where the expected net margin for Cosmo is to be above 20%. Medtronic will provide the devices for free in return for a modest fee per procedure. The estimated yearly fee per device in the US is expected to amount to USD 36,000 and in the EU to EUR 36,000. We estimate the number of colonoscopy towers/stacks where the AI Smart Box can easily be added in the US to amount to approximately 14,600 and in the EU/ROW to ~27,000. We conservatively forecast EUR 540 mn peak sales (booked by Medtronic). The AI Smart Box is already approved with a CE marking in the EU with commercialization expected to start in mid 2019. In the US, the regulatory pathway has to be finalized, but the company expects to start the US rollout in Q1 2020.

Aemcolo to be marketed directly to travelers in the US through DTC
Cosmo will market Aemcolo though a novel online DTC business model directly to US travelers. For instance, when travelers book a trip abroad online, an Aemcolo add pops up informing the traveler the need for Aemcolo to treat travelers' diarrhea. A button links the traveler to an online telemedicine provider offering an online consultation with a healthcare practitioner who can write an e-prescription to a pharmacy, where Aemcolo can be delivered at home. Cosmo has teamed up with renowned companies such as Ogilvy Health, a strong marketing partner and UpScriptHealth, a strong execution partner in e-Health. Pricing in the US is targeted at USD 150 for a 3-days treatment, with launch expected in June/July 2019. Cosmo guides for peak sales of EUR 300 mn, which management deems conservative.

CB-03-10 a novel androgen receptor for treating cancer; "wild card" upside
The pre-announced proprietary molecule CB-03-10, a synthetic steroidal antiandrogen, was also revealed at the R&D event. CB-03-10 is derived from cortexolone just like Cassiopea's Winlevi (acne) and Breezula (hair loss). Cassiopea is the spin-off of Cosmo's dermatology business and is listed on the SIX Swiss Stock Exchange, where Cosmo retained a 45.1% equity stake. Cosmo will start phase I trials in Q4 2019, with topline results due in ~18 months from trial start. On positive phase I results, Cosmo plans to seek a strong oncology partner to fully develop and commercialize CB-03-10 in return for upfront, development, regulatory and sales milestones and royalties on sales. We do not include any forecasts for CB-03-10 as the compound currently lacks clinical proof-of-concept, and therefore provides a potential real option.

May 5 – FDA allowance of IND application for CB-03-10 in cancer patients
The FDA allowed an IND (Investigational New Drug) application for CB-03-10 to start a phase I safety trial in patients with cancer. After completing phase I clinical development, Cosmo intends to partner CB-03-10 as it has no expertise in cancer and remains focused on gastrointestinal disorders and endoscopy. CB-03-10 is a new oral chemical entity based on Cassiopea's novel anti-androgen cortexolone, the active ingredient of Winlevi (acne) and Breezula (hair loss), which are both topical applications. Given the early stage

of development of CB-03-10 we do not account for any value until proof-of-concept has been established.

April 10 – New AI colonoscopy device and distribution agreement with Medtronic
Cosmo has developed a revolutionary artificial intelligence (AI) software and device for the detection of lesions during colonoscopy. The AI device operates in real time using proprietary software to assist the colonoscopist and is simple to use and is compatible with all endoscopes. Development was started years ago through Cosmo's subsidiary Linkverse and relied on the company's unique library of high definition colonoscopy videos gathered in the clinical trials of MethyleneBlue. In the EU, the AI device has obtained CE marking while the US regulatory pathway is ongoing. Cosmo will be the sole manufacturer. Cosmo entered into a global distribution agreement with Medtronic, which underlines the potential of the device. No financial terms were announced. More details of the new AI device will be provided at the R&D Day on May 8th.

April 9 – US NDA filing of Byfavo for procedural sedation
Remimazolam (now branded Byfavo) was filed for US approval in procedural sedation in line with expectations (Q1 2019 - albeit one week later). Cosmo acquired US rights to Byfavo from Paion in June 2016 and became Paion's largest shareholder with a 9.1% stake. We forecast US peak sales for Byfavo of EUR 150 mn in procedural sedation (in colonoscopy) alone. Byfavo could potentially be used in general anesthesia, a far larger indication and ICU sedation. Paion is developing Byfavo for general anesthesia in Europe/ROW (excluding the US).

March 29 – FY 2018 results in-line; return to profitability in 2020
Cosmo reported FY 2018 results, which were broadly in line with our estimates. No additional pipeline news was announced.

- **Revenue** amounted to EUR 65.5 mn (EUR 67.2 mn in 2017) slightly below our estimate of EUR 68 mn on lower revenues from Lialda and Uceris, which both are facing generic competition in the US.
- **Operating costs** amounted to EUR 82.2 mn (EUR 76.8 mn in 2017) slightly higher than our estimate of EUR 84 mn. In FY 2018, Cosmo continued to build up its US sales organization Aries Pharma in anticipation of an MethyleneBlue approval and launch, which unexpectedly received a Complete Response Letter in May.
- **Operating loss** amounted to EUR 16.6 mn (EUR 9.6 mn in 2017) slightly less than our estimate of EUR 22 mn.
- **The net loss** amounted to EUR 18.1 mn (including an FX gain of EUR 5.4 mn on Cosmo's US dollar cash position) (EUR 32.5 mn net loss in 2017) significantly lower than our net loss forecast of EUR 24 mn.
- **Cash, bonds and investments** amounted to EUR 375.8 mn (31 December 2018) boosted by the EUR 175 mn convertible bond issued in November 2018, which is more than sufficient for the company to reach profitability again in 2020.

Outlook 2019 Cosmo expects to reduce the operating loss to approximately EUR 12 mn in FY 2019, helped by cost savings of EUR 15 mn in the Aries US sales organization, and return to profitability again in 2020. We expected a larger loss of EUR 30 mn in FY 2019 with the company to return to profitability in FY 2020.

March 12 – FDA denial of MethyleneBlue appeal, Cosmo starts activity for 2nd trial

In line with our thinking, the FDA denied Cosmo's second appeal to the OND (Office of New Drugs) at the CDER (Center for Drug Evaluation and Research) for MethyleneBlue in colonoscopy. Cosmo has now decided to start activity for a second confirmatory phase III trial to gain US approval. The company will present a new clinical plan with different endpoints to the FDA. We expect the company to start the second confirmatory trial soon using largely the same clinical centers as in the first positive phase III trial. Although no timelines were given, we estimate US approval could occur in 2022 given a positive confirmatory trial.

February 2 – EU MAA filing of MethyleneBlue for colonoscopy

Cosmo announced that it has filed for EU approval of MethyleneBlue in colonoscopy, which is in line with their guidance (early 2019) and market expectations. The EU filing was granted Centralized Authorization Procedure allowing automatic approval in all EU member states on approval in the reference state. The review procedure is expected to take approximately 12 months with EU approval and launch expected in H1 2020. Cosmo intends to establish selective partnerships for the marketing of MethyleneBlue in the EU and ROW.

Strategy & Cash Position

Successful transformation from a manufacturing to a specialty GI pharma company
Cosmo Pharmaceuticals is a specialty pharmaceutical company focused on developing and commercializing best-in-class products in endoscopy and to treat gastrointestinal (GI) disorders. The company was founded in 1997 by the purchase of the Italian contract manufacturing facility from Parke Davis (when Parke Davis was acquired by Pfizer) in Lainate (Milan), Italy. Over the past two decades Cosmo was transformed into a GI product development company generating significant product sales through its commercialization partners. Cosmo was listed on the Swiss Stock Exchange (ticker: COPN) in March 2007. Only a year later the company became profitable, thanks to the successful launch of its first product Lialda/Mezavant for treating ulcerative colitis by Shire Pharmaceuticals reaching peak sales of USD 792 mn before generics entered the market. Cosmo aims to achieve superior long-term returns on investment by applying an entrepreneurial approach in assessing opportunities and risks. Existing financial resources need to be available for all projects before the company decides to start clinical development.

Cosmo's legal seat is in the Netherlands with headquarters in Dublin, Ireland; manufacturing facilities in Lainate, Italy; and a US sales office in San Diego, California.

Cassiopea IPO to benefit from long-term potential and offer cash for US operations
Cosmo spun-off its dermatology franchise in the newly formed company Cassiopea, which was listed on the Swiss Stock Exchange (ticker: SKIN) in July 2015. Cosmo received EUR 258 mn net offering proceeds of the IPO and retained a 45.1% stake in Cassiopea to benefit from the long-term upside potential of its differentiated dermatology pipeline. In July 2018, Cassiopea successfully concluded phase III development of lead pipeline compound Winlevi (clascoterone) in acne with the potential to become the first topical anti-androgen on the market with first launches expected in 2020 and estimated global peak sales of EUR 400+ mn.

US delay of MethyleneBlue changes US commercialization plans with Aries…
With sufficient financial resources available, Cosmo established a US subsidiary called Aries Pharmaceuticals in 2016 to directly market, sell and distribute its products Eleview, MethyleneBlue, Qolotag, Aemcolo, and Byfavo in the lucrative US market, with the potential of a separate US listing. In 2018, at its peak Aries employed approximately 82 people of whom 59 were in marketing and sales, with the remainder in medical affairs, medical science liaisons & scientific affairs, management and back office. The heavy upfront investment in the buildup of Aries and US launch of Eleview led to a net loss in 2017 (EUR 32.5 mn) and 2018 (EUR 18.1 mn) which will extend into 2019 (estimated at EUR 12 mn).

…with Medtronic becoming an important partner (with more in the future?)
After the unexpected US delay of MethyleneBlue by several years due to a Complete Response Letter issued by the FDA in May 2018, Cosmo decided to radically restructure Aries. Aries will be repositioned on an opportunity-by-opportunity basis. As a result, Cosmo projects cost saving of EUR 20 mln in 2019 with the company returning to profitability in 2020. The Aries sales force co-promoting Eleview with Olympus has been

replaced by Medtronic that acquired the US commercialization rights of Eleview in May 2019, including China and South America, effectively replacing the existing distribution agreement with Olympus, which was terminated by mutual consent. In the same month Cosmo signed a global distribution agreement for its revolutionary artificial intelligence enhanced colonoscopy device CB-17-08, which for clarity we dub the AI Smart Box, with Medtronic with Cosmo to retain a net margin of above 20%.

Medtronic with its global marketing muscle will be instrumental in the commercial success of the AI Smart Box in colonoscopy, while Eleview can piggyback on this success as more lesions are detected which need to be removed. Based on the same logic, we see Cosmo and Medtronic extending their global agreement with the AI Smart Box to include for instance MethyleneBlue. MethyleneBlue extends the number of lesions the AI system can currently detect with gold standard HDWL (high definition endoscopes with white light) by staining lesions across the entire colon in a convenient oral tablet taken together with the necessary bowel preparation agents prior to the colonoscopy.

Cosmo is engaged in two distinct business fields:

1. **Development and commercialization of proprietary pharmaceutical/medical products with a special focus on:**
    - **Gastrointestinal disorders:** treatments for digestive system disorders include:
        - **Lialda/Mezavant** (ulcerative colitis – marketed by Shire/Giuliani/Nogra)
        - **Uceris/Cortiment** (ulcerative colitis – marketed by Bausch Health/Ferring)
        - **Aemcolo/Relafalk** (travelers' diarrhea – approved in US and EU in November 2018, Dr. Falk is development & commercialization partner in EU/ROW; IBS-D – phase II ongoing)
    - **Endoscopy:** solutions to improve procedures to examine the digestive tract and prevent colorectal cancer, include:
        - **Eleview** (dyed lesion resection cushion – marketed in US by Medtronic; in EU, Asia, Africa, Australia/NZ by Fujifilm)
        - **AI Smart Box (CB-17-08)** (artificial intelligence enhanced colonoscopy – EU launch mid 2019, US launch Q1 2020 by global partner Medtronic)
        - **MethyleneBlue** (lesion detection dye for entire colon – activity started for a second confirmatory phase III trial in the US; EU filed in February 2019)
        - **Qolotag** (lesion detection dye for sigmoid colon – approved in EU)
        - **Byfavo** (fast-acting sedation for colonoscopy – US filed in April 2019)

2. **Manufacturing of pharmaceutical products for third parties** (at its own GMP-approved plant) **and the provision of related services** (e.g. product formulations & stability evaluations, document preparation for pharmaceutical product registration).

Targeting a 9.5 bn IBD market driven by biologics and new treatments
Cosmo's gastrointestinal drugs target a global IBD (inflammatory bowel disease) drug market estimated at USD 8.5 mn in 2016 and expected to increase to USD 9.5 bn in 2020, according to a report by Visiongain. The biologics submarket generated revenues of USD 5.8 bn accounting for 68% of the global IBD market. Biologic therapies are expected to be the main drivers of growth over the forecast period due to increased use and substantially

higher treatment costs than other IBD treatments such as 5-ASA's, corticosteroids, antibiotics and immunosuppressants. IBD affects approximately 0.5% of the Western global population. The main forms of IBD are Crohn's disease and ulcerative colitis. The ulcerative colitis market is valued at USD ~3bn, while the 5-ASA market is worth around USD 1.7 bn due to the lack of new branded treatments. Mainstay drugs are largely generically available. Nevertheless, Cosmo's treatments for ulcerative colitis Lialda/Mezavant and Uceris/Cortiment have established substantial market penetration in a relatively short time period due to their improved efficacy and safety profile.

New antibiotics needed for colon infections due to increasing bacterial resistance
Cosmo's therapeutic focus also includes colon infections caused by bacteria. These infections are among the most commonly encountered infections in primary care and span a wide range of diseases, which typically cause (bloody) diarrhea, dehydration and fever. While they may not always be severe and may often resolve rapidly, they can be serious in specific health care settings or patient populations. Cosmo's novel antibiotic rifamycin SV MMX (branded Aemcolo in the US and Relafalk in Dr. Falk territories outside the US) targets travelers' diarrhea and IBS-D (irritable bowel syndrome – diarrhea predominant) among others, which affect tens of millions of people annually, with increasing bacterial resistance to current antibiotic treatments.

Success in the USD 60 bn colonoscopy market should be transformational
Colorectal cancer is the third most common cancer diagnosed in the US, which can largely be prevented by timely and regular screening through e.g. colonoscopy. Cosmo's endoscopy product pipeline, with a special focus on cancer prevention through improved colonoscopies, targets a large market opportunity. With an estimated 14-15 mn colonoscopies per year in the US with an average cost of USD 3,081 per procedure (according to Blue Cross Blue Shield) and an additional 25 mn in EU/ROW (conservative number) with an assumed cost of USD 655 per procedure (2012 Comparative Price Report), we estimate the global market amounts to almost USD 60 bn per year. Additional costs of polyp removal and biopsy testing (USD ~200-300 per polyp) are excluded in these numbers. This number is set to grow with the aging of the population and structured cancer screening programs. Even low penetration rates for Cosmo's endoscopy products could be transformational, boosted further by capturing more value in the lucrative US market now through the partnership with Medtronic, the world's leading medical device company.

Proprietary "MMX" technology provides the base for new best in class GI drugs
At the core of Cosmo's product pipeline is the proprietary "MMX" (**M**ulti-**M**atri**X**) technology, a patented oral controlled-release formulation technology for off patent drugs that target the gastrointestinal tract. The MMX technology provides an excellent base for the development of new, patentable, but products with a lower risk than NCE's (new chemical entities) with a unique once a day dosing regimen. Cosmo may also target riskier NCE's that have longer composition of matter patent protection, to extend its business model once the MMX formulation patent expires in 2020.

Artificial intelligence a new and revolutionary pillar of growth for Cosmo
Artificial intelligence (AI) is an emerging technology that will become a new and revolutionary pillar of growth that should generate substantial revenues for Cosmo starting in endoscopy with potential additional applications. The AI Smart Box (CB-17-08) combined with the global marketing muscle of Medtronic is set to become a game changer

in colonoscopy, in our view. This real-time automatic polyp detection system based on AI can be seen as a "second set of eyes" that will alert the endoscopist in a more consistent and reliable way than a human assistant (and at significantly lower costs). Additional upgrades such as optical biopsy, other gastrointestinal applications or procedural documentation and administration could make this an invaluable system in colonoscopy. Other endoscopy products such as Eleview (lesion resection) and MethyleneBlue (lesion enhancing detection dye) can piggyback on the success of the AI Smart Box and the Medtronic partnership.

In-licensing opportunities to complement GI product offering and leverage Aries
Cosmo also seeks to in-license gastrointestinal products that complement its own product offering and leverage its US sales organization Aries. For instance, Byfavo, a fast-acting benzodiazepine sedative that can be used in endoscopic procedures complements MethyleneBlue and Eleview during colonoscopy. In 2016, Cosmo acquired the exclusive US rights of Byfavo from the listed biopharmaceutical company PAION AG (ticker: PA8), based in Aachen, Germany. Cosmo also took a 9.1% equity stake to benefit from the long-term equity upside of PAION and the value of Byfavo outside the US.

Near term key priorities and strategy in the next 12-18 months:

- **AI Smart Box (CB-17-08):** successfully launch in the EU (mid 2019) and US (Q1 2020) by global partner Medtronic
- **Aemcolo/Relafalk:** successfully launch in travelers' diarrhea in the EU and US in 2019; conclude IBS-D phase II and start phase III development; out license ex-US & EU rights
- **MethyleneBlue:** determine and start second confirmatory trial needed to file for US approval; gain EU approval in H1 2020
- **Eleview:** progress launch in the US with Medtronic; extend Eleview license agreements to ROW
- **Byfavo:** gain US approval for procedural sedation in H1 2020
- **CB-03-10:** start phase I development in patients with cancer (Q4 2019)
- **Qolotag:** determine US regulatory pathway & EU/ROW commercialization
- **Aries Pharmaceuticals:** position US commercial organization on an opportunity-by-opportunity basis
- **Further expand pipeline:** assess new chemical entities as possible MMX projects or in license new GI and endoscopy treatments with a "war chest" of EUR 348 mn

Near EUR 600 mn raised in a mix of placements, bonds & gains on partner stakes
Since inception in 1997, Cosmo raised a total of EUR 588 mn through its own IPO, the IPO of Cassiopea, private placements, convertible bonds, and investment gains on "Equity for Products" (gains from stakes in former development and commercialization partners).

MONEY RAISED	EUR MN
PRE-IPO	20
IPO (INITIAL PUBLIC OFFERING)	33
INVESTMENT GAINS ON "EQUITY FOR PRODUCTS"	264
CONVERTIBLE BONDS	175
PRIVATE PLACEMENTS	96
TOTAL RAISED	**588**

SOURCE: VALUATIONLAB, COSMO PHARMACEUTICALS

Sufficiently funded to execute clinical development and commercialization plans
Prior to the IPO, management raised EUR 20.4 mn in its first financing round. In March 2007, Cosmo raised EUR 33.2 mn with its successful IPO on the Swiss Stock Exchange. With the use of these relatively limited funds the company was able to turn cash positive in 2008 thanks to the successful launch of Lialda by Shire. Cosmo's willingness for "Equity for Product" deals has paid off nicely. Approximately EUR 123 mn was gained on the sale of Santarus shares in two tranches in 2013 and 2014. Santarus was the former US development and commercialization partner for Uceris where Cosmo acquired a stake to benefit from the upside potential of Uceris in the US. Salix acquired Santarus in 2013 largely on the sales prospects for Uceris. In 2014 Cosmo received a termination fee of EUR 17 mn from Salix after the company announced it was being acquired by Valeant and therefore terminated its previous merger agreement with Cosmo. In 2015, Cosmo gained EUR 123 mn from the sale of its stake in Cassiopea, its demerged dermatology franchise, in the IPO while maintaining a 45.1% stake to benefit from the long-term equity upside of Cassiopea. In 2017, Cosmo raised EUR ~96 mn through a private placement of around 1.3 mn shares.

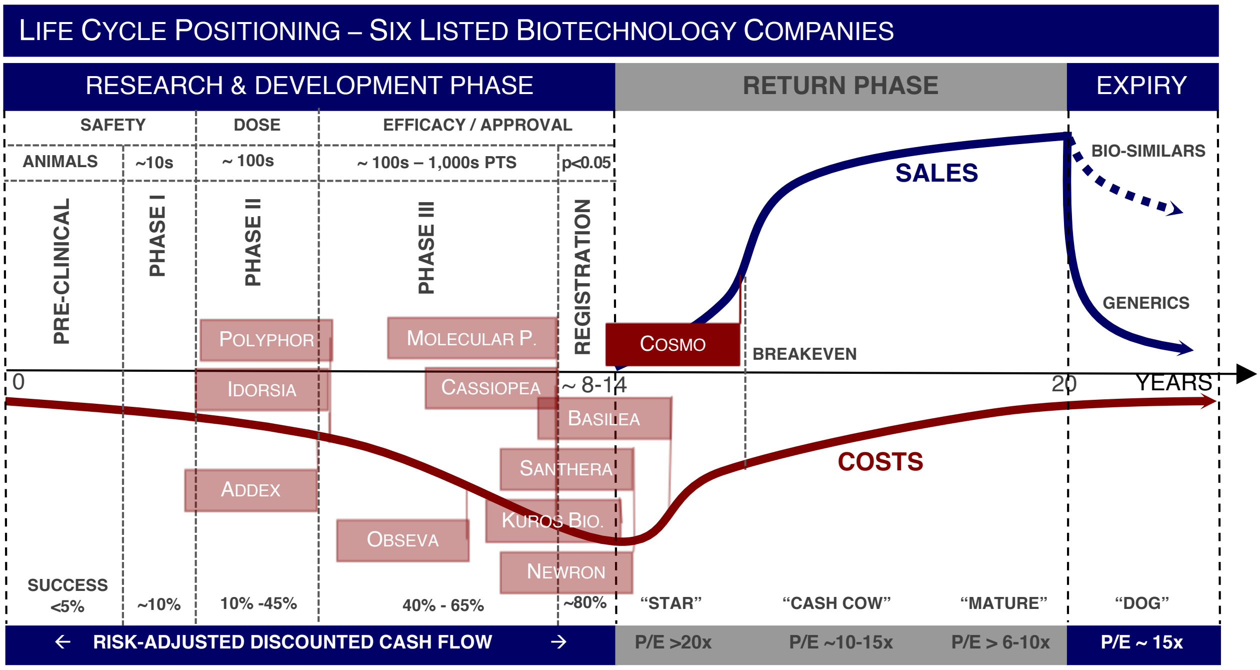
In October 2018, Cosmo provided Cassiopea a credit line of EUR 10 mn that can be increased to EUR 20 mn to fund Cassiopea's continued growth and expansion, and to minimize share dilution of its 45.1% stake until the company reaches new value inflection points at higher share prices. We assume Cassiopea to use the credit line up to EUR 20 mn and to fully refund Cosmo when it raises additional funds through a US-listing in 2019.

In November 2018, EUR 175 mn senior unsecured convertible bonds due 2023 were placed, sourced from existing authorized share capital on or after 15 January 2019. The bonds have a 2.50% coupon, payable semi-annually in arrear and a conversion price of EUR 122.6806, corresponding to a conversion premium of 20% above the reference price of the shares (95% of closing price CHF 121.40/share on 28 November 2018).

Cosmo's gross cash position (including bonds) of EUR 348 mn (CHF 428 mn) on 6 May 2019, is sufficient to finance all development and commercialization plans, extend financing to Cassiopea, and to fund potential acquisitions and in-licensing transactions. Consequently, the company needs no external funding to execute its clinical development plans, including a potential second pivotal phase III trial for MethyleneBlue. The substantial cash position is targeted to expand Cosmo's product offering through external transactions.

Life Cycle Positioning - Medium Risk

We consider an investment in Cosmo as medium risk due to its solid balance sheet; revenues from four marketed products (Lialda/Mezavant, Uceris/Cortiment, Aemcolo/Relafalk, Zacol NMX and Eleview) with more to follow with Aemcolo/Relafalk and the AI Smart Box in 2019 and MethyleneBlue, Qolotag, and Byfavo in the next 12-18 months; manufacturing revenues for third parties, and a 45.1% strategic stake in Cassiopea. Cosmo has always been prudent by never overstretching its financial reach when making investment decisions. With the delay of MethyleneBlue in the US and the restructuring on the US sales organization Aries, Cosmo expects to return to sustainable profitability in 2020 boosted by the rollout of new products and partnerships with strong players such as Medtronic in key markets.



SOURCE: VALUATIONLAB

Valuation Overview

Risk-adjusted sum-of-parts NPV points to CHF 211 per share

We derive a risk-adjusted (r)NPV for Cosmo of CHF 211 per share with estimated gross cash and bonds of CHF 26 per share (6 May 2019), and overhead expenses (conservatively including the repayment of the EUR 175 mn convertible bonds in 2023) of CHF 22 per share with a WACC of 7% (reflecting the low Swiss interest environment).

SUM OF PARTS

PRODUCT NAME	INDICATION	PEAK SALES	LAUNCH YEAR (EST)	UNADJUSTED NPV/SHARE	SUCCESS PROBABILITY	RISK-ADJUSTED NPV/SHARE	PERCENTAGE OF TOTAL
LIALDA / MEZAVANT	ULCERATIVE COLITIS	709	2007	5	100%	**5**	2%
UCERIS / CORTIMENT	ULCERATIVE COLITIS	149	2013	7	100%	**7**	3%
AEMCOLO / RELAFALK	TRAVELERS' DIARRHEA	92	2019	16	100%	**16**	7%
AEMCOLO / RELAFALK	IBS-D	483	2021	29	35%	**10**	4%
ELEVIEW	LESION RESECTION CUSHION	191	2017	22	100%	**22**	9%
AI SMART BOX (CB-17-08) - **NEW**	LESION DETECTION BY AI	540	2019 (EU)/2020 (US)	45	90%	**41**	18%
METHYLENEBLUE	LESION DETECTION DYE	572	2020 (EU)/2022 (US)	89	72.5%	**65**	28%
BYFAVO (REMIMAZOLAM)	FAST-ACTING SEDATION	154	2020	27	80%	**22**	9%
CB-03-10 - **NEW**	ONCOLOGY (NON-CORE)	TBD	TBD	TBD	<15%	**0**	0%
CONTRACT MANUFACTURING				5		**5**	2%
"EQUITY FOR PRODUCT" INVESTMENTS (E.G. CASSIOPEA (45.09%), PAION (9.0%))				15		**15**	6%
GROSS CASH & CASH EQUIVALENTS & BONDS (6 MAY 2019)		348		26		**26**	11%
TOTAL ASSETS				303		**233**	**100%**
OVERHEAD EXPENSES (INCL. REPAYMENT OF EUR 175 MN CONVERTIBLE BOND IN 2023)				-22		**-22**	
NPV/SHARE (CHF)				281		**211**	
SHARE PRICE ON JUNE 02, 2019						98	
PERCENTAGE UPSIDE / (DOWNSIDE)						117%	

* NOTE: 15 MN SHARES USED FOR NPV/SHARE CALCULATION AS WE CONSERVATIVELY ASSUME COSMO TO PAY BACK THE EUR 175 MN CONVERTIBLE BOND IN 2023(INCLUDED IN OVERHEAD EXPENSES)
NOTE: 16.3 MN SHARES OUTSTANDING INCLUDES 1.3 MN TREASURY SHARES RESERVED FOR POTENTIAL CONVERSION OF THE CONVERTIBLE BOND
ESTIMATES AS OF 3 JUNE, 2019

SOURCE: VALUATIONLAB ESTIMATES

Key drivers of growth for Cosmo include:

GASTROINTESTINAL DISORDERS:

Lialda/Mezavant (ulcerative colitis) - NPV of CHF 5 per share

Lialda/Mezavant (mesalamine MMX) is Cosmo's first prescription drug using its proprietary MMX technology for treating ulcerative colitis and was launched by Shire in 2007. Revenues for Cosmo are relatively low and now consist largely of manufacturing fees to produce Lialda tablets for Shire. In FY 2018, manufacturing and royalty income declined by 18%, hit by Zydus' generic version of Lialda in the US and partially offset by increases in Japan and the EU. The effect of US generics on Cosmo's revenues is limited as these are based on the volume of tablets shipped. We calculate an NPV of CHF 5 per share.

Uceris/Cortiment (ulcerative colitis) - NPV of CHF 7 per share

Uceris/Cortiment (budesonide MMX) is Cosmo's second treatment for ulcerative colitis with far better economics than Lialda. Ferring commercializes the drug in the EU and ROW (excluding Japan) branded Cortiment, while Bausch Health (formerly Valeant) sells the drug, branded Uceris, in the US. Although the peak sales potential is similar Lialda, our forecasts are significantly lower topping at EUR ~150 mn due the "at risk" launch of a generic version of Uceris by Actavis (Teva) last year in the US. Consequently, we lowered our US sales substantially, while maintaining a strong uptake outside the US. We calculate an NPV of EUR 7 per share. There is considerable upside were Bausch Health to win the appeal of a non-infringement ruling for Actavis by a US District Court.

Aemcolo/Relafalk (TD & IBS-D) – rNPV of CHF 26/share

Aemcolo/Relafalk (rifamycin SV MMX) has potential in TD (travelers' diarrhea) and IBS-D (irritable bowel syndrome – diarrhea predominant), among others. The antibiotic was approved in the US and EU for travelers' diarrhea in November 2018, with first launches in 2019. Dr. Falk has global rights, excluding the US, where Cosmo will sell the drug through a novel online DTC business model directly to US travelers. Dr. Falk brands the drug Relafalk. Outside Dr. Falk territories the antibiotic will be branded Aemcolo. We conservatively forecast peak sales of EUR ~90 mn in travelers' diarrhea due to the short treatment duration (3 days) with an NPV of CHF 16 per share. Aemcolo/Relafalk will also be developed in IBS-D, a far larger indication with longer treatment times (~14 days), with peak sales of EUR 450+ mn and a rNPV of CHF 10 per share with a 35% (phase II) success probability and first launches in 2022.

ENDOSCOPY:

Eleview (dyed lesion resection cushion) – rNPV of CHF 22 per share

Eleview is an injectable lesion resection cushion that allows physicians a faster and less risky excision of adenoma or polyps discovered during endoscopy. Eleview is injected between the mucosal layers where it separates and flags them with methylene blue dye for easy removal. Medtronic is now responsible for commercialization in the US, China and South America, replacing a previous US co-promotion agreement with Olympus. Fujifilm has a distribution agreement for Europe, South East Asia, Africa, Australia and New Zealand. We forecast EUR 150+ mn peak sales with a rNPV of CHF 22/share.

AI Smart Box (AI enhanced colonoscopy) NEW – rNPV of CHF 41 per share

The AI Smart Box is an artificial intelligence enhanced lesion detection system that can easily be integrated into existing colonoscopy towers/stacks, which alerts endoscopists in real-time the presence of lesions with high accuracy through a green highlighted box similar to face or eye detection systems in digital cameras. Together with the global marketing muscle of Medtronic, we believe this system will be a game changer in colonoscopy with substantial upside from future upgrades (not in our forecasts) and will be transformational for Cosmo. We conservatively forecast peak sales of EUR 540 mn (booked by Medtronic) with Cosmo retaining a net margin above 20%. We calculate a rNPV of CHF 41 per share with a 90% success rate, the average of EU (100% approved) and US (80% filing), with first launches in the EU in mid 2019 and in the US in Q1 2020.

MethyleneBlue (colonic lesion detection dye) - rNPV of CHF 65/share

MethyleneBlue is a novel MMX formulation of the existing liquid colon staining dye methylene blue, in a more convenient tablet with proven clinical efficacy in detecting lesions. We now assume a US launch of MethyleneBlue in 2022, following the FDA Complete Response Letter in May 2018 requesting a second phase III trial. Approval in the EU is expected in H1 2020 based on the filing in February 2019 where it will seek partners/distributors. We conservatively forecast peak sales of EUR 550+ mn, based on slightly lowered pricing assumptions, as pricing may be affected by the additional fees for the AI Smart Box, which will be on the market earlier. We calculate a rNPV of CHF 65 per share with a 72.5% success rate, the average of US (65% phase III) and EU (80% filing).

Byfavo (fast-acting sedation) – rNPV of CHF 22 per share

Remimazolam (now branded Byfavo) is a fast-acting sedative for procedural sedation in endoscopy, which Cosmo acquired the US rights from PAION in 2016. Byfavo nicely complements Cosmo's own endoscopy offering with the potential to leverage its investment in Aries or partnership with Medtronic. We forecast peak sales of EUR 150 mn in procedural sedation alone and calculate a rNPV of CHF 22 per share with an 80%

(filing) success probability, with US approval expected in H1 2020.

Contract manufacturing 3rd parties – NPV of CHF 5 per share
Cosmo continues to manufacture API's (active pharmaceutical ingredients) for third parties including generics and specialty drugs in the range of EUR 10 mn, which adds up to an NPV of CHF 5 per share.

"Equity for product" investments – NPV of CHF 14 per share
These investments consist of Cosmo's 45.1% stake in Cassiopea, a ~9% stake in PAION, and stakes in VolitionRx (3.5%) and AIMM Therapeutics (6.48%), which adds up to EUR 200 mn or CHF 15 per share.

No value contributed to Qolotag, CB-03-10 and MAOB MMX, yet
We have conservatively excluded Qolotag, a lesion detection dye for sigmoidoscopy, in our forecasts. Although Qolotag has been approved in the EU, no commercialization strategy has been announced, while Cosmo is also assessing the regulatory pathway for US approval. Based on limited data we believe Qolotag could achieve EUR ~100 mn peak sales.

We do not include any forecasts for CB-03-10 in cancer as the compound currently lacks clinical proof-of-concept, and therefore provides a potential real option. CB-03-10 is a synthetic steroidal antiandrogen and is derived from cortexolone just as Cassiopea's dermatology compounds Winlevi (acne) and Breezula (hair loss). Cosmo will start phase I trials of CB-03-10 in up to 90 cancer patients in Q4 2019, with topline results due in ~18 months from trial start. On positive phase I results, Cosmo plans to seek a strong oncology partner to fully develop and commercialize CB-03-10 in return for upfront, development, regulatory and sales milestones and royalties on sales.

We have also excluded forecasts for MAOB MMX, an oral "biobetter" anti-TNF alpha compound for maintenance of ulcerative colitis, which is in preclinical development.

Sensitivities that can influence our valuation

Development and regulatory risk: We believe the risk is not considerable considering three of Cosmo's prescription drugs (Lialda, Uceris, Eleview) are on the market, with the AI Smart Box and Aemcolo/Relafalk to be launched in 2019. Byfavo was filed for US approval in April 2019 leading to an 80% success rate with US launch expected in H1 2020. MethyleneBlue has been filed for EU approval in February 2019 with first launches in 2020. In the US, Cosmo will start a second confirmatory phase III trial with US approval now expected in 2022. We assume a 72.5% success rate for MethyleneBlue, the average of EU (80% filing) and US (65% phase III).

Pricing and reimbursement: Pricing for products such as Aemcolo and Byfavo is quite straightforward as there have been comparable branded products on the market treating the same indications to make a good pricing reference. Cosmo has put considerable effort in determining the right market price for its novel colonoscopy products such as Eleview, the AI Smart Box (determined by Medtronic) and MethyleneBlue, which provide cost-effective solutions compared to current standards. However, pricing may influence market penetration, reimbursement and ultimately the sales uptake. In the EU pricing and reimbursement occurs on a country-by-country base, which can lead to different pricing, reimbursement levels and sales uptake.

Partnering and commercialization: Outside the US, product sales will largely depend on external commercialization and distribution partners (e.g. Fujifilm for Eleview in Europe, Africa, Asia) to successfully position and market Cosmo's drugs. Cosmo intends to sign distribution and commercialization partners around market approval. In the US, the situation is less clear after the US delay of MethyleneBlue and the decision to restructure Aries. Future products may be sold by Aries, although we believe Cosmo will seek more distribution partnerships in the US such as with Medtronic. Medtronic will be instrumental in the success of the AI Smart Box and Eleview. Sales uptake and costs may differ from our forecasts as the pace of launching and signing on partners as well as terms may differ.

Patent and market exclusivity: Cosmo has built a comprehensive patent estate protecting it MMX technology and products from generic competition. Several market exclusivities such as 10 years data exclusivity in the EU, and 5 years NCE (new chemical entity) exclusivity or QIDP (qualified infectious disease product) designation with 5 years additional exclusivity, can further extend market protection. Finally, the MMX reformulation technology appears to be difficult to replicate by other manufacturers, potentially leading to only a handful of generic competitors entering the market. Although Lialda enjoys composition of matter protection until June 2020 in the US (US6773720) and EU (EU1198226, EU1287822), the FDA has approved a generic version of Lialda from the Indian generic manufacturer Zydus, which was recently launched. Lialda revenues for Cosmo are relatively low and now consist largely of manufacturing fees to produce Lialda tablets for Shire. Uceris has US patent protection until September 2031 through various patents. A US District Court ruled in favor of Actavis' generic version of Uceris that it does not infringe Cosmo's patents. Cosmo has appealed the ruling, which will take 12-18 months. In July 2018, Actavis' generic received FDA approval and has been launched "at risk". We assume patent protection and/or market exclusivity for MethyleneBlue (until 2033), Eleview (until 2034), Byfavo (until 2033), Aemcolo (until 2028), Qolotag (until 2035) and the AI Smart Box (until 2039 largely based on trade secrets).

Catalysts

CATALYST TIMELINES

TIME LINE	PRODUCT	INDICATION	MILESTONE	COMMENT
2019				
12 FEB	METHYLENEBLUE	LESION DETECTION (ENTIRE COLON)	EU FILING	IRRESPECTIVE OF FDA DISCUSSIONS; CENTRALIZED REGISTRATION WITH A 12 MONTH REVIEW PERIOD
12 MAR	METHYLENEBLUE	LESION DETECTION (ENTIRE COLON)	DENIAL 2ND APPEAL	FDA DENIED SECOND APPEAL; COSMO BEGINS ACTIVITY TO START SECOND CONFIRMATORY PHASE III TRIAL
	METHYLENEBLUE	LESION DETECTION (ENTIRE COLON)	ACTIVITY 2ND PHASE III TRIAL	ACTIVITY STARTED OF A SECOND CONFIRMATORY PHASE III TRIAL THAT IS REQUIRED FOR US APPROVAL
29 MAR			FY 2018 RESULTS	FY 2018 RESULTS: REVENUE: EUR 65.6 MN (EUR 67.2 MN IN FY 2017) IMPACTED BY US GENERIC OF UCERIS; OPERATING COSTS: EUR 82.2 MN (EUR 76.8 MN IN FY 2017) DUE TO FULL YEAR IMPACT US SALES INFRASTRUCTURE; OPERATING LOSS: EUR 16.6 MN (EUR 9.6 MN LOSS IN FY 2017) ; CASH AND BONDS: EUR 375.8 MN (EUR 247.2 MN IN YE 2017) THANKS TO EUR 175 MN CONVERTIBLE BOND
9 APR	REMIMAZOLAM	PROCEDURAL SEDATION (COLONOSCOPY)	US FILING	REMIMAZOLAM FILED IN THE US FOR PROCEDURAL SEDATION IN COLONOSCOPY ON 5 APRIL 2019, WITHIN 60 DAYS BY 4 JUNE ACCEPTANCE OF FILING EXPECTED; TRIGGERS EUR 7.5 MN REGULATORY MILESTONE PAYMENT TO PAION
10 APR	AI SMART BOX (CB-17-08)	LESION DETECTION	NEW PRODUCT ANNOUNCEMENT	NEW REVOLUTIONARY ARTIFICIAL INTELLIGENCE (AI) DEVICE IN COLONOSCOPY ANNOUNCED TO DETECT LESIONS WITH WORLDWIDE DISTRIBUTION AGREEMENT WITH MEDTRONIC
16 APR	BREEZULA (CASSIOPEA)	ALOPECIA (HAIR LOSS)	PHASE IIB RESULTS	POSITIVE TOPLINE RESULTS PHASE IIB DOSE RANGE TRIAL OF BREEZULA IN ALOPECIA (COSMO HAS A 45.1% STAKE IN CASSIOPEA)
8 MAY			R&D DAY	POTENTIAL GAME CHANGING ARTIFICIAL INTELLIGENCE (CB-17-08) DEVICE IN COLONOSCOPY PRESENTED TO HELP PHYSICIAN DETECT LESIONS MORE ACCURATELY, GLOBAL DISTRIBUTION AGREEMENT WITH MEDTRONIC, ESTIMATED NET MARGIN FOR COSMO ABOVE 20%; AEMCOLO US DTC/SOCIAL MEDIA MARKETING APPROACH; REMIMAZOLAM BRANDED BYFAVO; CB-03-10 TO START PHASE I, PARTNER ON POSITIVE RESULTS
4 JUN	BYFAVO (REMIMAZOLAM)	PROCEDURAL SEDATION (COLONOSCOPY)	ACCEPTANCE FILING	US ACCEPTANCE OF FILING EXPECTED; FULL FDA REVIEW TO START
JUN/JUL	AEMCOLO	TRAVELERS' DIARRHEA	US LAUNCH	NEW MARKETING APPROACH TARGETING TRAVELERS DIRECTLY THROUGH DTC/SOCIAL MEDIA INSTEAD OF PATIENTS/PHYSICIANS WITH A TRADITIONAL SALES FORCE; RENOWNED DTC HEALTHCARE PLAYERS SUCH AS OGILVY HEALTH (MARKETING PARTNER) AND UPSCRIPTHEALTH (EXECUTION PARTNER) ON BOARD
Q2	WINLEVI (CASSIOPEA)	ACNE	US FILING	US NDA FILING TO TREAT ACNE BASED ON POSITIVE PHASE III TRIAL, CASSIOPEA PLANS TO COMMERCIALIZE WINLEVI IN THE US MARKET
MID	AI SMART BOX (CB-17-08)	LESION DETECTION	EU LAUNCH	EXPECTED EU MARKET ENTRY BY MEDTRONIC BASED ON EUROPEAN CE MARKING
Q3	RELAFALK	TRAVELERS' DIARRHEA	EU LAUNCH	EU LAUNCH BY DEVELOPMENT AND COMMERCIALIZATION PARTNER DR. FALK
H2	WINLEVI (CASSIOPEA)	ACNE	US APPROVAL	CASSIOPEA INTENDS TO COMMERCIALIZE WINLEVI IN THE US EARLY 2020 WITH AN OWN US SALES FORCE FUNDED BY A US LISTING
Q4	CB-03-10	CANCER	START PHASE I	START PHASE I DEVELOPMENT IN UP TO 90 PATIENTS WITH ADVANCED REFRACTORY TUMORS; TRIAL DURATION ~18 MONTHS; ON POSITIVE RESULTS OUT LICENSE TO A STONG CANCER PLAYER
	AEMCOLO / RELAFALK	IBS-D	PHASE II	PHASE II TRIAL (342 PATIENTS; 25 SITES) FOR SECOND INDICATION OF IRRITABLE BOWEL SYNDROME WITH DIARRHEA (IBS-D) ONGOING
2020				
Q1	AI SMART BOX (CB-17-08)	LESION DETECTION	US LAUNCH	EXPECTED US MARKET ENTRY BY MEDTRONIC
H1	BYFAVO (REMIMAZOLAM)	PROCEDURAL SEDATION (COLONOSCOPY)	US APPROVAL	US APPROVAL; LAUNCH BY ARIES EXPECTED SHORTLY AFTER
MID	METHYLENEBLUE	LESION DETECTION (ENTIRE COLON)	EU APPROVAL	LAUNCH THROUGH SELECTIVE PARTNERSHIPS IN THE EU AND ROW
Q3/Q4	WINLEVI (CASSIOPEA)	ACNE	US APPROVAL	US APPROVAL; CASSIOPEA PLANS TO COMMERCIALIZE WINLEVI IN THE US MARKET THROUGH AN OWN SPECIALIST SALES FORCE
	AEMCOLO / RELAFALK	IBS-D	START PHASE III	START PHASE III DEVELOPMENT (TRIAL DURATION OF ~18 MONTHS) OF SECOND INDICATION IN IRRITABLE BOWEL SYNDROME WITH DIARRHEA (IBS-D)

ESTIMATES AS OF 3 JUNE, 2019 SOURCE: VALUATIONLAB, COSMO PHARI

Technology & Pipeline

Proprietary technology platform consisting of 2 core technologies and one non-core
Cosmo has expanded its technology platform beyond its core MMX technology and non-core anti-androgen receptor expertise into a new core technology of artificial intelligence with a continued focus on gastrointestinal disorders and endoscopy to prevent colon cancer:

1. **MMX technology:** core formulation technology that leads to a controlled release of drugs over the length of the colon with the potential to extend patent life such as with Lialda/Mezavant and Uceris/Cortiment in ulcerative colitis, Aemcolo/Relafalk in travelers' diarrhea, and MethyleneBlue in chromoendoscopy
2. **Artificial Intelligence:** new and emerging technology based on machine and deep learning to improve physician treatment outcomes such as better detection of lesions during colonoscopy with the AI Smart Box (CB-17-08)
3. **Antiandrogens (non-core):** expertise in antiandrogen compounds derived from cortexolone, involved in skin disorders and cancer, among others; non-core therapeutic areas for Cosmo, dermatology spun out through Cassiopea IPO (Winlevi for acne and Breezula for hair loss); new compound CB-03-10 discovered for treating cancer, which will be partnered on successful phase I development

1) MMX Technology - changing systemic drugs to convenient locally active agents
At the core of Cosmo's technology platform is the so-called **M**ulti **M**atri**x** "MMX" technology, a proprietary formulation technology that leads to a controlled release of existing drugs over the length of the colon. The company has developed a range of pharmaceutical products that are based on its MMX technology, including Lialda/Mezavant (mesalamine MMX), Uceris/Cortiment (budesonide MMX), Rifamycin SV/Relafalk (rifamycin SV MMX), and MethyleneBlue (methylene blue MMX).

The MMX technology allows the delivery of API's (active pharmaceutical ingredients) inside the interior of the colon through oral tablets in a delayed and controlled manner that the API can be applied to the entire length of the colon. The tablets manufactured according to the MMX technology are coated with pH-resistant acrylic copolymers, which delay the release until the tablet reaches the indicated intestinal location where the programmed dissolution begins. That allows for protection of the active substances from adverse pH (acidic) conditions and enzymatic presence in the upper digestive tracts (e.g. stomach, small intestines). The controlled release over the length of the colon not only simplifies the application for the patients, but also allows for the topical application of the API's to the whole bowel surface that is affected by inflammation or infection.

Key advantages of the MMX formulation technology include:
- Capitalizes on existing off-patent drugs, saves discovery efforts and costs
- Reduces multiple daily dosing to single daily dosing and lowers pill burden
- Improved efficacy, safety and more patient friendly (improved compliance)
- Lower regulatory approval risk than with a NCE (new chemical entity)
- Potential to extend patent life, up and beyond MMX patent protection
- Can also be used with new chemical entities (NCE's)

Cosmo developed its MMX technology based on a clear market need

Cosmo discovered that many drugs that were being developed and prescribed for colon diseases had compliance and safety issues, which could be addressed by their proprietary MMX technology platform. By developing new MMX compounds with existing drugs, the company established a broad knowledge of the colon's physiology and the absorption of pharmaceutical products in the gastrointestinal tract. The unique characteristics of the MMX technology, combined with the broad knowledge of the colon, provide Cosmo a strong competitive edge in developing new drugs for the colon, without the need to invest in expensive and high-risk NCE's. Cosmo's MMX compounds have improvements over existing drugs in terms of efficacy, safety and tolerability, with a lower pill burden that leads to higher patient compliance with a lower development and regulatory risk than NCE's.

Expanding the MMX strategy beyond off-patent molecules

With the MMX patent expiring in 2020, Cosmo is also targeting NCE's that could benefit from a delayed and controlled release formulation. In 2013, a first collaboration was announced with AIMM, a Dutch therapeutic antibody company. Cosmo intends to formulate a novel oral "biobetter" anti-TNF-alpha monoclonal antibody, MOAB MMX, for the maintenance of ulcerative colitis utilizing its MMX technology. Current TNF-alpha agents for ulcerative colitis are expensive monoclonal antibodies that are administered by a physician or nurse intravenously in an outpatient setting (e.g. Johnson & Johnson's Remicade (infliximab)) or by subcutaneous injection (e.g. Abvie's Humira (adalimumab)), which add to the total cost of therapy. This is more cumbersome than a simple daily oral tablet that can be taken by the patient at home.

2) Artificial Intelligence – Emerging technology radically changing business models

Artificial intelligence (AI) will become a second technology platform that will transform Cosmo. AI systems for healthcare have the potential to transform the diagnosis and treatment of disease, which could help ensure that patients get the right diagnosis, the right treatment at the right time, enhancing physician treatment outcomes. AI is an area of computer science that emphasizes the creation of intelligent machines that work and react like humans based on machine and deep learning. Machine learning uses algorithms to analyze data, learn from data, and make informed decisions based on what it has learned. A subfield of machine learning is deep learning, which structures algorithms in layers to an artificial neural network that can learn and make intelligent decisions on its own. This technology can be used to help physicians and patients to make better healthcare decisions.

Prime examples of artificial intelligence outside healthcare include smartphones with speech recognition assistants such as Alexa or Siri, smart cars with autonomous driving, digital cameras with face, eye or even smile detection, and social media feeds, to name a few. These AI platforms have revolutionized existing business models or have created totally new business models often with rapid adoption.

AI Smart Box thanks to MethyleneBlue development and Linkverse cooperation

Thanks to the development of MethyleneBlue generating thousands of videos of colonoscopies stored in the first high definition lossless video database and the cooperation and investment in Linkverse that produced the ad-hoc recording devices and the cloud platform dedicated to this service, Cosmo is now at the frontline of artificial intelligence enhanced colonoscopy with the AI Smart Box. Linkverse, based in Rome and now a subsidiary of Cosmo, is an innovative company at the forefront of healthcare information technology, specializing in cloud-based management systems and AI analysis tools for biomedical images, video and data either for medical practice or for clinical research. Applying modern computer science, Linkverse provides a new, intelligent way of presenting data to make complex problems easily understandable.

AI Smart Box and Medtronic agreement to capitalize on emerging AI in colonoscopy
Cosmo plans to capitalize on the arrival of AI in colonoscopy through its revolutionary AI Smart Box, which provides physicians a “second set of expert eyes”, combined with Medtronic’s global distribution platform. Medtronic is the world’s leading medical device company with the knowledge, capital, drive and marketing muscle to successfully launch Cosmo’s AI Smart Box in colonoscopy. Key is to rapidly establish and lock-in a customer base, and to leverage this base with future upgrades such as optical biopsy, other GI applications or procedural documentation. Medtronic will provide the AI Smart Box for free, which can easily be fitted in the existing colonoscopy towers/stacks, in return for a relatively small fee per colonoscopy with an estimated yearly fee per AI Smart Box of USD 36,000 in the US and EUR 36,000 in the EU/ROW. The estimated net margin for Cosmo is expected to be above 20%.

3) Antiandrogens (non-core) - generating value through Cassiopea or out licensing
Cosmo owns a compound library with focus on diseases dependent on the androgen receptor or so-called antiandrogens. This is a class of drugs that prevent androgens like testosterone or dihydrotestosterone (DHT) from mediating their biological effects in the body and are involved in skin disorders such as acne or hair loss, and various cancers such as prostate cancer, among others. Research in these therapeutic areas are considered non-core, with Cosmo capturing value in dermatology through its 45.1% stake in Cassiopea and through potential development and commercialization partnerships in oncology after completion of phase I development, a critical value creating step in cancer.

Several Cosmo compounds were derived from cortexolone and were screened for use in a specific treatment. Most notably is Cosmo’s novel antiandrogen clascoterone, a new chemical entity and core compound for Cassiopea that is being developed for treating acne (branded Winlevi) and androgenic alopecia also known as pattern hair loss (branded Breezula) in different topical formulations and strengths. Clascoterone is quickly metabolized to cortexolone, a naturally occurring metabolite found throughout all human tissues, cells, blood and urine, with a well characterized safety and metabolic profile. Due to its rapid metabolism and local activity, clascoterone does not produce systemic side effects.

CB-03-10 is a potent oral antiandrogen, also derived from cortexolone, with potent anti-tumor activity across many different cancers such pancreatic, colon and prostate cancer. In Q4 2019, Cosmo will start a phase I multicenter trial in patients with advanced refractory tumors in up to 90 patients. On completion of phase I development, Cosmo will seek a strong cancer player for further development and commercialization in return for upfront, development, regulatory and sales milestones and royalties on sales.

Uniquely positioned with four marketed products and another five close to market
Cosmo’s therapeutic focus is on the endoscopic oral and pharmaceutical treatment of colon disorders. At present, Cosmo has four products on the market, including Lialda/Mesavant and Uceris/Cortiment, both prescription drugs for treating mild-to-

moderate ulcerative colitis; the nutraceutical Zacol NMX, a dietary supplement for mild ulcerative colitis, and Eleview, for endoscopic lesion resection.

PRODUCT PIPELINE

PRODUCT	DRUG CLASS	INDICATION	STATUS	LAUNCH YEAR	PARTNER	PEAK SALES
GASTROINTESTINAL DISORDERS						
LIALDA / MEZAVANT	5-ASA	ULCERATIVE COLITIS (INDUCTION & MAINTENANCE)	MARKETED	2007	SHIRE	EUR 700 MN
UCERIS / CORTIMENT	ORAL GLUCOCORTICOSTEROID	ULCERATIVE COLITIS (INDUCTION)	MARKETED	2013	BAUSCH HEALTH (US) FERRING (ROW)	EUR 150 MN
AEMCOLO / RELAFALK	ANSAMYCIN ANTIBIOTIC	TRAVELER'S & INFECTIOUS DIARRHEA	FILING (EU)	2019	DR. FALK (EU/AUS)	EUR 90 MN
AEMCOLO / RELAFALK	ANSAMYCIN ANTIBIOTIC	IRRITABLE BOWEL SYNDROME WITH DIARRHEA (IBS-D)	PHASE II	2022	DR. FALK (EU/AUS)	EUR 450+ MN
ZACOL NMX	DIETARY SUPPLEMENT (NUTRACEUTICAL)	INTESTINAL DISORDERS	MARKETED	2011	DR. FALK (ITALY, EASTERN EUROPE)	N.A.
MOAB MMX	ORAL "BIOBETTER" ANTI-TNFα	ULCERATIVE COLITIS (MAINTENANCE)	PRECLINICAL	TBD	AIMM	TBD
ENDOSCOPY						
METHYLENEBLUE	COLONIC LESION STAINING DYE	LESION DETECTION (COLONOSCOPY)	FILING (EU) PHASE III (US)	2020 2022	EX-US RIGHTS TO BE PARTNERED	EUR 550+ MN
AI SMART BOX (CB-17-08)	ARTIFICIAL INTELLIGENCE ENHANCED IMAGING DEVICE	LESION DETECTION (COLONOSCOPY)	LAUNCH (EU) FILING (US)	2019 2020	MEDTRONIC (GLOBAL RIGHTS)	EUR 500+ MN
ELEVIEW	LOW-VISCOSITY EMULSION	ENDOSCOPIC RESECTION CUSHION	MARKETED	2017	MEDTRONIC (US, CHINA, S.AM.) FUJIFILM (EU/ASIA/AFRICA)	EUR 150+ MN
QOLOTAG	COLONIC LESION STAINING DYE	LESION DETECTION (SIGMOIDSCOPY)	APPROVED (EU)	2018	EX-US RIGHTS TO BE PARTNERED	EUR 100 MN
BYFAVO (REMIMAZOLAM)	FAST-ACTING BENZODIAZAPINE DERIVATIVE	PROCEDURAL SEDATION (E.G. COLONOSCOPY)	FILED (US)	2019 2020	US RIGHTS IN-LICENSED FROM PAION	EUR 150 MN
ONCOLOGY (NON-CORE)						
CB-03-10	ANDROGEN RECEPTOR ANTAGONIST	ONCOLOGY	PHASE I	TBD	PARTNER ON SUCCESSFUL PHASE I	TBD

ESTIMATES AS OF 3 JUNE, 2019 SOURCE: VALUATIONLAB, COSMO PHARMACEUTICALS

Five other products are close to market, including: 1) Aemcolo/Relafalk approved for travelers' diarrhea with global launches in 2019; 2) the AI Smart Box (CB-17-08) for AI enhanced colonoscopy to be launched by Medtronic in the EU in mid 2019 and in the US in Q1 2020; 3) MethyleneBlue for lesion detection during colonoscopy filed for EU approval in February 2019, 4) Qolotag approved in the EU for lesion detection during sigmoidscopy, and 5) Byfavo (remimazolam) a fast-acting sedative for colonoscopy that was filed for US approval in procedural sedation in April 2019 with approval expected in H1 2020.

CB-03-10 is a non-core oncology compound derived from Cosmo's novel anti-androgen cortexolone, which will start phase I development cancer in Q4 2019. After successful completion of phase I Cosmo plans to license CB-03-10 to a strong oncology player in return for upfront, clinical, regulatory and sales milestone payments and royalties on sales.

In the following section we will provide an in-depth analysis and forecast for Cosmo's key drivers for:

Endoscopy (page 21)**:**

- **AI Smart Box (CB-17-08)** (AI enhanced lesion detection entire colon)
- **MethyleneBlue** (dye stained enhanced lesion detection entire colon)
- **Eleview** (endoscopic resection cushion)
- **Byfavo** (procedural sedation for e.g. colonoscopy)

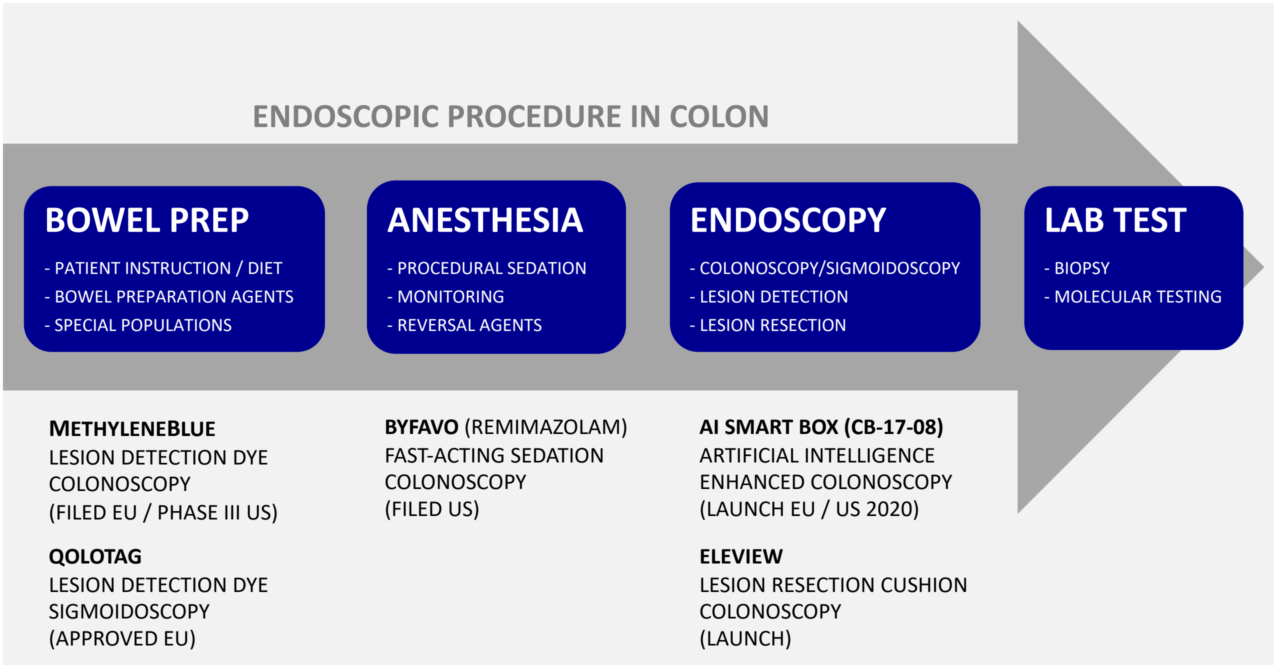
Gastrointestinal (page 49)**:**

- **Aemcolo/Relafalk** (travelers' diarrhea & IBS-D)
- **Uceris/Cortiment** (ulcerative colitis)
- **Lialda/Mezavant** (ulcerative colitis)

Endoscopy pipeline

Cosmo's endoscopy/colonoscopy pipeline products are targeted to reduce the risk of colorectal cancer by improving the outcomes of preventive colonoscopy screening with better detection of lesions in the colon such as precancerous adenomas and polyps (**MethyleneBlue**, **Qolotag, AI Smart Box**), safer and faster removal of adenomas and polyps (**Eleview**) and faster sedation and recovery times (**Byfavo**).

COMPREHENSIVE PORTFOLIO FOR ENDOSCOPY IN COLON



SOURCE: GASTRO HEALTH; VALUATIONLAB

A **colonoscopy** is often used as an effective screening test for colorectal cancer, which reduces the risk of death from colorectal cancer by more than 50% due to the early detection and removal adenomas and polyps. It is recommended that people of average risk get a colonoscopy or other type of screening every 10 years starting at age 50. People at high risk should begin screening earlier, and sometimes more often, according to the American Cancer Society. The patient must have an empty bowel. A restricted diet refraining from solid foods at least 24 hours before the procedure is required. Bowel preparation agents are given to cleanse and empty the bowel. During the colonoscopy procedure the patient is sedated and monitored by an anesthetist. The physician uses a flexible tube with a camera and light on it – a flexible endoscope - to examine the rectum and the inside of the full length of the colon. If something suspicious is found such as an adenoma or polyp, these will be removed, often with a wire loop and/or burning with an electrical current. A sample for biopsy will be taken and sent to the lab to determine the tissue type and to detect any cancer. After the colonoscopy, the patient will be given time to recover from the sedation. A colonoscopy typically takes about 20 minutes to an hour and another hour to recover from the sedative. An alternative to colonoscopy is a so-called **sigmoidoscopy**, which is less invasive than a colonoscopy. A sigmoidoscopy only examines up to the sigmoid, from the rectum to the last part of the colon, while a colonoscopy examines the entire colon. Sedation is not required. Here too, the bowel must be fully emptied through a laxative and an enema (a liquid solution that washes out the intestines) prior to the procedure. The procedure takes 10-20 minutes and is often used to find the cause of diarrhea, abdominal pain or constipation.

AI Smart Box (CB-17-08) – AI enhanced colonoscopy

Product Analysis

AI Smart Box peak sales of EUR 500+ mn - rNPV of CHF 41/share

We conservatively forecast the AI (artificial intelligence) Smart Box (CB-17-08) to generate EUR 540 mn peak sales in enhanced colonoscopy detection only (booked by global partner Medtronic). First European launches are expected in mid 2019 and in the US in Q1 2020. We assume the adoption rate for computer-aided (= artificial intelligence) detection in colonoscopy to rapidly increase to 95% in the US and 90% in the EU/ROW by 2025. As first mover and global player, Medtronic will initially have a dominant market share, which we assume will gradually be eroded to 25% by rival systems, albeit in a larger market, as more AI players grow the market. The estimated net margin for Cosmo is expected to be above 20%, consisting of 22% royalties on sales, while incurring ~2% COGS. Medtronic provides the AI Smart Box for free in return for an estimated fee per procedure ranging between EUR 31 (US) and EUR 37 (EU). We calculate a rNPV of EUR 612 mn or CHF 41 per share assuming a 90% success rate, the average of EU (100% approved) and US (80%filing), and a WACC of 7% (for detailed forecasts see page 27).

NOTE: We have not included revenues for future upgrades to the AI Smart Box such as optical biopsy, procedural documentation & administration or other GI indications, which provide substantial upside to our forecasts.

AI Smart Box & Medtronic: a game changer in colonoscopy

The healthcare market is on the verge of revolutionary change with the arrival of artificial intelligence (AI) systems based on machine and deep learning combined with significant improvements in hardware (e.g. processing power) that will lead to better physician treatment outcomes. We believe Cosmo's AI colonoscopy device CB-17-08, which for clarity we dubbed the "AI Smart Box", combined with the global marketing muscle of Medtronic, the world's leading medical device company, will become a game changer in how colonoscopy will be performed in the near future. The AI Smart Box provides physicians with a simple and effective interface – the operator is alerted in real-time by a dynamic green box around the lesion similar to face or eye detection on digital cameras - to reduce the risk of missing a lesion and ultimately improving the detection rate during colonoscopy. Together with MethyleneBlue, a potential new gold standard image enhancing staining agent for colonoscopy that complements the AI Smart Box, Cosmo is set for transformational change once both products are successfully launched in the next few years.

The most preventable cancer depends on the ADR and finding lesions early

Colorectal cancer is the third most common cause of cancer death in the world. In the US there are 150,000 new cases and 50,000 deaths due to colorectal cancer per year. Colorectal cancer is considered a disease of the older people with more than 90% of patients being diagnosed after the age of 55 years. However, colorectal cancer is also considered one of the most preventable cancers. Colonoscopy is the primary screening tool to prevent colorectal cancer by early detection and removal (resection) of precancerous lesions (adenomas) and cancerous lesions and polyps. Screening is advised typically for most people from age 50 years until age 75 years. If a colonoscopy does not find adenomas or cancer and there are no other risk factors, the next exam should be performed in ten years. If one or two small, low-risk adenomas are removed the colonoscopy should be repeated in five to ten years.

Not all adenomas turn into cancer, but all colon cancers were previously adenomas
The aim of colonoscopy is to detect adenomas. Not all adenomas turn into cancers, but all cancers were previously adenomas. Therefore, the effectiveness of the colonoscopy depends on the adenoma detection rate (ADR). Ultimately, the more adenomas are detected and extracted, the less cancers will subsequently develop. Most polyps look something like a mushroom growing from the colon wall and are easily seen and can be easily removed during colonoscopy. Diminutive (tiny) polyps, measuring between 1 and 5mm, represent the vast majority of colorectal polyps observed during screening colonoscopy. There are also flat polyps that grow wide, spreading along the colon wall, usually in the right colon. Flat polyps are believed to make up about 9% of all polyps. But because they are difficult to find and remove completely, they are believed to be responsible for most of the colon cancers that occur in people who are up to date with their colonoscopies.

Large variability in ADR increases the risk of interval colorectal cancer
Colonoscopists vary widely in their ability to find adenomas, with an ADR ranging from 7% to 54% with a mean of ~30%. Approximately 26% of diminutive polyps are missed. The detection rate for adenomas from flat polyps is even worse with a national mean of 2%. Medicare expects a 25% ADR among women and 30% among men. The prevalence of adenomas is estimated to be >50%. If one or more adenomas are missed, the patient has an increased risk for developing colorectal cancer before their next colonoscopy. A large study by Corley et al. showed that every 1% increase in the adenoma detection rate was associated with a 3% decrease in the risk of colorectal cancer before the next exam.

Two main factors are considered to affect the low adenoma detection rate:

- **Lesions that are difficult to spot:** this can be improved for instance by using high definition wide-angle endoscopes with white light (HDWL), devices to clean and visualize the entire surface area or image-enhancing dyes that mark difficult-to-spot (flat or tiny) adenomas (e.g. MethyleneBlue).
- **Human error:** this is not easily overcome and is dependent on multiple factors such as motivation, training, manual skills, and intrinsic abilities such as observer-dependent visual acuity and pattern recognition.

Colonoscopy is an expensive screening tool with room to improve
Colonoscopy is also the costliest screening tool to prevent colorectal cancer. Any solution that significantly increases the adenoma detection rate is expected to be integrated in the procedure and included in treatment guidelines. Particularly, if the solution has proven efficacy and is simple to adopt. This is where computer-aided detection or artificial intelligence can play an important role. AI systems such as Cosmo's AI Smart Box can be easily added to a colonoscopy tower/stack while implementation is simple with no extensive training needed.

AI Smart Box is a "second set of expert eyes" to assist the colonoscopy operator
AI is an area of computer science that emphasizes the creation of intelligent machines that work and react like humans based on machine and deep learning. Machine learning uses

algorithms to analyze data, learn from data, and make informed decisions based on what it has learned. A subfield of machine learning is deep learning, which structures algorithms in layers to an artificial neural network that can learn and make intelligent decisions on its own.

AI is rapidly making inroads in healthcare, with most promising results in imaging (computer-aided detection) and diagnosis (computer-aided diagnosis e.g. optical biopsy). Digital images provide huge amounts of high-quality data with very complete data sets, which is crucial for AI and deep learning. AI processes the data and tries to replicate a physician understanding that data and determine what is normal and what may need to be addressed medically. Moreover, the human eye is often blind to some patterns that could be present in these images. As stated, in colonoscopy, reported miss rates of lesions range between 20-40% due to both polyp and operator characteristics.

Cosmo's AI Smart Box intends to provide the colonoscopy operator a "second set of expert eyes" to reduce the rate of missed lesions and thereby improve the overall lesion detection rate. The AI Smart Box provides physicians with a simple and effective interface to detect significantly more lesions during colonoscopy than with current gold standard HDWL (High Definition endoscope with White Light). When a lesion is detected, the AI Smart Box projects in real-time a dynamic green box around the lesion on the operator's screen. This convenient and simple interface highlights the lesion until it is removed.

Highly accurate lesion detection rate thanks to MethyleneBlue development
The system has proven to be very accurate with a true positive rate per polyp (sensitivity) of 99.7% while the number of false positives frames in a full procedure (activation noise = false positives divided by the number of frames) amounted to 0.9%. In other words, the system was as good as an expert colonoscopist in detecting lesions and the extremely low amount of false activations does not slow down or negatively alter the conventional colonoscopy procedure.

The accuracy of the AI Smart Box is based on the quality and increasing quantity of Cosmo's data set when developing MethyleneBlue as an image enhancing agent for detecting lesions during colonoscopy. The first dataset used for AI algorithm development in Q1 2017 contained 500 images of easy-to-detect polyps. In Q1 2018, the size of the dataset increased to 15,000 images from the MethyleneBlue phase III clinical trial. In September 2018, the size of the dataset for regulatory approval was frozen at over 700,000 images in HDWL on different endoscopes in Europe, the US and Asia. Cosmo continues to improve the dataset to tens of millions as they record new data with a novel protocol to be used with improved AI algorithms and for new features.

AI Smart Box and Medtronic agreement to capitalize on emerging AI in colonoscopy
Cosmo plans to capitalize on the arrival of AI in colonoscopy through its AI Smart Box, which provides physicians a "second pair of expert eyes" combined with Medtronic's global distribution platform. Medtronic is the world's leading medical device company with the knowledge, capital, the drive and marketing muscle to successfully launch Cosmo's AI Smart Box in colonoscopy. Key is to establish and lock-in a customer base as soon as possible and to leverage this base with future upgrades such as optical biopsy, other GI applications or procedural documentation modules. Medtronic will provide the AI Smart Box for free, which can easily be fitted in the existing colonoscopy towers/stacks, in return

for a modest fee per colonoscopy with an estimated yearly fee per AI Smart Box of USD 36,000 in the US and EUR 36,000 in the EU/ROW.

Future upgrades to the AI Smart Box could generate substantially higher revenues
Cosmo intends to improve the AI Smart Box constantly through the distribution of new software upgrades on a regular basis. New core functionalities are already under development, including:

Optical biopsy: Cosmo's high-quality data set is being used to train the deep neural network to classify diminutive (tiny) polyps as neoplastic (adenomas), which need to be removed or hyperplastic, which can stay. For instance, a suspected lesion that needs to be removed is alerted in a red box, while a lesion that can stay is highlighted in a green box, all in real time, conveniently projected on the operator's screen.

Additional GI & other applications: The AI system can be used to detect and monitor inflammation in chronic gastrointestinal diseases such as IBD (inflammatory bowel disease), identifying gastrointestinal bleeding or even diagnose certain gastrointestinal infections.

Other implementations not yet mentioned by Cosmo could include:

Procedural documentation: While performing a colonoscopy AI algorithms can observe and record all the elements that need to go into a procedural note such as time of insertion and withdrawal, findings, locations and tools used according to medical insurance codes, thereby reducing the administrative burden for the colonoscopist and converting documentation time to more patient (treatment) time.

Augmented reality: Augmented reality can superimpose computer-generated objects and data over existing real structures seen on the screen to improve the operators ability to perform a task in real-time such as project the probability of malignancy for each polyp, detect the presence and type of polyposis according to the number and pattern of polyps that may become malignant, and provide a much more hands-on way for colonoscopists to begin training and for gastroenterologists to confirm a diagnosis.

These new applications, which can be delivered through software upgrades, provide substantial upside to our forecasts for the AI Smart Box through additional fees, faster and higher adoption rates and market share.

We conservatively forecast EUR 540 mn peak sales for the AI Smart Box
Although we believe Cosmo's AI Smart Box, together with the marketing muscle of Medtronic, will be a game changer in colonoscopy, it is difficult to provide accurate forecasts for disruptive technologies in their early years. We have based our forecasts largely on US sources, which are more detailed and easily available, and extrapolated our findings for other regions.

We calculated the estimated number of colonoscopy towers/stacks that are needed to perform the annual number of colonoscopies in each region. In the US, we estimate there are roughly 14,600 stacks, based on 250 operational days per year and 4 procedures per day (~50% capacity utilization) resulting in 1,000 colonoscopies per year per stack to perform the yearly ~14.6 mn colonoscopies.

Critical will be the adoption rate of computer-aided detection (CAD) in colonoscopy and the market share Medtronic captures. Medtronic is expected to launch the AI Smart Box in mid 2019 in the EU. Cosmo's AI Smart Box is likely the first commercial launch of such a CAD system in the EU and the US. Therefore, we forecast Medtronic to initially have a dominant market share of 100% in the EU gradually declining to 25% as new players enter the market. Conversely, we initially forecast a low adoption rate of CAD in stacks, as Medtronic will be the only player promoting and offering such commercial systems. Going forward, we expect existing colonoscopy players such as Olympus, but also AI tech companies outside colonoscopy (e.g. Google, Apple?), to launch rival CAD systems and rapidly increase the CAD adoption rate to peak at around 90-95%. We do not forecast an increase of colonoscopy stacks as we expect the CAD systems to increase capacity utilization.

We only include forecasts for the higher-priced markets such as the US, Europe (excluding CEE), Japan and Australia. Large markets such as, CEE, Asia or China could provide substantial upside to our forecasts. First launches in the US are expected to occur in Q1 2020. We assume a similar increase in CAD adoption rate and market share development for the AI Smart Box as in the EU.

Cosmo indicated that the annual fee per AI Smart Box will amount to approximately USD 36,000 in the US and EUR 36,000 in the EU/ROW. Based on the above, we calculate peak sales to amount to EUR 540 mn, which will be booked by Medtronic. Cosmo will retain a net margin of above 20%, consisting of a 22% royalty on sales, while incurring COGS of ~2%. Our rNPV amounts to CHF 612 mn or CHF 45 per share with a 90% success rate, the average of the EU (100% approved) and the US (80% filing), with a 7% WACC.

Forecasts & Sensitivity Analysis

AI SMART BOX (CB-17-08) - FINANCIAL FORECASTS FOR AI ENHANCED COLONOSCOPY IMAGING

INDICATION	COLONOSCOPY - ARTIFICIAL INTELLIGENCE ENHANCED ACCURATE AND CONVENIENT EARLY LESION DETECTION TO PREVENT COLON CANCER
DOSAGE	TO BE USED IN EVERY COLONOSCOPY
PRICING	WE CALCULATE A PER PROCEDURE FEE RANGING BETWEEN EUR 31 (US) AND EUR 37 (EU)
STANDARD OF CARE	CURRENT GOLD STANDARD IS HIGH DEFINITION ENDOSCOPE WITH WHITE LIGHT (HDWL)
UNIQUE SELLING POINT	"SECOND SET OF EYES" THAT DETECTS LESIONS IN REAL TIME WITH EXTREME ACCURACY, MARKED BY A GREEN BOX, WHICH REDUCES FAILURE TO RECOGNIZE LESIONS

7Ps ANALYSIS

PATENT	WE CONSERVATIVELY ASSUME MARKET EXCLUSIVITY UNTIL 2039 AS THE ARTIFICIAL INTELLIGENCE TECHNOLOGY IS BASED ON PROPRIETARY DATA (TRADE SECRETS)
PHASE	EU; APPROVED WITH CE MARKING; ROLLOUT MID 2019; US: REGULATORY PATHWAY TO BE DETERMINED, APPROVAL EXPECTED IN Q1 2020
PATHWAY	MEDICAL DEVICE REGULATORY PATHWAY; EU: APPROVED WITH CE MARKING; US: REGULATORY PATHWAY TO BE DETERMINED (510K OR PMA)
PATIENT	HIGHER ADR DETECTION RATE LEADS TO LOWER PROBABILITY OF DEVELOPING COLORECTAL CANCER BEFORE NEXT COLOTECTAL EXAM
PHYSICIAN	"SECOND SET OF "EYES" THAT DETECTS LESIONS IN REAL TIME WITH EXTREME ACCURACY, MARKED BY A GREEN BOX, REDUCES FAILURE TO RECOGNIZE LESIONS
PAYER	SMALL ADDITIONAL COST TO PROCEDURE WHILE EARLY DETECTION OF COLON CANCER REDUCES LONG-TERM COSTS SUBSTANTIALLY
PARTNER	GLOBAL PARTNERING WITH MEDTRONIC; ESTIMATED YEARLY FEE PER DEVICE IN US/EU OF USD/EUR 36,000; ESTIMATED NET MARGIN FOR COSMO TO BE ABOVE 20%

REVENUE MODEL

UNITED STATES - SOLD BY MEDTRONIC	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
PEOPLE OF SCREEN-ELIGIBLE AGE (50-74 YEARS) (MN)	75	76	78	79	81	83	84	86	88	89	91
GROWTH (%)	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
PERCENTAGE COLONOSCOPIES (%)	19%	19%	19%	19%	19%	19%	19%	19%	19%	19%	19%
ANNUAL NUMBER OF COLONOSCOPIES (MN)	15	15	15	15	16	16	16	17	17	17	18
NUMBER OF COLONOSCOPY TOWERS (STACKS)	14,566	14,566	14,566	14,566	14,566	14,566	14,566	14,566	14,566	14,566	14,566
GROWTH (%)	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
ANNUAL NUMBER OF COLONOSCOPIES PER STACK	1,000	1,020	1,040	1,061	1,082	1,104	1,126	1,149	1,172	1,195	1,219
ADOPTION RATE COMPUTER-AIDED DETECTION IN STACKS (%)	0%	0%	5%	20%	45%	65%	80%	90%	95%	95%	95%
STACKS WITH COMPUTER-AIDED DETECTION	0	0	728	2,913	6,555	9,468	11,652	13,109	13,837	13,837	13,837
PENETRATION (%)	0%	0%	95%	85%	75%	65%	55%	45%	35%	25%	25%
STACKS USING AI SMART BOX	0	0	692	2,476	4,916	6,154	6,409	5,899	4,843	3,459	3,459
ANNUAL FEE PER AI SMART BOX (EUR)	30,592	31,801	31,801	31,801	31,801	31,801	31,801	31,801	31,801	31,801	31,801
SALES (EUR MN) - BOOKED BY MEDTRONIC	**0**	**0**	**22**	**79**	**156**	**196**	**204**	**188**	**154**	**110**	**110**
CHANGE (%)				258%	99%	25%	4%	-8%	-18%	-29%	0%
ROYALTY (%)	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%
ROYALTIES (EUR MN)	0	0	5	17	34	43	45	41	34	24	24
COGS (%)			2%	2%	2%	2%	2%	2%	2%	2%	2%
COGS PER AI DEVICE (EUR)	-500	-500	-500	-500	-500	-500	-500	-500	-500	-500	-500
COGS (EUR MN)	0	0	0	-1	-2	-3	-3	-3	-2	-2	-2
PROFIT BEFORE TAX (EUR MN)	**0**	**0**	**4**	**16**	**32**	**40**	**42**	**38**	**31**	**22**	**22**
TAX RATE (%)	0%	0%	0%	0%	20%	20%	20%	20%	20%	20%	20%
TAXES (EUR MN)	0	0	0	0	-6	-8	-8	-8	-6	-4	-4
PROFIT (EUR MN)	**0**	**0**	**4**	**16**	**26**	**32**	**33**	**31**	**25**	**18**	**18**

EUROPE (EXCL. CEE) / JAPAN / AUSTRALIA - SOLD BY MEDTRONIC	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
PEOPLE OF SCREEN-ELIGIBLE AGE (50-74 YEARS) (MN)	134	137	140	143	146	148	151	154	158	161	164
GROWTH (%)	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
PERCENTAGE COLONOSCOPIES (%)	19%	19%	19%	19%	19%	19%	19%	19%	19%	19%	19%
ANNUAL NUMBER OF COLONOSCOPIES (MN)	26	27	27	28	28	29	29	30	31	31	32
NUMBER OF COLONOSCOPY TOWERS (STACKS)	26,727	26,727	26,727	26,727	26,727	26,727	26,727	26,727	26,727	26,727	26,727
GROWTH (%)	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
ANNUAL NUMBER OF COLONOSCOPIES PER STACK	980	1,000	1,020	1,040	1,061	1,082	1,104	1,126	1,148	1,171	1,195
ADOPTION RATE COMPUTER-AIDED DETECTION IN STACKS (%)	0%	2%	12%	32%	47%	62%	72%	82%	87%	90%	90%
STACKS WITH COMPUTER-AIDED DETECTION	0	535	3,207	8,553	12,562	16,571	19,243	21,916	23,252	24,054	24,054
PENETRATION (%)	0%	100%	95%	85%	75%	65%	55%	45%	35%	25%	25%
STACKS USING AI SMART BOX	0	535	3,047	7,270	9,421	10,771	10,584	9,862	8,138	6,014	6,014
ANNUAL FEE PER AI SMART BOX (EUR)	36,000	36,000	36,000	36,000	36,000	36,000	36,000	36,000	36,000	36,000	36,000
SALES (EUR MN) - BOOKED BY MEDTRONIC	**0**	**17**	**97**	**231**	**300**	**343**	**337**	**314**	**259**	**191**	**191**
CHANGE (%)			470%	139%	30%	14%	-2%	-7%	-17%	-26%	0%
ROYALTY (%)	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%	22%
ROYALTIES (EUR MN)	0	4	21	51	66	75	74	69	57	42	42
COGS (%)		2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
COGS PER DEVICE (EUR)	-500	-500	-500	-500	-500	-500	-500	-500	-500	-500	-500
COGS (EUR MN)	0	0	-2	-4	-5	-5	-5	-5	-4	-3	-3
PROFIT BEFORE TAX (EUR MN)	**0**	**3**	**20**	**47**	**61**	**70**	**69**	**64**	**53**	**39**	**39**
TAX RATE (%)	0%	0%	0%	0%	20%	20%	20%	20%	20%	20%	20%
TAXES (EUR MN)	0	0	0	0	-12	-14	-14	-13	-11	-8	-8
PROFIT (EUR MN)	**0**	**3**	**20**	**47**	**49**	**56**	**55**	**51**	**42**	**31**	**31**

	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
GLOBAL SALES (EUR MN)	**0**	**17**	**119**	**310**	**456**	**538**	**540**	**501**	**413**	**301**	**301**
CHANGE (%)			599%	161%	47%	18%	0%	-7%	-18%	-27%	0%
GLOBAL PROFIT (EUR MN)	**0**	**3**	**24**	**63**	**75**	**88**	**88**	**82**	**67**	**49**	**49**
CHANGE (%)			599%	161%	18%	18%	0%	-7%	-18%	-27%	0%

WACC (%)	7%
NPV TOTAL PROFIT (CHF MN)	**683**
NUMBER OF SHARES (MN)	15.0
NPV PER SHARE (CHF)	**45**
SUCCESS PROBABILITY	90% (AVERAGE EU (100%) APPROVED & US (80%) FILING SUCCESS RATE)
RISK ADJUSTED NPV PER SHARE (CHF)	**41**

SENSITIVITY ANALYSIS

		WACC (%)						
	CHF/SHARE	5.5	6.0	6.5	7.0	7.5	8.0	8.5
	100%	51	49	48	46	44	42	41
	95%	49	47	45	43	42	40	39
	90%	46	44	43	**41**	40	38	37
SUCCESS PROBABILITY	85%	44	42	40	39	37	36	35
	80%	41	40	38	37	35	34	33
	75%	39	37	36	34	33	32	31
	65%	33	32	31	30	29	28	27

ESTIMATES AS OF 3 JUNE, 2019

SOURCE: VALUATIONLAB ESTIMATES

Unique Selling Point

The AI Smart Box is a convenient and easy to use artificial intelligence enhanced colonoscopy system that flags lesions in real-time with a green box (similar to face or eye detection in a digital camera) with the accuracy of an experienced colonoscopy operator and can be considered a "second set of expert eyes" to reduce the risk of missing lesions and ultimately increasing the lesion detection rate.

7P's Analysis

Patent: The AI Smart Box is protected by AI patents. Key to Cosmo's AI system are proprietary algorithms and imaging datasets, which are not patent protected but are Cosmo's trade secrets. These provide strong differentiation against rival AI systems and are relevant to capturing and maintaining market share. At market saturation, we expect Medtronic to maintain a dominant 25% market share with a few large players similar to the smartphone market. Our forecasts include 20 years of revenues for the AI Smart Box.

Phase: The AI Smart Box is already approved in the EU and has received CE marking with first launches to occur in mid 2019 by global partner Medtronic. The US regulatory path is underway, and Cosmo expects US market launch in Q1 2020. We assume a 90% success rate, the average of EU/ROW (100% approved) and US (80% filed) for the AI Smart Box.

Pathway: The approval for the AI Smart Box follows the medical device regulatory pathway, which in the EU is CE marking and, in the US, the Premarket Approval (PMA) de novo application.

Patient: There is no difference for the patient than with a conventional colonoscopy. However, the AI Smart Box has the accuracy of an experienced colonoscopist, which increases the rate of lesion detection and reduces the risk of missing a lesion. A 1% increase in the detection rates leads to a 3% decrease

Physician: The AI Smart Box detects lesions in real-time and highlights these in a dynamic green box on the screen (similar to face or eye detection in digital cameras) with the accuracy of an experienced colonoscopist, which significantly increases the likelihood of finding polyps and adenomas and reducing the risk of missing something. Additional upgrades could enhance the uses of the endoscope.

Payer: The incremental cost of the modest fee (EUR ~35) per procedure to standard colonoscopy should be largely be offset by detecting more lesions and the reduced risk of missing lesions and therefore considerable future savings made by having to treat less colorectal cancer patients due to the AI enhanced colonoscopy screening procedure.

Partner: In May 2019, Cosmo signed a global distribution agreement with Medtronic. To speed up the adoption rate and capture market share, Medtronic will offer the AI Smart Box for free in return for a modest fee per procedure. Each AI Smart Box is expected to generate yearly around USD 36,000 in the US and EUR 36,000 in the EU/ROW. Medtronic will book the sales, while Cosmo will retain a net margin of above 20%. Cosmo will provide Medtronic with AI Smart Boxes incurring estimated COGS of ~2%.

MethyleneBlue – Colonic lesion detection dye

Product Analysis

MethyleneBlue peak sales of EUR 550+ mn - rNPV of CHF 64/share

We forecast peak sales of EUR 572 mn for MethyleneBlue in chromoendoscopy. Following the Complete Response Letter in May 2018, two appeals at the FDA declined, requiring a second confirmatory phase III trial for US approval, we now assume a US launch in 2022. In the EU/ROW we expect first launches in H1 2020 based on the EU filing in February 2019. We conservatively assume a slightly lower cost per procedure ranging between USD 130 (US) and EUR 30 (EU/ROW) possibly impacted by the additional fee for the AI Smart Box. We maintain our conservative market penetrations peaking at 15% (EU/ROW) and 20% (US), respectively. We assume commercialization partners in the EU/ROW with Cosmo receiving EUR 75 mn in upfront and commercialization milestones and 30% royalties on sales. In the US, we continue to assume Cosmo will sell MethyleneBlue directly through its own sales organization Aries, booking all sales and accounting for COGS and M&S costs. Our rNPV amounts to CHF 969 mn, or CHF 64 per share with a 72.5% success rate, the average of the EU (80% filing) and the US (65% phase III), and a WACC of 7% (for detailed forecasts see page 35).

Bringing added color & profits in colonoscopy lesion detection

We believe MethyleneBlue (methylene blue MMX) is one of Cosmo's most valuable pipeline assets together with the AI Smart Box, which should be transformational for the company and its valuation. MethyleneBlue could become the new gold standard image enhancing agent in colonoscopy with peak sales amounting to EUR 550+ mn, which may prove conservative. MethyleneBlue provides physicians with a simple and effective visualization aid to detect significantly more lesions in less time during colonoscopy than with current gold standard HDWL (High Definition endoscope with White Light). Any solution that significantly increases the detection rate is expected to be integrated in the colonoscopy procedure and included in treatment guidelines. Particularly, if the solution has proven clinical efficacy and is simple to adopt. The only adjustment to the entire treatment protocol is that the patient takes 8 oral MethyleneBlue tablets during or at the end of the bowel preparation (required in all colonoscopies) a day before the procedure and arrive with a fully dyed colon at the beginning of the procedure, with no further hassle for the endoscopist. No special equipment or training is needed. It is that simple.

The AI Smart Box is as good as the eye sees – MethyleneBlue shows more contrast

The introduction of AI enhanced colonoscopy with devices such as Cosmo's AI Smart Box will radically change the way lesions are detected with a "second set of expert eyes" that reduce the chance of missing lesions and ultimately improve the detection rate. Nevertheless, the AI Smart Box can only detect lesions as good as the human eye. Therefore, anything that improves the detection rate of the human eye, automatically improves the lesion detection rate of the AI Smart Box. MethyleneBlue with proven clinical efficacy increasing the ADR (adenoma detection rate) compared to mainstay HDWL complements the AI Smart Box and will be used frequently together in colonoscopy, in our view. To be conservative, we have slightly lowered our pricing per procedure for MethyleneBlue to compensate for the additional fee for the AI Smart Box of approximately EUR 35 per procedure.

New dynamics after the US delay of MethyleneBlue and the AI Smart Box reveal
The delay of the US launch of MethyleneBlue after the FDA turned down approval in May 2018 and the introduction of the AI Smart Box to be commercialized globally by Medtronic has led to new dynamics in Cosmo's business strategy for its endoscopy unit. The company has stopped distribution of medical devices in the US through its US sales organization Aries, saving EUR 20 mn in 2019, with Medtronic now as partner of choice. In May 2019, Cosmo announced the termination of the US co-promotion agreement of Eleview with Olympus, which has been replaced with a new exclusive agreement with Medtronic, which has been extended to China and South America.

FDA request for 2nd phase III trial to gain US approval comes totally out of the blue
US approval of MethyleneBlue was initially expected on the May 21st, 2018 PDUFA (Prescription Drug User Fee Act) date based on the single positive phase III trial showing a statistically significant impact on detecting more lesions during colonoscopy. Instead, Cosmo received a CRL (Complete Response Letter) from the FDA, stating that "although the outcome of the phase III trial has translated in a statistically significant outcome, the outcome is not sufficiently "robust" and thus recommends Cosmo to provide confirmation of effectiveness with a second phase III trial". This came as a nasty surprise as the first phase III trial was conducted under SPA (Special Protocol Assessment). Filing under SPA enables the FDA to provide valuable input into the phase III trial design and streamline the approval process, because the scientific and regulatory requirements such as clinical trial design, efficacy endpoints and statistical analysis have already been agreed upon and pre-specified before the trial begins. Typically, when the trial is conducted according to the pre-specified SPA and the efficacy endpoints are reached, approval should follow for the targeted label with potential post marketing requirements and commitments.

U-turn at FDA? – MethyleneBlue considered a drug instead of a visualization aid
It appears the FDA made a U-turn during the review process and suddenly considered MethyleneBlue a pharmaceutical compound instead of an image enhancing agent to detect lesions in the colon during colonoscopy. Something must have been lost in translation during the review process, in our view. The FDA requiring a second phase III trial to confirm the positive results of the first phase III trial follows the normal FDA approval procedure for a pharmaceutical compound where two positive phase III trials are mandatory for US approval.

Although MethyleneBlue is taken orally together with the bowel preparation a day before the colonoscopy, its only purpose is to enhance the visualization and detection of lesions in the colon, and not to have any systemic effect, what is typically to be expected from a pharmaceutical compound that is ingested. MethyleneBlue was categorized as a pharmaceutical compound because it is taken orally and therefore absorbed systematically. However, the MMX delivery technology limits absorption to the colon containing any systemic effect or side effect of methylene blue in the body. The sole intention is to stain the colon blue to enhance the detection of lesions during colonoscopy as seen in the single positive phase III trial. Thanks to the MMX delivery technology and the one-time dosing ahead of the colonoscopy, no safety issues were seen during development. The FDA also stated in the CRL that no safety or manufacturing concerns were raised.

MethyleneBlue is not a diagnostic to identify adenomas either. This happens in the lab where the lesions are sent to for diagnosis. Therefore, MethyleneBlue does not qualify as a medical device. Hence, Cosmo's intensive discussions with the FDA and key opinion leaders in the past on the specific phase III development pathway for MethyleneBlue, including the design of the single pivotal phase III clinical trial and clinical endpoints required to secure US approval of MethyleneBlue under SPA.

Two appeals denied by FDA – activity for second trial started – filed in the EU

In an effort to gain US approval without conducting a second confirmatory phase III trial, Cosmo decided to appeal the CRL. After two successive appeals were turned down by the FDA in November 2018 and March 2019, respectively, the company has now started activity for the second confirmatory phase III trial. Nevertheless, the time spent in the appeal process was essential in helping Cosmo and the FDA to fully understand the potential of MethyleneBlue that will be taken by millions of patients undergoing colonoscopy to prevent colorectal cancer. Cosmo intends to present a new clinical plan with different endpoints that will take into account the positive results of the first phase III trial. Upon agreement with the FDA on the new trial design, the confirmatory trial will start immediately. We expect the trial to start in 2019/2020 and to be completed in only 2 years, one year faster than the first phase III trial. Cosmo will basically use the same clinical sites and systems used in the first trial. Assuming filing shortly after with a standard 10-months review period, US approval could be granted in 2022. The setback in the US has not changed the plans for MethyleneBlue in the EU. The EU MAA (Marketing Authorisation Application) was filed in February 2019 with EU/ROW approval expected approximately one year later.

Simple but brilliant MMX reformulation of a messy and time-consuming blue dye

MethyleneBlue is a "simple" but brilliant MMX reformulation of liquid methylene blue dye. This dye was discovered in 1876 and was first used by Japanese gastroenterologists as a staining agent for polyps via a catheter almost 50 years ago. In spite of recommendations for increasing so-called chromoendoscopy (endoscopy with an image enhancing agent), this has never really taken off. Liquid methylene blue dye has turned out to be a time consuming and "messy" procedure. Moreover, the detection of polyps and adenomas largely depend on the expertise of the endoscopist on when and where to spray the dye during the colonoscopy. As a result, methylene blue dye is used in less than 3% of colonoscopies, despite better detection rates. And detection rates of in particular small polyps and adenomas are crucial in preventing colorectal cancer.

In 2010, Cosmo started developing a convenient oral formulation of methylene blue using its MMX formulation technology with the aim to deliver enough of the coloring agent along the entire length of the colon to increase the adenoma detection rate compared to gold standard white light high-definition endoscopy. MethyleneBlue penetrates the mucosal cells in such a way that significantly enhances the detection of adenomas by the endoscopist. This enables endoscopists to detect pre-cancerous (adenomas) and cancerous lesions and polyps throughout the entire colon, without the expertise and need to spray a dye for better detection. This saves the physician valuable time, and the hospital saves the cost of a spray catheter (approximately USD 80 – USD 150) that is no longer needed. This alone, is already an immediate payback for the additional cost of using MethyleneBlue, which Cosmo expects to price around USD 175 – 200 per procedure, after extensive market research.

Excellent adenoma detection rate (ADR) seen in phase II with no side effects

In a phase II study MethyleneBlue demonstrated a high rate of adenoma detection of almost 47%, which is an excellent result in comparison with published data where detection rates rate ranges from around 20% (Screening Berlin Gut) to around 35% (NBI meta-analysis GIE) for colonoscopies. Importantly, a significant portion of adenomas detected in this study were <10 mm in size and located in the right colon. These are generally the difficult to find adenomas. Importantly, there were no related side effects, due to the local activity.

Filing under SPA in the US usually eliminates the regulatory risk

Based on the positive phase II results Cosmo conducted a pivotal phase III trial after extensive discussions with key opinion leaders, the FDA and EMA. In 2013, Cosmo secured a SPA (Special Protocol Assessment) for the pivotal phase III trial design from the FDA. Filing under SPA enables the FDA to provide valuable input into the phase III trial design and streamline the approval process, because the scientific and regulatory requirements have already been agreed upon. Usually, this eliminates the regulatory risk. Still, the FDA has the final decision if it believes the results are not sufficiently “robust”, as Cosmo experienced when it received the CRL in May 2018.

Positive phase III trials announced at a special R&D event in 2016

Positive pivotal phase III results were announced at Cosmo’s special R&D event in Zurich on November 29th, 2016. MethyleneBlue was compared to current gold standard HDWL (High Definition endoscope with White Light). The primary endpoint was the number of patients with at least one histologically proven adenoma or carcinoma, or the difference in ADR (adenoma detection rate) compared to HDWL.

MethyleneBlue’s pivotal phase III trial was conducted in 18 centers in 8 countries in North America and Europe. Cosmo enrolled 1,249 patients, the ITT (intent to treat) population. This resulted in a FAS (full analysis set) of 1,205 patients, a Per Protocol population (patients who completed the procedure according to the trial protocol) of 1,137 and a safety population of 1,208 patients. The endpoints were determined according to the FAS.

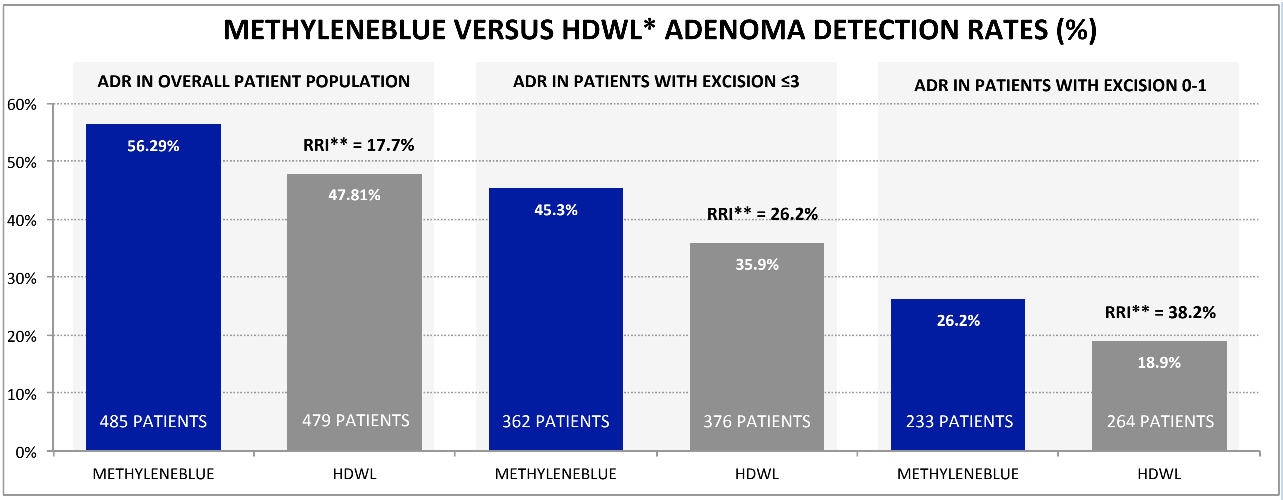
Due to the nature of MethyleneBlue, a blue colored dye, the pivotal trial could not be blinded, which is usually needed to gain approval. It was agreed with the FDA that the trial would be randomized in three arms in a ratio of 2:1:2, a 200 mg MethyleneBlue + HDWL, HDWL (placebo), and 100 mg MethyleneBlue + HDWL confounding arm (a control group to exclude potential bias).

The patient breakdown per treatment arm FAS population:

1. **200 mg MethyleneBlue treatment arm:** 479 patients; 61.6% males; 47.8% first time screening colonoscopies; 6.3% surveillance colonoscopies performed < 2 years; 45.9% surveillance colonoscopies performed > 2 years from first colonoscopy
2. **HDWL (placebo) arm:** 485 patients; 60.6% males; 48% first time screening colonoscopies; 5.8% surveillance colonoscopies performed < 2years; 46.2% surveillance colonoscopies performed > 2 years from first colonoscopy
3. **100 mg MethyleneBlue confounding arm:** 241 patients (not statistically powered)

Two central histolabs, one in the US and one in Europe, conducted histological analysis, while five endoscopy centers were randomly assigned videos for review.

Primary and secondary endpoints achieved across several patient populations



* HDWL = HIGH DENSITY WHITE LIGHT; ** RRI = RELATIVE RISK INCREASE

SOURCE: COSMO PHARMACEUTICALS, VALUATIONLAB

As can be seen in the chart above MethyleneBlue was superior in all patient subgroups based on the FAS (Full Analysis Set) population:

- MethyleneBlue achieved it primary endpoint in the overall patient population where it achieved a higher ADR than HDWL. MethyleneBlue identified 17.7% more patients with adenomas and carcinomas than HDWL, with a p-value of 0.009, indicating a highly statistical significant result
- MethyleneBlue was also statistically superior and clinically meaningful in the segment of patients with 0-3 excisions, where 75%-80% of the patients are. 26.2% more patients were identified with MethyleneBlue than with HDWL with a highly statistical p-value of 0.0107
- The largest difference in ADR was in patients with 0-1 excisions amounting to 38.2% in favor of MethyleneBlue.
- No major drug related adverse events were reported

The FPR (false positive rate), an important secondary endpoint, in the MethyleneBlue treatment arm was 21.5% lower than in the HDWL arm with a highly statistically significant p-value of < 0.001. A false positive is a resected lesion that is initially recognized as an adenoma or carcinoma, but after histological analysis proves not to be the case. In the MethyleneBlue arm 356 out of 485 patients had an excision. 83 excisions or 23.3% were false positives. In the HDWL arm 326 out of 479 patients had an excision of which 97 excisions or 29.7% were false positives.

METHYLENEBLUE FLAGS MORE DIMINUTIVE ADENOMAS

	WLHD*	METHYLENE BLUE
PATIENTS WITH DIMINUTIVE ADENOMAS	144	178
PERCENTAGE OVERALL POPULATION	30.06%	36.70%
RELATIVE RISK RATE		1.221
P-VALUE		0.0342
ODDS RATIO		1.35 (1.02, 1.76)

METHYLENEBLUE FLAGS MORE NON-POLYPOID LESIONS

	WLHD*	METHYLENE BLUE
PATIENTS WITH NON-POLYPOID LESIONS	168	213
PERCENTAGE OVERALL POPULATION	35.07%	43.92%
RELATIVE RISK RATE		1.252
P-VALUE		0.0056
ODDS RATIO		1.45 (1.12, 1.88)

* WLHD = WHITE LIGHT WITH HIGH DEFINITION ENDOSCOPE

SOURCE: COSMO PHARMACEUTICALS, VALUATIONLAB

Further analysis of the pivotal trial showed that MethyleneBlue identified more patients with hard to detect lesions than HDWL, such as diminutive adenomas (5 mm or less in diameter) and non-polypoid (flat or depressed) lesions, as can be seen in the tables above.

Conclusion: breakthrough in colorectal cancer prevention and saving lives
The increase in ADR has important clinical relevance. Scientific studies have shown that each 1% increase in ADR results in a 3% decline in incidence of interval cancer and a 5% decline in incidence of fatal colorectal cancer. Consequently, use of MethyleneBlue in combination with HDWL endoscopy substantially increases the ADR and therefore provides a major contribution in colorectal cancer prevention, and ultimately save lives.

Full steam ahead in the EU with partnerships – US distribution through Aries?
Following the EU MAA filing of MethyleneBlue in February 2019, first launches in the EU are expected in H1 2020. The company has built a dedicated plant in Lainate, Italy, which has already been inspected and approved by the FDA and can be on stream to fulfill expected demand. Cosmo intends to establish selective partnerships for the marketing of MethyleneBlue in the EU and ROW. In March 2018, an exclusive license agreement was signed with EA Pharma for MethyleneBlue (and Eleview) for Japan and South Korea for undisclosed upfront, development, and sales milestones and royalties on sales. We believe a potential distribution agreement with Fujifilm that acquired the exclusive rights for Eleview in the EU, Africa, South East Asia, Middle East, Australia and New Zealand could be in the cards. We still assume Cosmo will market MethyleneBlue directly in the US through its Aries sales organization to maximize long-term value. MethyleneBlue should benefit from all the accounts that are being opened for Eleview with less administrative issues, as both products target the same accounts, physicians, hospitals and endoscopy centers. This should lead to a steeper uptake for MethyleneBlue. Alternatively, Cosmo could strike a partnership with Medtronic that already distributes the AI Smart Box and Eleview in the US, providing substantial marketing muscle and cost synergies.

Peak sales of EUR 550+ mn despite US delay, success rate currently at 72.5%
With the introduction of the AI Smart Box ahead of the EU and US launch of MethyleneBlue, we have conservatively lowered the pricing of MethyleneBlue to compensate for the additional fee for the AI Smart Box. We assume a fee per procedure of EUR 30 (from EUR 40) in the EU/ROW and USD 130 (from USD 175) for in the US. Maintaining our conservative peak market penetration rates at 15% (EU/ROW) and 20% (US), we forecast global MethyleneBlue peak sales of EUR 572 mn. We account for EUR ~15 mn development costs for the second confirmatory phase III trial required for US approval, which is now expected in 2022. Our rNPV for MethyleneBlue amounts to CHF 65 per share with a 72.5% success rate, the average of the EU/ROW (80% filing) and US (65% phase III).

Forecasts & Sensitivity Analysis

METHYLENEBLUE - FINANCIAL FORECASTS FOR CHROMOENDOSCOPY

INDICATION	CHROMOENDOSCOPY - EARLY LESION DETECTION BY METHYLENE BLUE STAINING TO PREVENT COLON CANCER
DOSAGE	SINGLE 200 MG (8X 25 MG) DOSE DURING OR AT END OF THE INTAKE OF THE BOWEL CLEANSING PREPARATION
PRICING	PRICE PER PROCEDURE: US: USD 130 (COSMO GUIDED USD 175 - 200); EU/ROW: EUR 30
STANDARD OF CARE	TIME CONSUMING "MESSY" METHYLENE BLUE DYE SPRAY
UNIQUE SELLING POINT	CONVENIENT TABLETS WITH ENHANCED STAINING TO DETECT POLYPS AND ADENOMAS IN THE ENTIRE COLON BACKED BY CLINICAL TRIAL RESULTS; NO COMPETITION

7PS ANALYSIS

PATENT	SEP 2033 GRANTED GLOBAL USE PATENT - THREE GRANTED US PATENTS EXPIRE IN MARCH 2031; ONE GRANTED EU PATENT EXPIRES MARCH 2031
PHASE	PHASE III COMPLETED; US: COMPLETE RESPONSE LETTER MAY 2018, 2ND PHASE III TRIAL REQUIRED (~ 3 YEARS DELAY); EU: FILED FEB 2019, APPROVAL H1 2020
PATHWAY	PHARMACEUTICAL COMPOUND - REGULATORY PATHWAY DETERMINED IN CLOSE COOPERATION WITH EMA AND FDA
PATIENT	8 TABLETS TAKEN WITH BOWEL PREPARATION A DAY BEFORE PROCEDURE; HIGHER ADR DETECTION RATE, LOWER CHANCE OF DEVELOPING COLORECTAL CANCER
PHYSICIAN	INCREASE TIME EFFICIENCY OF COLONOSCOPIST, ENHANCED VISUALISATION OF SMALL POLYPS AND ADENOMAS, LOWER RISK OF MISSING SOMETHING
PAYER	SMALL ADDITIONAL COST TO COLONOSCOPY WHILE EARLY DETECTION OF COLON CANCER REDUCES LONG-TERM COSTS SUBSTANTIALLY
PARTNER	US: SOLD DIRECTLY BY COSMO'S ARIES SALES ORGANIZATION IN THE US; EU/ROW: COMMERCIALIZATION PARTNERS IN RETURN FOR MILESTONES AND SALES ROYALTIES

REVENUE MODEL

EUROPE / REST OF WORLD - SOLD BY PARTNER(S) TBD	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
PEOPLE OF SCREEN-ELIGIBLE AGE (50-74 YEARS) (MN)	134	137	140	143	146	148	151	154	158	161	164
GROWTH (%)	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
NUMBER OF COLONOSCOPIES (MN)	26	27	27	28	28	29	29	30	31	31	32
PENETRATION (%)	0%	0%	2%	7%	11%	14%	15%	15%	15%	15%	15%
NUMBER OF COLONOSCOPIES WITH LUMEBLUE (MN)	0.0	0.0	0.4	1.8	3.0	3.9	4.3	4.4	4.4	4.5	4.6
COST PER PROCEDURE (EUR)	30	30	30	30	30	30	30	30	30	30	30
SALES (EUR MN) - BOOKED BY PARTNER(S)	**0**	**0**	**12**	**54**	**89**	**117**	**128**	**131**	**133**	**136**	**139**
CHANGE (%)				342%	65%	31%	10%	2%	2%	2%	2%
ROYALTY (%)	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
ROYALTIES (EUR MN)	0	0	4	16	27	35	38	39	40	41	42
UPFRONT & MILESTONE PAYMENTS (EUR MN)		1	30		10		15				
PROFIT BEFORE TAX (EUR MN)	**0**	**1**	**34**	**16**	**37**	**35**	**53**	**39**	**40**	**41**	**42**
TAX RATE (%)	0%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
TAXES (EUR MN)	0	0	-7	-3	-7	-7	-11	-8	-8	-8	-8
PROFIT (EUR MN)	**0**	**1**	**27**	**13**	**29**	**28**	**43**	**31**	**32**	**33**	**33**

UNITED STATES - SOLD BY ARIES PHARMACEUTICALS	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
PEOPLE OF SCREEN-ELIGIBLE AGE (50-74 YEARS) (MN)	75	76	78	79	81	83	84	86	88	89	91
GROWTH (%)	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
NUMBER OF COLONOSCOPIES (MN)	15	15	15	15	16	16	16	17	17	17	18
PENETRATION (%)	0%	0%	0%	0%	2%	6%	11%	16%	18%	19%	20%
NUMBER OF COLONOSCOPIES WITH LUMEBLUE (MN)	0.0	0.0	0.0	0.0	0.3	1.0	1.8	2.7	3.1	3.3	3.5
COST PER PROCEDURE (EUR)	110	115	115	115	115	115	115	115	115	115	115
SALES (EUR MN) - BOOKED BY COSMO (ARIES PHARMA)	**0**	**0**	**0**	**0**	**36**	**111**	**207**	**307**	**353**	**380**	**398**
CHANGE (%)						206%	87%	48%	15%	8%	5%
COGS (%)	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
COGS (EUR MN)	0	0	0	0	-2	-6	-10	-15	-18	-19	-20
R&D COSTS (EUR MN)	-1	-7	-6	-2	0	0	0	0	0	0	0
M&S (%)					110%	35%	35%	30%	30%	30%	30%
M&S COSTS (EUR MN)	-4	-2	-2	-2	-40	-39	-73	-92	-106	-114	-119
PROFIT BEFORE TAX (EUR MN)	**-5**	**-9**	**-8**	**-4**	**-5**	**66**	**124**	**200**	**229**	**247**	**258**
TAX RATE (%)	0%	0%	0%	0%	20%	20%	20%	20%	20%	20%	20%
TAXES (EUR MN)	0	0	0	0	1	-13	-25	-40	-46	-49	-52
PROFIT (EUR MN)	**-5**	**-9**	**-8**	**-4**	**-4**	**53**	**99**	**160**	**183**	**198**	**207**

	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
GLOBAL SALES (EUR MN)	**0**	**0**	**12**	**54**	**126**	**228**	**336**	**438**	**486**	**516**	**536**
CHANGE (%)				342%	132%	82%	47%	31%	11%	6%	4%
GLOBAL PROFIT (EUR MN)	**-5**	**-8**	**19**	**9**	**25**	**81**	**142**	**191**	**215**	**230**	**240**
CHANGE (%)	-40%	58%	-336%	-50%	165%	223%	75%	34%	13%	7%	4%

WACC (%)	7%	
NPV TOTAL PROFIT (CHF MN)	**1,344**	
NUMBER OF SHARES (MN)	15.0	
NPV PER SHARE (CHF)	**89**	
SUCCESS PROBABILITY	72.5%	(AVERAGE EU 80% FILING & US 65% PHASE III SUCCESS RATE)
RISK ADJUSTED NPV PER SHARE (CHF)	**65**	

SENSITIVITY ANALYSIS

		WACC (%)						
	CHF/SHARE	5.5	6.0	6.5	7.0	7.5	8.0	8.5
SUCCESS PROBABILITY	100%	102	98	94	90	86	83	79
	95%	97	93	89	85	82	79	75
	90%	92	88	84	81	78	74	71
	85%	87	83	80	76	73	70	67
	80%	82	78	75	72	69	66	63
	72.5%	74	71	68	**65**	62	60	57
	65%	66	64	61	58	56	54	52

ESTIMATES AS OF 3 JUNE, 2019

SOURCE: VALUATIONLAB ESTIMATES

Unique Selling Point

MethyleneBlue is a convenient, orally available, staining tablet that complements current standard colonoscopy diagnosis practice with the ability to significantly improve detection rates of polyps and adenomas and allows for faster diagnosis and perception of the lesion. It provides a homogenous and reliable flagging of the entire colon with less subjectivity with the potential to further improve detection rates when combined with the AI Smart Box.

7P's Analysis

Patent: MethyleneBlue is protected by 3 granted US patents (US8545811, US9402922, US9402923), 1 granted EU patent (EP2542268) providing protection until March 2031 and one granted global method of use patent (PCT/EP2013/070060) providing protection until September 2033.

Phase: MethyleneBlue successfully completed phase III development and was filed in the US under SPA in June 2017. In May 2018, MethyleneBlue received a Complete Response Letter, with the request for a second phase III trial for US approval. After two unsuccessful appeals, Cosmo has started activity for a second phase III trial for US approval, which is now expected in 2022. In February 2019, Cosmo filed for EU approval and expects a normal 12 months review. First EU/ROW launches could occur in H1 2020. We assume a 72.5% success rate, the average of the US (65% phase III) and the EU/ROW (80% filed).

Pathway: MethyleneBlue has been developed as a pharmaceutical compound and not a medical device. Consequently, Cosmo has conducted clinical trials to demonstrate its efficacy and benefit/risk profile. Although this was a costly and risky strategy, the positive phase III results and expected EU/ROW and (delayed) US approvals, now provide a strong rational for use, pricing and reimbursement, and a strong barrier to competition.

Patient: MethyleneBlue is a convenient oral tablet that can be taken together with the bowel cleansing preparation, which is required to clean the bowel roughly 12-24 hours ahead of the colonoscopy. Patients come to the physician with a fully dyed colon with no loss of time for the procedure. Detection allows immediate excision and less discomfort for the patient.

Physician: The flagging significantly increases the likelihood of finding polyps and adenomas (also reducing the risk of missing them), a faster diagnosis and perception of the lesion boundary, and additional reimbursement for removing histological active lesions.

Payer: The incremental cost of adding MethyleneBlue to standard colonoscopy should be largely be offset by no need of a catheter to spray generic methylene blue or other liquid staining agents and considerable future savings made by having to treat less colorectal cancer patients due to the improved colonoscopy screening procedure.

Partner: Initially, Cosmo planned to sell MethyleneBlue directly in the US through Aries and seek distribution partners outside the US. Following the US delay and restructuring of Aries, Cosmo could opportunistically seek a US distribution partner. Medtronic would be ideally positioned having a global distribution agreement for the AI Smart Box. Outside the US, Cosmo will out license to key player(s) in the field such as Fujifilm for the EU/ROW in return for upfront and commercial milestone payments and an assumed 30% royalty on sales, with the partner booking sales.

Eleview – Colonic lesion resection cushion

Product Analysis

Eleview peak sales of EUR 190 mn - NPV of CHF 22 per share

We forecast peak sales of EUR 190 mn for Eleview in endoscopic lesion resection. Medtronic will sell Eleview in the US from May 2019 (from previously Olympus in co-promotion with Aries Pharmaceuticals) next to China and South America, while Fujifilm is the distributor for Europe, Africa, South East Asia, Middle East, Australia and New Zealand. We assume a cost per vial between USD 81 (US) and EUR 35 (EU/ROW) and 1.5 vials used per procedure, with a market penetration peaking at 50% in the US and a more conservative 20% in the EU/ROW. Our NPV amounts to CHF 326 mn, or CHF 22 per share, with Cosmo booking sales in EU/ROW at a 50% transfer price to distributor Fujifilm, with COGS of 5%, while receiving an estimated 25% royalty rate on US sales from Medtronic with 5% COGS and a WACC of 7% (for detailed forecasts see page 40).

First of a new wave of colonoscopy products to reach market

Eleview is the first of Cosmo's endoscopic product pipeline to reach the market. Eleview is an injectable solution specifically designed and approved for use in gastrointestinal endoscopic procedures such as colonoscopies. It is targeted to replace the use of (unapproved) saline solutions in the removal of challenging lesions in these procedures. Eleview is a solution that is injected in the submucosal layer in the colon wall directly beneath a lesion such as an adenoma or polyp. Once injected, the solution reconfigures creating an artificial net formed by polymer chains and traps water to immediately form a long-lasting, up to 45 minutes, (methylene) blue colored cushion. The cushion lifts the lesion and makes it easier for the physician to remove (resect) a challenging polyp. Moreover, the blue dye improves the visibility of the margins of the polyp thereby decreasing the risk of gastrointestinal perforation and damage to the external muscular layer, a major complication that requires immediate surgery. In clinical trials Eleview decreased the time and volume needed to resect a lesion, while also reducing reinjections required and piecemeal excisions as compared to saline injections.

Off to a slow US start despite Olympus co-promotion – Medtronic now in charge

In May 2017, Eleview was launched in the US by Cosmo's own US sales organization Aries Pharmaceuticals, as an FDA 510(k) cleared class II medical device. In October 2018, Aries had a staff of 82 people, with in 59 marketing & sales, 10 in medical science & scientific affairs providing product support, and 13 in management. The uptake was hampered by administrative issues such as setting up new hospital accounts and getting state specific licenses to sell medical devices. To further speed up the US launch of Eleview, Cosmo entered into an exclusive co-promotion agreement with Olympus America Inc., a global leader in the endoscopy area, in early October 2017. The agreement added 200 sales representatives, 35 clinical education specialists, and considerably increased the number of targeted accounts. In May 2019, Cosmo announced a new exclusive agreement for Eleview with Medtronic in the US, China and South America, effectively replacing the existing distribution agreement with Olympus in the US, which was terminated by mutual consent. Cosmo decided to stop direct distribution of medical devices in the US by Aries, leading to cost savings of EUR 20 mn in 2019, with Medtronic now as partner of choice. Medtronic, which also sells the AI Smart Box globally, has the ability to maximize Cosmo's returns in the US, through its marketing muscle with significant cost-synergies selling the AI Smart Box that detects lesions and Eleview that removes challenging lesions. The guided 2019 sales of EUR 13 mn for Eleview in the US may be slightly affected by the transition of the commercialization responsibility to Medtronic from Aries and Olympus. Hereafter, we expect Eleview sales in the US to accelerate leading to higher US peak sales of EUR 100 mn (booked by Medtronic) from previously EUR 80 mn (booked by Cosmo).

Fujifilm responsible for distribution in Europe, Africa, SE Asia, Australia & NZ

In October 2017, Cosmo also entered into an exclusive distribution agreement for Eleview in Europe and South Africa with Fujifilm Europe, another global leader in the endoscopy area. The agreement was expanded under the same terms to South East Asia, Middle East, Africa, Australia and New Zealand in March 2018. The agreement provides Cosmo with a 45% share of gross revenues (including COGS). In the EU, Eleview is also approved as a medical device with a CE marking.

Eleview's attractive profile backed by post-marketing trials

Eleview is the only endoscopic lesion resection filler specifically approved for this indication. The FDA and EMA approvals are based on trials comparing Eleview with standard of practice saline injections. In May 2017, Cosmo announced the results of a "first in human" exploratory post-marketing trial comparing Eleview to a standard saline solution in patients undergoing endoscopic mucosal resection of colonic lesions ≥20 mm. Even though the trial was not powered to show statistical significance several endpoints were statistically significant, while other endpoints showed a numerical trend in favor of Eleview. Eleview required less volume injected, less time, less reinjections, and there were a smaller number of resection pieces with Eleview.

Favorable outcomes for Eleview in all primary endpoints compared to saline

The trial enrolled in total 226 patients with complex lesions, of which 211 patients completed the trial according to the protocol and were used in the primary analysis set. The lesions' size and location varied greatly. The mean lesion size in the Eleview arm was 31.64 mm (ranging from 20 mm to 100 mm). In the comparator arm (standard saline solution), the mean lesion size was 32.31 mm (ranging from 20 mm to 70 mm). The location varied from the caecum (beginning of colon) to the rectum, with the majority in the right section of the colon (typically the most difficult to reach and challenging for polyp removal).

PRIMARY ENDPOINTS ALL IN FAVOR OF ELEVIEW

PRIMARY ENDPOINT	STATISTICS	ELEVIEW (N=102)	REFERENCE COMPARATOR (SALINE) (N=109)
1) MEAN TOTAL INJECTED VOLUME TO COMPLETE EMR* PROCEDURE (ML)	**MEAN (± SD)**	**16,1 (± 9.8) ****	**31.6 (± 32.1)**
	RANGE (MIN - MAX)	3.0 - 41.0	4.0 - 248.0
	% DIFFERENCE	**-49.1% ****	
	P-VALUE	< 0.001	
2) TOTAL INJECTED VOLUME PER LESION SIZE (ML/MM)	**MEAN (± SD)**	**0.53 (±0.32) ****	**0.92 (± 0.65)**
	RANGE (MIN - MAX)	0.09 - 1.75	0.20 - 4.96
	% DIFFERENCE	**-42.4% ****	
	P-VALUE	< 0.001	
3) TIME TO RESECT THE LESION (MINUTES)	**MEAN (± SD)**	**19.15 (± 16.80) *****	**29.70 (± 69.18)**
	RANGE (MIN - MAX)	1 - 100	0.20 - 4.96
	% DIFFERENCE	**-35.5% *****	
	P-VALUE	0.326	

* EMR = ENDOSCOPIC MUCOSAL RESECTION; ** STATISTICALLY SIGNIFICANT; *** FAVORABLE NUMERICAL DIFFERENCE

SOURCE: COSMO PHARMACEUTICALS, VALUATIONLAB

1) Mean total injected volume to complete EMR procedure: in the Eleview arm was 16.1 ml (range 3-41). In the comparator arm 49.2% more liquid had to be injected with the mean volume reaching 31.6 ml (range 4-248).
2) Total injected volume per lesion size: was 0.53 ml per mm (range 0.09-1.75). In the comparator arm 42.4% more volume per mm was needed with the volume per lesion size reaching 0.92 ml per mm (0.2-4.96). Both these endpoints reached statistical significance ($p < 0.001$).
3) Time to resect the lesion: was notably lower in the Eleview arm with mean time taking 19.15 minutes (1-100) while it took 35.5% longer in the comparator arm taking 29.7 minutes with ranges of 2-687 minutes, therefore showing that lesion removal with Eleview took one third less time.

Forecasts & Sensitivity Analysis

ELEVIEW - FINANCIAL FORECASTS FOR COLONIC LESION RESECTION

INDICATION	ENDOSCOPIC MUCOSAL RESECTION OF LARGE SESSILE POLYPS IN THE GASTROINTESTINAL TRACT
DOSAGE	SUBMUCOSAL INJECTION FORMULATION; 1-2 10 ML VIALS REQUIRED PER REMOVED LESION
PRICING	US: USD 92.50 PER VIAL / EU/ROW: EUR 30 PER VIAL; APPROXIMATELY 1 1/2 VIALS ARE REQUIRED PER ADENOMA
STANDARD OF CARE	SUBMUCOSAL SALINE INJECTIONS; SEIKAGAKU CORP'S MUCOUP (JAPAN ONLY), LIFEEUROPE'S SIGMAVISC (EU ONLY) - BOTH DO NOT CONTAIN DYE TO IMPROVE VISIBILITY
UNIQUE SELLING POINT	FIRST INJECTABLE EMULSION CONTAINING A VISIBILITY ENHANCING DYE WITH LONG-LASTING CUSHION TO FACILITATE LESION RESECTION

7Ps ANALYSIS

PATENT	EXPIRY: NOV 2034; 3 GRANTED US PATENTS (US9226996; US9364580; US9522216) AND 1 GRANTED EU PATENT (EP2911707)
PHASE	APPROVED IN THE EU AND US IN MAY 2017; MARKETING TRIALS IN FOUR US SITES ONGOING (SPEED AND SAFETY VS. STANDARD CARE IN EMR)
PATHWAY	CLASSIFIED AS A CLASS II MEDICAL DEVICE IN US AND EU; CLINICAL TRIALS PROVIDE MARKETING ADVANTAGE AND BARRIER TO ENTRY
PATIENT	LESS RISK OF COLON PERFORATION THAT LEADS TO INVASIVE EMERGENCY REPAIR SURGERY AND LONG RECOVERY TIME
PHYSICIAN	EASIER AND FASTER REMOVAL OF LESIONSREDUCING THE RISK OF COLON PERFORATION AND ITS COMPLICATIONS
PAYER	SUBSTANTIAL COST SAVINGS DUE TO FASTER AND EASIER PROCEDURE AND LESS COSTLY COLON PERFORATIONS AND COMPLICATIONS
PARTNER	US: NEW MEDTRONIC (MAY 2019) DISTRIBUTION DEAL; EU, ASIA, AFRICA, AUS/NZ: FUJIFILM DISTRIBUTION DEAL (COSMO RETAINS 45% GROSS REVENUES (INC. COGS))

REVENUE MODEL

EUROPE / REST OF WORLD - FUJIFILM (EU, ASIA, AFRICA, AUS/NZ)	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
PEOPLE OF SCREEN-ELIGIBLE AGE (50-74 YEARS) (MN)	137	141	145	150	154	159	164	169	174	179	184
GROWTH (%)	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
NUMBER OF COLONOSCOPIES (MN)	27	28	29	30	31	32	33	34	35	36	37
PREVALENCE OF ADENOMATOUS POLYPS (%)	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
COLONOSCOPIES WITH ADENOMATOUS POLYPS (MN)	8.2	8.5	8.7	9.0	9.3	9.5	9.8	10.1	10.4	10.7	11.1
NUMBER OF SIGMOIDOSCOPIES (MN)	5.5	5.7	5.8	6.0	6.2	6.4	6.6	6.7	6.9	7.2	7.4
PREVALENCE OF ADENOMATOUS POLYPS (%)	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
SIGMOIDOSCOPIES WITH ADENAMATOUS POLYPS (MN)	0.5	0.6	0.6	0.6	0.6	0.6	0.7	0.7	0.7	0.7	0.7
TOTAL CASES WITH ADENOMOTOUS POLYPS (MN)	32.9	33.9	34.9	36.0	37.0	38.2	39.3	40.5	41.7	42.9	44.2
LIFTING AGENT REQUIRED (%)	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
PROCEDURES WHERE LIFTING AGENT REQUIRED (MN)	**6.6**	**6.8**	**7.0**	**7.2**	**7.4**	**7.6**	**7.9**	**8.1**	**8.3**	**8.6**	**8.8**
PENETRATION (%)	0%	2%	4%	6%	8%	10%	12%	13%	14%	15%	16%
NUMBER OF PROCEDURES WITH ELEVIEW (MN)	0.0	0.2	0.3	0.5	0.6	0.8	1.0	1.1	1.2	1.3	1.4
COST PER VIAL (EUR)	35	35	35	35	35	35	35	35	35	35	35
NUMBER OF VIALS PER PROCEDURE	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
COST PER PROCEDURE (EUR)	53	53	53	53	53	53	53	53	53	53	53
ELEVIEW PRODUCT SALES (EUR MN)	**1**	**8**	**16**	**24**	**32**	**41**	**51**	**57**	**63**	**69**	**76**
TRANSFER PRICE (%)	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
COSMO SALES EUROPE / ROW	**1**	**4**	**8**	**12**	**16**	**21**	**25**	**28**	**31**	**34**	**38**
CHANGE (%)		690%	93%	51%	36%	28%	23%	11%	11%	10%	10%
COGS (%)	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
COGS (EUR MN)	0	0	-1	-1	-2	-2	-3	-3	-3	-3	-4
PROFIT BEFORE TAX (EUR MN)	**0**	**4**	**7**	**11**	**15**	**19**	**23**	**25**	**28**	**31**	**34**
TAXES (EUR MN)	0	-1	-1	-2	-3	-4	-5	-5	-6	-6	-7
PROFIT (EUR MN)	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**20**	**23**	**25**	**27**

UNITED STATES - SOLD BY MEDTRONIC (FROM MAY 2019)	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
PEOPLE OF SCREEN-ELIGIBLE AGE (50-74 YEARS) (MN)	76	79	81	83	86	88	91	94	97	100	102
GROWTH (%)	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
NUMBER OF COLONOSCOPIES (MN)	15	15	16	16	17	17	18	18	19	19	20
PREVALENCE OF ADENOMATOUS POLYPS (%)	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
COLONOSCOPIES WITH ADENOMATOUS POLYPS (MN)	4.5	4.6	4.7	4.9	5.0	5.2	5.3	5.5	5.6	5.8	6.0
NUMBER OF SIGMOIDOSCOPIES (MN)	3.0	3.1	3.2	3.2	3.3	3.4	3.5	3.7	3.8	3.9	4.0
PREVALENCE OF ADENOMATOUS POLYPS (%)	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
SIGMOIDOSCOPIES WITH ADENAMATOUS POLYPS (MN)	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.4	0.4	0.4
TOTAL CASES WITH ADENOMOTOUS POLYPS (MN)	4.8	4.9	5.0	5.2	5.3	5.5	5.7	5.8	6.0	6.2	6.4
LIFTING AGENT REQUIRED (%)	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
PROCEDURES WHERE LIFTING AGENT REQUIRED (MN)	**1.0**	**1.0**	**1.0**	**1.0**	**1.1**	**1.1**	**1.1**	**1.2**	**1.2**	**1.2**	**1.3**
PENETRATION (%)	5%	7%	12%	20%	27%	33%	38%	43%	46%	48%	49%
NUMBER OF PROCEDURES WITH ELEVIEW (MN)	0.0	0.1	0.1	0.2	0.3	0.4	0.4	0.5	0.6	0.6	0.6
COST PER VIAL (EUR)	79	82	82	82	82	82	82	82	82	82	82
NUMBER OF VIALS PER PROCEDURE	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
COST PER PROCEDURE (EUR)	127	133	133	133	133	133	133	133	133	133	133
SALES (EUR MN) - BOOKED BY MEDTRONIC (FROM MAY 2019)	**6**	**9**	**16**	**28**	**38**	**48**	**57**	**67**	**74**	**79**	**83**
CHANGE (%)	298%	49%	75%	71%	39%	26%	19%	16%	10%	7%	5%
ROYALTY (%)	0%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
ROYALTIES (EUR MN)	0	3	5	8	12	15	17	20	22	24	25
COGS (%)	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
COGS (EUR MN)	0	0	-1	-1	-2	-2	-3	-3	-4	-4	-4
M&S TOTAL (%)	545%	48%	0%	0%	0%	0%	0%	0%	0%	0%	0%
M&S COSTS TOTAL (EUR MN)	-34	-4	0	0	0	0	0	0	0	0	0
PROFIT BEFORE TAX (EUR MN)	**-28**	**-2**	**4**	**7**	**10**	**12**	**14**	**17**	**18**	**20**	**21**
TAXES (EUR MN)	0	0	-1	-1	-2	-2	-3	-3	-4	-4	-4
PROFIT (EUR MN)	**-28**	**-2**	**3**	**6**	**8**	**10**	**11**	**13**	**15**	**16**	**17**

	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
GLOBAL SALES (EUR MN)	**7**	**17**	**32**	**52**	**71**	**90**	**108**	**123**	**136**	**148**	**159**
CHANGE (%)	364%	140%	83%	61%	37%	27%	21%	14%	10%	9%	7%
GLOBAL PROFIT (EUR MN)	**-28**	**1**	**9**	**14**	**19**	**25**	**30**	**34**	**37**	**41**	**44**
CHANGE (%)	-2%	-103%	950%	58%	37%	27%	21%	13%	11%	9%	8%

WACC (%)	7%
NPV TOTAL PROFIT (CHF MN)	**326**
NUMBER OF SHARES (MN)	15.0
NPV PER SHARE (CHF)	**22**

SENSITIVITY ANALYSIS

		WACC (%)						
	CHF/SHARE	5.5	6.0	6.5	7.0	7.5	8.0	8.5
PEAK SALES (EUR MN)	340	44	43	41	39	37	36	34
	290	38	36	35	33	32	30	29
	240	31	30	29	28	26	25	24
	190	25	24	23	**22**	21	20	19
	140	18	18	17	16	15	15	14
	90	12	11	11	10	10	9	9
	40	5	5	5	5	4	4	4

ESTIMATES AS OF 3 JUNE, 2019

SOURCE: VALUATIONLAB ESTIMATES

Unique Selling Point

Eleview is the first FDA and EMA approved injectable solution specifically designed for colonic lesion resection based on clinical trials against standard saline injections. Eleview provides an immediate and long-lasting cushion that lifts the lesion and makes it easier for the physician to remove, while the blue dye improves margin visibility of the polyp, reducing the risk of gastrointestinal perforation.

7P's Analysis

Patent: Eleview is protected by 3 granted US patents (US9226996, US9364580, US9522216) and an EU composition of matter patent (EU2911707) providing patent protection until November 2034.

Phase: Eleview has successfully completed clinical development and has shown a favorable profile compared to injectable saline, the current standard of care. Eleview required less volume injected, less time, less reinjections, and there were a smaller number of resection pieces with Eleview, than with injectable saline. Eleview received FDA and EMA approval in 2017 and are currently being rolled out.

Pathway: In 2017, Eleview was approved as an FDA 510(k) cleared class II medical device in the US and received CE marking as a medical device in the EU.

Patient: Lesion resection with Eleview provides a safer procedure than with standard injectable saline, reducing the risk of gastrointestinal perforation, a major complication that requires immediate surgery.

Physician: Clinical evaluation shows that Eleview requires less volume injected, less time, less reinjections, than with injectable saline solution, and with Eleview there are less number of resection pieces.

Payer: Eleview is a safer alternative in lesion colonic lesion resection lowering the risk of costly surgery in case of a gastrointestinal perforation, with better treatment outcomes and saving considerable treatment time than standard of care injectable saline solution.

Partner: In October 2017, Cosmo signed two major license agreements to enhance and broaden Eleview's sales reach. In the US an exclusive co-promotion agreement was signed with Olympus America Inc., while an exclusive distribution agreement for Europe, South East Asia, Africa, Middle East, Australia and New Zealand was signed with Fujifilm Europe. The agreement provides Cosmo with a 45% share of gross revenues (including COGS). In the EU/ROW we assume Cosmo books sales at a 50% transfer price to Fujifilm. Furthermore, the company signed an exclusive agreement for Eleview (and MethyleneBlue) with EA Pharma for Japan and South Korea in return for undisclosed upfront, development and sales milestones and royalties on sales. In May 2019, the agreement with Olympus was terminated and replaced with a distribution agreement with Medtronic, which is now responsible for commercialization of Eleview in the US. Cosmo's US sales organization Aries was restructured leading to EUR 20 mn cost savings in 2019. We now assume Cosmo to receive a 25 % net royalty from Medtronic after COGS.

Byfavo – Procedural sedation in colonoscopy

Product Analysis

Byfavo peak sales of EUR 150 mn - rNPV of CHF 21 per share

We forecast peak sales of EUR 154 mn for Byfavo (remimazolam) in procedural sedation alone, assuming a US launch in H1 2020, a cost of USD 30 per procedure, and a market penetration peaking at around 45% in conscious and deep sedation. We assume that Byfavo will be sold through Cosmo's US sales organization Aries Pharmaceuticals. Our rNPV amounts to CHF 323 mn, or CHF 27 per share, with Cosmo booking all sales and incurring all M&S costs and paying PAION up to EUR 42.5 mn milestones and tiered royalties on sales ranging between 20% and 25%, with an 80% (filing) success probability and a WACC of 7% (for detailed forecasts see page 45).

NOTE: We have not accounted for additional US indications in our forecasts such as bronchoscopy or general anesthesia, nor have we accounted for the potential upside of Cosmo's 9% equity stake in PAION.

Natural fit with MethyleneBlue, the AI Smart Box and Eleview

Remimazolam (now branded Byfavo) is an ultra-short-acting IV (intravenous) benzodiazepine sedative/anesthetic that has completed phase III development for procedural sedation, including colonoscopy and bronchoscopy, and was filed for US approval in April 2019 for these indications triggering a EUR 7.5 mn milestone payment to PAION. Byfavo is a natural fit with Cosmo's endoscopy product pipeline as sedation is a crucial procedure in colonoscopy and it targets largely the same physicians. In June 2016, Cosmo acquired the exclusive US rights for the development and commercialization of Byfavo from PAION (ticker: PA8 GR) based in Aachen, Germany. Cosmo paid EUR 10 mn upfront and became PAION's largest shareholder with a 9.1% equity stake, following their "equity for product strategy". We conservatively forecast peak sales of EUR 150 mn in procedural sedation for colonoscopy, alone. Byfavo also has potential in for instance general anesthesia or ICU sedation, which provides further upside for Cosmo in the US, as well as for its equity stake in PAION. PAION has completed a full clinical development program for general anesthesia in Japan, and a phase II trial in the EU, but further phase III trials will be needed to gain US approval.

Increasing use of procedural sedation outside the hospital setting in the US

Procedural sedation is the technique of administering sedatives with or without analgesics (painkillers) to induce a state that allows the patient to tolerate unpleasant procedures while maintaining cardiorespiratory function. It is intended to result in a depressed level of consciousness that allows the patient to maintain oxygenation and airway control independently and is often performed in interventional or diagnostic procedures. PAION estimates that approximately 43 million procedures using procedural sedation took place in the US alone in 2013, predominantly outside the hospital setting. It is estimated that 75% of colonoscopies and endoscopies were conducted in an outpatient setting due to higher reimbursement fees compared to hospital. Growth has been driven by the increase in medical interventions requiring procedural sedation, such as colorectal cancer screening using colonoscopy, and an increase in demand for preventive screenings. The market for endoscopies in gastroenterology represents the most lucrative market segment for Byfavo in procedural sedation with approximately 20 million procedures per year.

Lack of innovation with generic midazolam and propofol used in 50% of procedures
In the past decade, there has been a lack of innovation in sedation and anesthesia. The most widely used drugs in procedural sedation are midazolam, a short-acting benzodiazepine synthesized in 1975 and branded Versed by Roche; and propofol, a $GABA_A$ receptor agonist, discovered in 1977 and branded Diprivan by AstraZeneca. Both are generically available, with a market share of approximately 50% in terms of volume of procedures performed in the outpatient market for colonoscopies. Improvements in efficacy and safety are still needed, including unintended intra-operational awareness, respiratory depression, hemodynamic stability, post-operative/procedure emergence and recovery, long-term effects of anesthesia, and patient morbidity.

For instance, the use of propofol requires the presence of an anesthesia professional throughout the procedure due to propofol's potential for cardiorespiratory-depressive effects, which results in additional cost. For midazolam, these side effects are less pronounced and have a different relevance, since an undesirably deep sedation can be reversed with flumazenil. Midazolam has a slower onset and a longer duration of action, which impacts patient throughput and overall efficiency.

Favorable safety and efficacy profile demonstrated in over 1,700 subjects
Byfavo has demonstrated safety and efficacy in over 1,700 patients and volunteers. The compound has shown a rapid onset and offset of action combined with a favorable cardiorespiratory safety profile. Byfavo is rapidly metabolized to an inactive metabolite by tissue esterases and not metabolized by cytochrome-dependent hepatic pathways, contributing to its favorable safety profile. Like other benzodiazepines, Byfavo can be reversed with flumazenil to rapidly terminate sedation and anesthesia if necessary.

Successful US phase III development program in procedural sedation
Byfavo has successfully completed US phase III development in procedural sedation as set out by the FDA with positive phase III trial results announced in colonoscopy (June 2016), bronchoscopy (March 2017), and in high-risk (ASA class III/IV) patients undergoing colonoscopy (March 2017). Primary endpoints and important secondary endpoints were reached with high statistical significance, and all trial data confirmed Byfavo's safety and efficacy profile.

OVERVIEW REMIMAZOLAM US PHASE III TRIAL RESULTS IN COLONOSCOPY

	REMIMAZOLAM	PLACEBO	MIDAZOLAM (OPEN LABEL)
PROCEDURAL SUCCESS (PRIMARY ENDPOINT)	**91.3%**	**1.7%**	**25.2%**
USE OF RESCUE SEDATION	3.4%	95.0%	64.7%
AVERAGE FENTANYL DOSE	88.9 MCG	121.3 MCG	106.9 MCG
START OF MEDICATION TO START OF PROCEDURE (MEDIAN)	4.0 MINUTES	19.5 MINUTES	19.0 MINUTES
END OF PROCEDURE TO FULLY ALERT (MEAN)	7.2 MINUTES	21.3 MINUTES	15.7 MINUTES
TIME 1ST DOSE TO DISCHARGE (MEAN)	58 MINUTES	86 MINUTES	75 MINUTES
TIME TO BACK TO NORMAL (PATIENT REPORTED)	331 MINUTES	572 MINUTES	553 MINUTES

SOURCE: PAION, COSMO PHARMACEUTICALS, VALUATIONLAB

The US phase III trial in patients undergoing endoscopist-administered sedation for colonoscopy enrolled a total of 461 patients at 13 US sites and was designed to evaluate the efficacy and safety of Byfavo compared to placebo (with open label midazolam rescue arm). The primary endpoint was a composite endpoint defined as: no need for rescue medication, completion of the procedure and no more than 5 top-up doses within any 15-minute window.

The primary endpoint was reached in 91.3% of the patients in the Byfavo arm compared to 1.7% in the placebo arm, and 25.2% in the open label midazolam rescue arm. Byfavo also required less use of rescue sedation with lower average doses of fentanyl.

Important secondary endpoints in the Byfavo arm showed improvements over placebo and the open label midazolam rescue arm in terms of: median time from start of medication to start of procedure, median time from end of procedure to return to full alertness; mean time first dose to discharge, time to “back to normal” as reported by patients.

No serious adverse events related to treatment occurred in the trial. Hypotension (low blood pressure) was 44.3% with Byfavo, 47.5% with placebo, and 67.3% with midazolam, and accounted for most of the adverse events in all study arms. Hypoxia occurred in 1.0% of patients given Byfavo, 3.4% in the placebo, and 1.0% given midazolam. The results of the open label midazolam arm will not be part of the label claims but will serve as valuable data to plan future studies and perform pharmacoeconomic modeling.

US approval in procedural sedation expected in H1 2020

In April 2019, Cosmo filed for US approval of Byfavo for procedural sedation. Assuming a normal FDA review of 10-12 months, Byfavo is expected to be approved in H1 2020, which will trigger a EUR 15 mn milestone payment to PAION. We forecast US peak sales for Byfavo of EUR 150 mn in procedural sedation (in colonoscopy), alone. Cosmo stated it will position its US commercial organization Aries Pharmaceuticals on an opportunity-by-opportunity basis. Therefore, we continue to assume Byfavo will be commercialized by Aries to maximize long-term profitability and account for COGS and M&S costs. Alternatively, Cosmo could sign on a US marketing partner if the economics are favorable. Byfavo could potentially be used in general anesthesia, a far larger indication and ICU sedation as well. PAION is developing Byfavo for general anesthesia in Europe/ROW (excluding the US). However, a confirmatory US pivotal trial will be needed to untap these additional indications.

Forecasts & Sensitivity Analysis

BYFAVO - FINANCIAL FORECASTS FOR PROCEDURAL SEDATION (COLONOSCOPIES)

INDICATION	PROCEDURAL SEDATION IN COLONOSCOPY TO REDUCE RECOVERY TIME
DOSAGE	AVERAGE 24 MG USED PER PROCEDURE
PRICING	ASSUMED COST PER PROCEDURE IN THE US OF USD 30 (AVERAGE 24 MG USED OR USD 1.25/MG)
STANDARD OF CARE	PROCEDURAL SEDATION IS USED IN ALL COLONOSCOPIES IN THE US, PROPOFOL AND MIDAZOLAM ARE USED IN ~50% OF CASES
UNIQUE SELLING POINT	TIME SAVINGS OF APPROXIMATELY 18 MINUTES PER COLONOSCOPY - POTENTIAL FOR HIGHER THROUGHPUT IN LARGE CENTERS

7Ps ANALYSIS

PATENT	EXPIRY APRIL 2033E; 5 US GRANTED PATENTS (US7485635/US7435730/US9193730/US9561236/US9737547); 1 US PATENT ALLOWED (US14/948,889)
PHASE	COMPLETED PHASE III IN COLONOSCOPY & BRONCHOSCOPY, SAFETY IN HIGH-RISK COLONOSCOPY PTS., ABUSE LIABILITY PROGRAM; FILED APRIL 2019; APPROVAL H1 2020
PATHWAY	TWO PIVOTAL PHASE III ENDOSCOPY TRIALS (ONE GI, ONE NON-GI); >100 PATIENTS AGED OVER 65, >100 HIGH-RISK ASA III/IV PATIENTS
PATIENT	RAPID ONSET AND OFFSET, FASTER PROCEDURE; LESS TIME PATIENT BACK TO NORMAL
PHYSICIAN	HIGHER PROCEDURAL SUCCESS RATE, LESS USE RESCUE MEDICATION; RAPID ON & OFFSET, LESS TIME TOTAL PROCEDURE; POTENTIAL FOR HIGHER PATIENT THROUGHPUT
PAYER	HIGHER THROUGHPUT OF PATIENTS AND BETTER USE OF FACILITIES LEADS TO HIGHER REVENUES, CAPACITY UTILIZATION, PROFITS
PARTNER	US RIGHTS FOR BYFAVO ACQUIRED FROM PAION FOR EUR 10 MN UPFRONT & 9.1% STAKE; PAION ENTITLED UP TO EUR 42.5 MN MILESTONES, ROYALTIES FROM 20-25%

REVENUE MODEL

UNITED STATES - SOLD BY ARIES PHARMA	**2018E**	**2019E**	**2020E**	**2021E**	**2022E**	**2023E**	**2024E**	**2025E**	**2026E**	**2027E**	**2028E**
PEOPLE OF SCREEN-ELIGIBLE AGE (50-74 YEARS) (MN)	76	79	81	83	86	88	91	94	97	100	102
GROWTH (%)	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
NUMBER OF COLONOSCOPIES (MN)	15	15	16	16	17	17	18	18	19	19	20
CONSCIOUS SEDATION (E.G. MIDAZOLAM) (%)	48%	48%	48%	48%	48%	48%	48%	48%	48%	48%	48%
COLONOSCOPIES WITH CONSCIOUS SEDATION (MN)	7.1	7.3	7.6	7.8	8.0	8.3	8.5	8.8	9.0	9.3	9.6
PENETRATION (%)	0%	0%	12%	20%	27%	33%	38%	41%	43%	44%	45%
TREATMENTS CONSCIOUS SEDATION (MN)	0.0	0.0	0.9	1.6	2.2	2.7	3.2	3.6	3.9	4.1	1.8
DEEP SEDATION (E.G. PROPOFOL) (%)	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
COLONOSCOPIES WITH CONSCIOUS SEDATION (MN)	3.0	3.1	3.2	3.2	3.3	3.4	3.5	3.7	3.8	3.9	4.0
PENETRATION (%)	0%	0%	12%	20%	27%	33%	38%	41%	43%	44%	45%
TREATMENTS DEEP SEDATION (MN)	0.0	0.0	0.4	0.6	0.9	1.1	1.3	1.5	1.6	1.7	1.8
TOTAL PROCEDURAL SEDATION TREATMENTS (MN)	0.0	0.0	1.3	2.2	3.1	3.9	4.6	5.1	5.5	5.8	3.6
COST PER PROCEDURE (EUR)	25	27	27	27	27	27	27	27	27	27	27
SALES (EUR MN) - BOOKED BY COSMO (ARIES PHARMA)	**0**	**0**	**34**	**58**	**81**	**102**	**121**	**135**	**146**	**154**	**95**
CHANGE (%)				72%	39%	26%	19%	11%	8%	5%	-38%
ROYALTY TO PAION (%)	0%	20%	20%	21%	21%	22%	22%	23%	23%	24%	24%
ROYALTIES TO PAION (EUR MN)	0	0	-7	-12	-17	-23	-27	-31	-34	-37	-23
UPFRONT & MILESTONE PAYMENTS (EUR MN)	0	-7.5	-15	0	0	0	0	0	0	0	0
M&S (%)			52%	33%	25%	20%	17%	15%	14%	13%	21%
M&S COSTS (EUR MN)	0	-1	-18	-19	-20	-20	-20	-20	-20	-20	-20
PROFIT BEFORE TAX (EUR MN)	**0**	**-7**	**-2**	**27**	**44**	**60**	**74**	**84**	**92**	**96**	**52**
TAX RATE (%)	0%	0%	0%	20%	20%	20%	20%	20%	20%	20%	20%
TAXES (EUR MN)	0	0	0	-5	-9	-12	-15	-17	-18	-19	-10
PROFIT (EUR MN)	**0**	**-7**	**-2**	**21**	**35**	**48**	**60**	**67**	**74**	**77**	**42**

	2018E	**2019E**	**2020E**	**2021E**	**2022E**	**2023E**	**2024E**	**2025E**	**2026E**	**2027E**	**2028E**
GLOBAL SALES (EUR MN)	**0**	**0**	**34**	**58**	**81**	**102**	**121**	**135**	**146**	**154**	**95**
CHANGE (%)				72%	39%	26%	19%	11%	8%	5%	-38%
GLOBAL PROFIT (EUR MN)	**0**	**-7**	**-2**	**21**	**35**	**48**	**60**	**67**	**74**	**77**	**42**
CHANGE (%)			-69%	-1114%	64%	36%	25%	12%	10%	5%	-46%

WACC (%)	7%	
NPV TOTAL PROFIT (CHF MN)	**406**	
NUMBER OF SHARES (MN)	15.0	
NPV PER SHARE (CHF)	**27**	
SUCCESS PROBABILITY	80%	(FILING SUCCESS PROBABILITY)
RISK ADJUSTED NPV PER SHARE (CHF)	**22**	

SENSITIVITY ANALYSIS

		WACC (%)						
	CHF/SHARE	5.5	6.0	6.5	7.0	7.5	8.0	8.5
SUCCESS PROBABILITY	100%	30	29	28	27	26	25	24
	95%	29	28	27	26	25	24	23
	90%	27	26	25	24	24	23	22
	85%	26	25	24	23	22	21	21
	80%	24	23	23	**22**	21	20	19
	75%	23	22	21	20	20	19	18
	65%	20	19	18	18	17	16	16

ESTIMATES AS OF 3 JUNE, 2019

SOURCE: VALUATIONLAB ESTIMATES

Unique Selling Point

Byfavo is an ultra-short-acting intravenous benzodiazepine sedative/anesthetic that has a higher patient and overall efficiency in procedural sedation than widely used generic anesthetics such as midazolam and propofol. There is no need for an anesthesia professional to be present in case of cardiorespiratory depression which can occur with propofol and results in additional costs.

7P's Analysis

Patent: Byfavo has 6 granted US patents (US7485636, US7435730, US9193730, US14/948,889, US9561236, US9737547) consisting of compound, composition of matter and method of treating patents. The last patent expires in 2033. The compound will also enjoy 5 years NCE (new chemical entity) exclusivity in the US.

Phase: Byfavo has completed the clinical development for procedural sedation in the US and Cosmo filed an NDA (new drug application) in April 2019. In 2016, PAION successfully completed the first phase III trial in colonoscopy. In 2017 the company completed the second confirmatory phase III trial in bronchoscopy, a clinical safety trial in high-risk patients undergoing colonoscopy, and a human abuse liability program in the US.

Pathway: For approval the FDA requires two positive phase III trials in procedural sedation (e.g. colonoscopy and bronchoscopy), a clinical safety trial in high-risk (ASA class III/IV) patients undergoing colonoscopy, and a human abuse liability program (if Byfavo could inappropriately be used as a knock-out cocktail in combination with alcohol) to assess the safety and efficacy of Byfavo. Trials must include >100 patients aged over 65 years, >100 high-risk ASA III/IV patients (severe systematic disease), and a non-gastrointestinal indication with sicker patients than typically undergoing colonoscopy.

Patient: Byfavo can speed up the colonoscopy procedure with a quicker onset of sedation, a faster recovery time with less side effects than current sedation.

Physician: Byfavo has a rapid onset and offset of action combined with a favorable cardio-respiratory safety profile, allowing for a higher patient throughput than with midazolam and propofol without the need for an anesthesia professional to be present in case of cardiorespiratory-depression which can occur with propofol.

Payer: Time savings of ~20 minutes per colonoscopy lead to higher patient throughput and lower recovery times and costs, which allow for higher margins per procedure in hospital and endoscopy centers. With no need for an anesthesia specialist during the procedure, such as with propofol, substantial additional cost savings can be made.

Partner: Cosmo acquired the exclusive US rights for Byfavo for procedural sedation in June 2016. Cosmo made a EUR 10 mn upfront payment and acquired a ~9% stake in PAION. PAION is entitled to up to EUR 42.5 mn milestone payments and tiered royalties on sales ranging from 20% up to 25%, which may be adjusted under certain conditions but not to below 15% of sales. The US filing triggered a EUR 7.5 mn milestone payment to PAION, while US approval will trigger an additional EUR 15 mn milestone payment. We continue to assume that Cosmo will commercialize the compound through its own US sales organization Aries to maximize long-term profitability, as the company stated it will position Aries on an opportunity-by-opportunity basis.

Colorectal cancer diagnostic market

We conservatively estimate that globally, at least USD 60 bn is spent annually on colonoscopies alone, of which roughly USD 4.8 bn is spent on endoscopes, catheters, bowel cleansing preparation, et cetera. A sizeable portion can be attributed to colorectal cancer screening. This market is set to grow due to the aging of the population, colorectal cancer screening programs, and new diagnostics entering the market.

COLON CANCER DIAGNOSTIC MARKET - KEY FACTS

MARKET SIZE	USD ~60 BN (USING AVERAGE COST OF A COLONOSCOPY)
NUMBER OF COLONOSCOPIES	~60 MN GLOBALLY; ~14 MN US, ~25 MN EU/JAP
MAIN GOAL	TO IDENTIFY AND REMOVE ALL POLYPS AND ADENOMAS GROWING IN THE COLON, INCLUDING THOSE IN EARLY STAGE (WITH FLAT MORPHOLOGY AND SMALL SIZE) AS THESE ARE ALL PRECURSORS OF COLON CANCER.
TARGET POPULATION / RISK FACTORS	- OLDER THAN 50 YEARS (ABOUT 90% OF COLON CANCER PATIENTS ARE OLDER THAN 50) AT RISK POPULATION: - PATIENTS WITH ULCERATIVE COLITIS - PATIENTS WITH CROHN'S DISEASE - AFRICAN AMERICAN RACE - A PERSONAL OR FAMILY HISTORY OF COLON CANCER OR POLYPS - OBESITY, PHYSICAL INACTIVITY, SMOKING, HEAVY ALCOHOL USE, DIET HIGH IN RED MEATS
AMERICAN CANCER SOCIETY GUIDELINES EARLY DETECTION OF CANCER	ALL PEOPLE 50 OR OLDER SHOULD FOLLOW ONE OF THE TESTING SCHEDULES: 1) TESTS THAT FIND POLYPS AND CANCER: - FLEXIBLE SIGMOIDSCOPY (EVERY 5 YEARS) - COLONOSCOPY EVERY (10 YEARS) - DOUBLE CONTRAST BARIUM ENEMA (EVERY 5 YEARS) - VIRTUAL COLONOSCOPY - CT SCAN (EVERY 5 YEARS) 2) TESTS THAT PRIMARILY FIND CANCER: - FBOT - FECAL OCCULT BLOOD TEST (EVERY YEAR) - FIT - FECAL IMMUNOCHEMICAL TEST (EVERY YEAR) - SDNA - STOOL DNA TEST (EVERY YEAR - NOT YET APPROVED IN US)
DIAGNOSTICS	INVASIVE DIAGNOSTICS: - COLONOSCOPY (ENDOSCOPE COVERS ENTIRE COLON - STANDARD OF CARE DIAGNOSTIC) - SIGMOIDOSCOPY (SHORTER ENDOSCOPE, COVERS ONLY 1/3 OF COLON) - CHROMOENDOSCOPY (COLONOSCOPY WITH IMAGE ENHANCING CAPABILITIES) - ARTIFICIAL INTELLIGENCE (AI) ENHANCED COLONOSCOPY LESS-INVASIVE DIAGNOSTICS: - DOUBLE-CONTRAST BARIUM ENEMA (X-RAY WITH CONTRAST MEDIA) - FECAL OCCULT BLOOD TEST (MICROSCOPIC TRACES OF BLOOD IN STOOL) - VIRTUAL COLONOSCOPY (MRI OR CT SCAN) - STOOL DNA TEST (IDENTIFY DNA MARKERS IN STOOL) - UNDER REVIEW - SEPTIN-9 TEST (BLOOD-BASED DNA MYELATION TEST) - UNDER REVIEW NOTE: WHEN LESS-INVASIVE TESTS ARE POSITIVE, THE PATIENT NEEDS A COLONOSCOPY TO CONFIRM FINDINGS AND REMOVE POLYPS OR ADENOMAS
DIAGNOSTIC (MAJOR PLAYERS)	- ENDOSCOPES (OLYMPUS, PENTAX, FUJINON, STRYKER, ENDOMED, WELCH ALLYN) - MRI/CT SCANS (PHILIPS, GENERAL ELECTRICS, SIEMENS, 3M, HITACHI, TOSHIBA) - CONTRAST MEDIA (BAYER, BRACCO, COVIDIEN) - CHROMOENDOSCOPY (COSMO WITH METHYLENEBLUE (FILING), VALEANT/PHOTOCURE WITH LUMACAN (PHASE I/II)) - STOOL DNA TEST (EXACT SCIENCES) - BLOOD-BASED MYELATION TEST (EPIGENOMICS WITH EPI PROCOLON) - AI ENHANCED COLONOSCOPY (MEDTRONIC / COSMO WITH AI SMART BOX)

SOURCE: VALUATIONLAB, NIH, WHO, MAYO CLINIC, ACS, COMPANIES

Colorectal cancer is the third most common cancer diagnosed in the US. The American Cancer Society estimates that annually there are >100,000 new cases of colon cancer and >40,000 new cases of rectal cancer. Only 65% of the target population gets screened. The goal is to raise this to 80% by 2018 (National Colorectal Cancer Roundtable). Regular colorectal screening is one of the most powerful, and cost effective, weapons for preventing colorectal cancer. Screening is the process of looking for cancer or pre-cancer in people who have no symptoms of the disease.

Before a cancer develops, a growth of tissue or tumor usually begins as a non-cancerous "polyp" on the inner lining of the colon or rectum. The chance of changing into cancer depends upon the type of polyp:

- **Adenomas** are polyps that can change into cancer. Because of this, adenomas are called a pre-cancerous condition.

- **Hyperplastic and inflammatory polyps**, in general, are not pre-cancerous. But some doctors think this may be a first sign of having a greater risk of developing adenomas, in particular when they appear in the ascending colon.

Dysplasia is another kind of pre-cancerous condition. These are cells in the lining of the colon or rectum where the cells appear abnormal (but not like true cancer cells). Dysplasia is usually seen in people who have ulcerative colitis or Crohn's disease for many years, which cause chronic inflammation of the colon.

From the time the first abnormal cells start to grow into polyps, it usually takes about 10-15 years for them to develop into colorectal cancer, often with no symptoms. Regular screening can, in many cases, prevent colorectal cancer altogether, because most polyps can be found and removed before they turn into cancer. Screening can also result in finding colorectal cancer early, when it is highly curable. Early stage (I) CRC has a 74% 5-year survival rate vs. 6% in late stage (IV) cancer.

Screening can be divided into two broad groups:
1) Tests that find both polyps *and* cancer. These are the preferred tests that look at the structure of the colon itself to find abnormal areas. This is done either with a scope inserted into the rectum or with special imaging (X-ray/CT scan) tests. Polyps found before they become cancerous can be removed, so they may prevent colorectal cancer. These tests include flexible sigmoidoscopy, colonoscopy, double contrast barium enema (X-ray), and CT colonography (virtual colonoscopy).
2) Tests that mainly find cancer. These test the stool (feces) for signs that cancer may be present and include fecal occult blood test (FOBT), fecal immunochemical test (FIT), and stool DNA test (sDNA). These tests are less invasive and easier to do but are less likely to detect polyps. Furthermore, when polyps or cancer is detected, patients are referred to colonoscopy to confirm the diagnosis and to remove the polyps.

New colon diagnostics are expected to improve early detection of colorectal cancer
After a lull in the development of new colorectal cancer diagnostics, several companies are now developing new approaches to detect colorectal cancer or to enhance detection of polyps and lesions. For instance, Epigenomics has developed a new blood-based DNA technology branded **Epi ProColon** (septin 9 test), while Exact Sciences has a stool-based DNA technology branded **Cologuard** that detects polyps and cancer in feces. A positive result from both tests will require a follow-up colonoscopy. Cosmo is at the forefront of AI enhanced colonoscopy with its **AI Smart Box**, which will be commercialized globally by Medtronic. First EU launches are expected in mid 2019 followed by a US rollout in 2020.

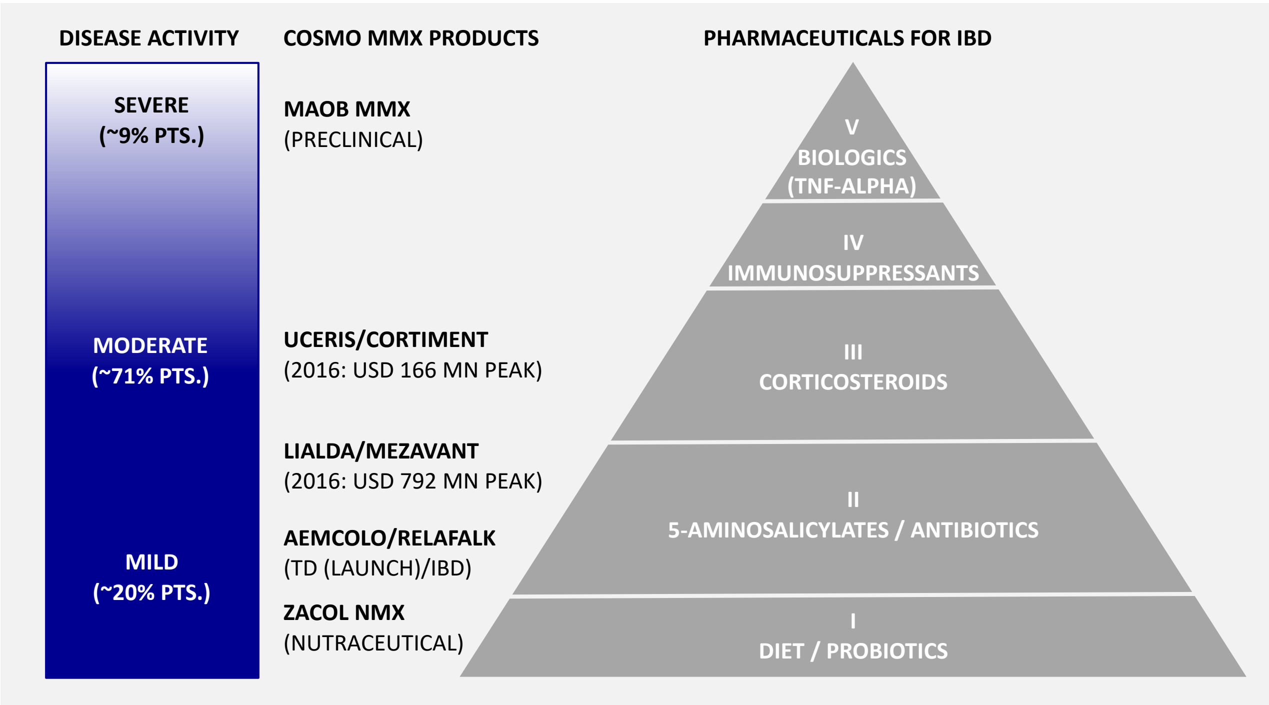
Cosmo and Photocure are developing image-enhancing agents for use in detecting cancerous and pre-cancerous lesions during so-called chromoendoscopy. Cosmo's **MethyleneBlue** is a novel oral MMX formulation of methylene blue that has proven to enhance the detection of lesions but has not been used frequently in its current liquid form as a "messy" and time-consuming spray. US approval of MethyleneBlue was surprisingly turned down by the FDA with Cosmo required to perform a second confirmatory trial, delaying US approval to 2022. The EU filing occurred in February 2019 with EU approval expected in H1 2020. Photocure is developing an oral photodynamic (fluorescence) colorectal diagnostic called **Lumacan**, which was originally designed to be given by enema. Lumacan contains hexamiolevulinate and is already on the market in the U.S. and Europe for use in detecting bladder cancer. Lumacan is in phase I/II development.

Gastrointestinal disorders pipeline

1) Inflammatory Bowel Disease

Cosmo has built a comprehensive drug portfolio for treating IBD (inflammatory bowel disease), a group of inflammatory conditions of the colon and small intestines. IBD is a complex disease, which arises as a result of the interaction of environmental and genetic factors leading to immunological responses and inflammation in the intestine. Crohn's disease and ulcerative colitis are the principal types of IBD. Ulcerative colitis primarily affects the colon and rectum, while Crohn's disease primarily affects the small and large intestine but also the mouth, esophagus, stomach and the anus. In spite of Crohn's disease and ulcerative colitis being very different diseases, both may present with any of the following symptoms: abdominal pain, vomiting, diarrhea, rectal bleeding, severe internal cramps/muscle spasms in the region of the pelvis and weight loss.

COMPREHENSIVE PORTFOLIO FOR INFLAMMATORY BOWEL DISESE



SOURCE: HENDRIKSEN C, KREINER S, BINDER V, GUT 1985; D'HAENS GR, ET AL. LANCET 2008; VALUATIONLAB

Cosmo aims to cover every step in treating IBD

Cosmo's aim is to cover all disease stages and drug treatment steps in IBD, in particular in ulcerative colitis, through compounds utilizing its proprietary MMX technology platform.

The first step in treating mild ulcerative colitis is with dietary supplements and probiotics. Cosmo offers its dietary supplement **Zacol NMX**, a so-called nutraceutical that uses an amended form of the MMX technology. Zacol NMX, is a relatively small product, largely sold in Italy, and is being rolled out in selected Eastern European countries. Zacol NMX sales have not been disclosed, yet.

The second step in treating ulcerative colitis when it progresses to mild-to-moderate disease is with prescription drugs that belong to the aminosalicylates or so-called 5-ASA's. **Lialda/Mezavant** (mesalamine MMX), has the highest amount of mesalamine per tablet, and was approved for mild-to-moderate ulcerative colitis in 2007, initially for induction, and in 2011 for maintenance of remission, a larger indication area. Sales of Lialda/Mezavant peaked at USD 792 mn in 2016 before cheap generics entered the market.

The third step in mild-to-moderate disease is treatment with (systemic) corticosteroids such as prednisone. These drugs have been used reluctantly due to severe side effects, despite being more effective than 5-ASA's in inflammatory bowel diseases, such as Crohn's disease. Cosmo's locally acting **Uceris/Cortiment** (budesonide MMX) was approved in the US in 2013 and the EU in 2014 for induction of remission. Thanks to the MMX technology, the drug has a clean side effect profile, and therefore has the potential to also be used for maintenance of remission. Peak sales forecasts are limited due to the "at risk" launch of Actavis' generic version of Uceris in the US in July 2018, offsetting increasing sales of Cortiment sales by Ferring outside the US.

The fourth and fifth step in moderate-to-severe ulcerative colitis patients, who do not respond to standard treatments, is treatment with immunosuppressants (e.g. thiopurines) or biologicals (e.g. TNF-alpha inhibitors such as Humira). Cosmo has **CB-01-12/MOAB MMX** (antibody TNF-alpha inhibitor) a biological in preclinical development as an oral "bio-better" in a strategic partnership with AIMM Therapeutics, a therapeutic antibody company based in Amsterdam, the Netherlands. Cosmo acquired a 6.48% stake in AIMM Therapeutics when they started the strategic partnership in 2012.

2) Colon infections – new antibiotics are needed to fend bacterial resistance

Gastrointestinal infections are viral, bacterial or parasitic infections that cause gastroenteritis, an inflammation of the gastrointestinal tract involving both the stomach and the small intestine or cause colon infections where the colon is primarily affected. These infections are quite common. Symptoms include diarrhea, vomiting, and abdominal pain. Dehydration is the main danger of gastrointestinal infections. Most gastrointestinal infections are self-limited and resolve within a few days. However, in a hospital setting and in specific populations (newborns/infants, immuno-compromized patients or elderly populations), they are potentially serious. Rapid diagnosis, appropriate treatment and infection control measures are therefore particularly important. In the case of gastrointestinal infections caused by bacteria, increasing bacterial resistance against current treatments is a major concern, making these antibiotics redundant. Novel antibiotics are needed to supplement or replace current treatments.

Aemcolo/Relafalk has promise in several bacterial infections of the colon

Cosmo's Aemcolo/Relafalk (rifamycin SV MMX) is a reformulation of the generic broad-spectrum antibiotic rifamycin using Cosmo's MMX technology. The MMX technology allows the antibiotic to be delivered directly into the colon, avoiding unwanted effects on beneficial bacterial flora living in the upper gastrointestinal tract. The compound is being developed for travelers' diarrhea and IBS-D (irritable bowel syndrome – diarrhea predominant), two common colon infections affecting millions of people globally. The antibiotic received US and EU approval for travelers' diarrhea in November 2018 with first launches expected in 2019. In the US, Aemcolo received QIDP (Qualified Infectious Disease Product) and Fast Track designations for travelers' disease, which underlines the importance of treating colon infections with new chemical entities due to the increasing rise in antibiotic resistance. Aemcolo is eligible for an additional five years market exclusivity and priority review (6 months instead of 10-12 months) in the US. patients A phase II trial in IBS-D patients started at the end of 2017 and is still enrolling.

Aemcolo/Relafalk – Travelers' disease & IBS-D

Product Analysis

1) Travelers' diarrhea peak sales EUR ~90 mn - NPV of CHF 16/share

We forecast peak sales of EUR 92 mn for Aemcolo/Relafalk in travelers' diarrhea assuming a US launch in June/July 2019 and an EU launch in Q3 2019, a (3-days) treatment cost of USD 150 (US) and EUR 48 (EU/ROW), and a market penetration conservatively peaking at around 11-13% of treated patients. In the US, Cosmo will market Aemcolo though a novel online DTC business model directly to US travelers which could provide substantial upside to our US forecasts. Cosmo books the sales and accounts for the COGS and M&S costs. In the EU/ROW, where Dr. Falk is largely responsible for commercialization, we assume royalties of ~12%, manufacturing income of 10% and COGS of 1%. Our NPV amounts to CHF 243 mn, or CHF 16 per share with a WACC of 7% (see detailed forecasts on page 57).

2) IBS-D peak sales of EUR 450+ mn - rNPV of CHF 10/share

In IBS-D (irritable bowel syndrome with diarrhea) we forecast peak sales of EUR 483 mn assuming first market launches in 2022, a (14-days) treatment cost of USD 1,575 (US) and EUR 504 (EU/ROW) and a market penetration conservatively peaking between ~7% (EU/ROW) and 9% (US). Accounting for the R&D costs for IBS-D and comparable assumptions as for travelers' diarrhea, our rNPV amounts to CHF 153 mn, or CHF 10 per share for IBS-D with a 35% (phase II) success rate (see detailed forecasts on page 58).

Likely most underestimated product and indication area

Rifamycin SV MMX (branded Aemcolo in the US and Relafalk in the Dr. Falk territories) is the third gastrointestinal prescription drug to reach the market based on Cosmo's proprietary MMX formulation technology and is likely the most underestimated product in the company's pipeline. The US and EU approval of Aemcolo/Relafalk in its first indication of travelers' diarrhea in November 2018, marks the first new gastrointestinal disease-specific antibiotic in ~15 years. The US launch through a novel online DTC business model directly targeting travelers is expected to start in June/July 2019, followed by a traditional EU launch by Dr. Falk in Q3 2019. We conservatively forecast global peak sales of EUR ~90 mn in travelers' diarrhea related to the short 3-days treatment course. Substantial upside to our US travelers' diarrhea forecasts could occur if Cosmo succeeds with its novel online DTC business model directly targeting the yearly 46 mn US travelers. Cosmo guides for gross sales of USD 15 mn for 2019. The novel antibiotic is also being developed for treating IBS-D (irritable bowel syndrome – diarrhea predominant) an indication with far higher peak sales potential of EUR 450+ mn thanks to a longer 14-days treatment regimen. The phase II trial in IBS-D is progressing, the trial is open in Belgium, Italy, Spain and Germany and recruitment is ongoing.

Targeting US travelers timely when they book a trip to an "at risk" country is key

In the US, Cosmo will market Aemcolo though a novel online DTC business model directly to travelers. Cosmo estimates there are approximately 46 mn Americans traveling every year to "at risk" countries where the ISTM (International Society of Travel Medicine) recommends travelling with an antibiotic as a precaution. Additionally, the ISTM specifically mentions Aemcolo as a first line antibiotic for a travel kit for self-treatment in case of infection. To be successful, Cosmo needs to target travelers while they are making their travel plans and to make it easy to get Aemcolo, which is a prescription drug that cannot be bought over-the-counter. This asks for a different approach than traditionally targeting physicians as most travelers do not visit their doctor before traveling. However, over a third of travelers do seek health advice mostly online before leaving, paying out of pocket for OTC products such as Imodium (loperamide) for diarrhea or travel vaccines. Note that in the case of travelers' diarrhea, cheap OTC diarrhea products such Imodium decrease the motility of the colon thus stopping diarrhea, but do not treat the underlying infection. Consequently, these treatments can exacerbate the underlying infection, which in some cases persist upon return or even leads to lasting complications.

Ordering Aemcolo to be as simple as pushing an online button with home delivery

When travelers book a trip abroad online, an Aemcolo add pops up informing the traveler the need for Aemcolo to treat travelers' diarrhea. The key message is that travelers' diarrhea can destroy the traveler's costly business trip or vacation and can keep the traveler on the toilet for a week. Aemcolo can heal in 24 hours and should be part of a travel kit as a precaution when traveling to "at risk" countries. A button links the traveler to an online telemedicine provider offering an online consultation with a healthcare practitioner who can write an e-prescription to a pharmacy, where Aemcolo can be delivered at home. Cosmo has teamed up with renowned companies such as Ogilvy Health, an experienced marketing partner with a strong international team with direct experience in travelers' health, and UpScriptHealth, a strong end-to-end execution partner with expertise in telemedicine through warehousing, pharmacy dispensing and home delivery.

A small penetration in travelers could lead to substantial upside to Aemcolo sales

Pricing in the US is targeted at USD 150 for a 3-days treatment, with launch expected in June/July 2019. Cosmo guides for peak sales of EUR 300 mn, which management deems conservative. We conservatively base our forecasts on the penetration of patients treated for travelers' diarrhea and not as a precaution that is bought ahead of traveling to "at risk" countries. A small penetration in travelers could lead to substantial upside to our current Aemcolo sales forecasts of EUR ~90 mn.

Traditional launches outside the US by Dr. Falk to start in Q3 2019

Dr. Falk, which has development and commercialization rights for Europe (excluding Italy), selective Eastern European countries and Australia, will market the antibiotic under the brand Relafalk, by traditionally targeting physicians that treat patients with travelers' diarrhea. We assume Cosmo will receive royalties on sales in the low mid teen range. Cosmo will manufacture Aemcolo for Dr. Falk and receive a manufacturing fee. In November 2018, the antibiotic was approved for travelers' diarrhea in the EU through the European Decentralized Procedure in Germany, UK, Spain, Portugal, Sweden, Norway, Denmark, Finland, Greece, Hungary, Poland, and Bulgaria, with first launches by Dr. Falk expected in Q3 2019.

Broad use in colon infections likely replicating Bausch Health's Xifaxan success

Aemcolo/Relafalk is a reformulation of the generic broad-spectrum, semi-synthetic, orally non-absorbable antibiotic rifamycin using Cosmo's MMX technology. The MMX technology allows the antibiotic to be delivered directly into the colon, avoiding unwanted effects on beneficial bacterial flora living in the upper gastrointestinal tract. Aemcolo/Relafalk has the potential to be used in a range of bacterial colon infections such as travelers' diarrhea,

infectious diarrhea, infectious colitis, IBS-D and diverticulitis, among others, which affect millions of people every year.
The hallmark of colon infections is that they are typically treated based on symptoms, of which diarrhea caused by the underlying bacterial infection is one of the main reasons for patients to seek treatment. Most physicians treat patients empirically, without a specific diagnosis, as the results of pathogen testing typically takes too long and it is critical to treat the infection as soon as possible. A broad-spectrum antibiotic is often sufficient to treat the infection and provide symptom relief.

For instance, the success of Bausch Health's antibiotic Xifaxan (rifaximin), which grew by +22% to USD 1.2 bn sales in 2018 is related to the broad use for colon infections outside its approved indications such as travelers' diarrhea and IBS-D. Aemcolo/Relafalk appears to have an improved efficacy, safety and tolerability profile compared to Xifaxan. Therefore, we believe the initial uptake of Aemcolo/Relafalk may be underestimated as it is likely that it will also be prescribed empirically outside its first approved indications. Critical will be an approval for IBS-D as the treatment course consists of a 14-days pack compared to a short 3-days pack for travelers' diarrhea.

Travelers' diarrhea (rollout), diverticulitis and IBS-D targeted as first indications
Cosmo currently targets travelers' diarrhea (we forecast EUR ~90 mn peak sales), IBS-D (EUR 450+ mn peak sales) and diverticulitis (to be determined) as first indications. Aemcolo/Relafalk completed phase III development for travelers' diarrhea where it demonstrated superiority compared to placebo and non-inferiority compared to ciprofloxacin in two separate pivotal phase III trials.

Key QIDP and Fast Track designations in travelers' disease underline importance
In the US, Aemcolo received QIDP (Qualified Infectious Disease Product) and Fast Track designations for travelers' disease, which underlines the importance of treating colon infections with new antibiotics. The increasing rise in antibiotic resistance makes current antibiotic treatments redundant. Aemcolo is eligible for additional five years market exclusivity from the day of approval in the US, based on the GAIN (Generating Antibiotic Incentives Now) Act of 2012. The US NDA (new drug application) filing occurred in March 2018 and thanks to the priority review Aemcolo received its first approval in the US in November 2018, just ahead of the EU approval.

Current treatments for travelers' diarrhea have certain limitations
Travelers' diarrhea is the most common travel-related illness affecting millions of international travelers each year. It can occur anywhere, but the highest-risk destinations are in most of Asia (except for Japan) as well as the Middle East, Africa, Mexico, and Central and South America. Travelers' diarrhea is a digestive tract disorder that commonly causes loose stools, abdominal cramps and dehydration. Eating contaminated food or drinking contaminated water causes travelers' diarrhea. The most common cause is enterotoxigenic Escherichia coli (ETEC) bacteria. These bacteria attach themselves to the lining of the intestine and release a toxin that causes diarrhea and abdominal cramps, causing discomfort. In healthy adults, diarrhea is rarely serious or life threatening, and symptoms typically resolve after several days. However, in certain high-risk populations such as people with weakened immune systems, diabetes, inflammatory bowel disease, cirrhosis of the liver or people who take acid blockers or antacids, symptoms may become severe. Treatments include broad-spectrum antibiotics such as Bayer's Cipro (ciprofloxacin), which is generically available and Bausch Health's Xifaxan. However,

bacterial resistance to current antibiotics is increasing and Cipro and Xifaxan have certain limitations compared to Aemcolo, including a “black box” warning (Cipro) or are less potent (Xifaxan).

Positive phase III trial results in travelers’ diarrhea show an attractive profile
Aemcolo successfully completed its phase III development in 2016 when the results of two pivotal phase III with different trial designs were announced. The antibiotic demonstrated an attractive and competitive profile in travelers’ diarrhea. Aemcolo has been administered in more than 600 patients in phase III alone and was well tolerated with only 5.5% of adverse events possibly drug-related.

The first phase III trial (performed by Santarus) in 264 patients with travelers’ diarrhea randomized in two treatment arms (400 mg Aemcolo versus placebo) treated for 3 days, demonstrated Aemcolo’s superiority compared to placebo.

- Aemcolo achieved the primary endpoint of superiority over placebo with a Clinical Cure rate (percentage of patients showing clinical symptoms remission) for Rifamycin SV of 81.4% versus 56.9% with a statistically significant p-value of 0.0008.
- The main parameter to show efficacy in travelers’ diarrhea is TLUS (Time to Last Unformed Stools). TLUS was significantly shorter in Aemcolo compared to placebo.
- Aemcolo had higher microbiological eradication by pathogen than placebo.

The second phase III trial (performed by Dr. Falk) in 835 patients with travelers’ diarrhea in two treatment arms (400 mg Relafalk versus 500 mg ciprofloxacin) treated for 3 days; Relafalk demonstrated non-inferiority compared to ciprofloxacin (branded Cipro by Bayer) the current standard of care in travelers’ diarrhea.

- Relafalk achieved the primary endpoint of non-inferiority with a Clinical Cure Rate (percentage of patients showing clinical symptoms remission) for Relafalk of 85.0% versus 84.8% for ciprofloxacin, with a hazard ratio of ≤ 0.764 and a statistically significant p-value of 0.0018.
- Relafalk also showed good efficacy in eradicating the whole E. coli bacteria family (65.9% versus 63.7% for ciprofloxacin) and a similar failure rate to ciprofloxacin (14.8 vs. 15.2 for ciprofloxacin).
- Relafalk’s TLUS in the Per Protocol Patient population was equivalent to ciprofloxacin at 33.3 hours versus 32.8 hours.
- In terms of Microbiological Cure Rate, in the patients that had a least one isolated microorganism, the efficacy was also equivalent to ciprofloxacin at 49.24% versus 49.60%.

Competitive advantage compared to competitor drugs in travelers’ diarrhea
In preclinical and clinical trials, Aemcolo/Relafalk demonstrated to have a competitive advantage compared to key competitor antibiotics in travelers’ diarrhea (and IBS-D). First of all, Aemcolo/Relafalk has no systemic absorption, which is important in avoiding bacterial resistance. Thanks to Cosmo’s MMX technology, Aemcolo/Relafalk is delivered topically only in the colon where the main infection is, avoiding earlier delivery in the upper gastrointestinal tract with unnecessary destruction of beneficial saprophytic flora. Specific competitive advantages in respect to competitor drugs, include:

- **Ciprofloxacin:** has a so-called FDA "black box" warning, flagging an increased risk of tendinitis and tendon ruptures in all ages, limiting its use to severe bacterial infections. The risk is further increased in older patients (>60 years of age), patients taking corticosteroids, and in patients with kidney, heart or lung transplants.
- **Xifaxan** (rifaximin)**:** Bausch Health's Xifaxan (2018 sales +22% to USD 1.2 bn) is also a key competitor to Aemcolo/Relafalk and has been approved in travelers' diarrhea, IBS-D, and hepatic encephalopathy. In a double-blind phase II clinical trial Aemcolo/Relafalk showed non-inferiority versus Xifaxan in TLUS and treatment success rates. Aemcolo/Relafalk also has a clear edge in anti-inflammatory properties. Based on the EC_{50} values, Aemcolo/Relafalk is 100 times more potent than Xifaxan, and at least 1,000 times more potent at stimulating PXR transcriptional activity in a cell line engineered to express a fusion human PXR protein than Xifaxan. In terms of the maximum possible stimulation of PXR activity, Xifaxan at 30 µM only activates up to 60% of the maximum activity with Aemcolo/Relafalk at 0.3 µM.

IBS-D a common GI disorder largely under diagnosed and untreated

Aemcolo/Relafalk's potentially second indication that we have included in our forecasts, targets patients with irritable bowel syndrome – diarrhea predominant (IBS-D). IBS is the most common functional gastrointestinal disorder that can cause abdominal pain, bloating, and altered bowel function causing diarrhea (IBS-D), constipation (IBS-C) or both (IBS-M), the three major subtypes of IBS. Studies show that the prevalence of IBS may range from 10% to 25% and frequently occurs in young adulthood. Prevalence rates in women are approximately 1.5 to 3-fold higher than those in men. Although IBS may occur at any age, about half of the people with IBS experienced initial symptoms before the age of 35 years. IBS tends to be under-diagnosed, because people with symptoms of IBS often do not seek medical attention, as there is a significant stigma associated with IBS, and are often not properly diagnosed. It has been reported that only 30% of people with symptoms of IBS, mainly IBS-D, will consult with a physician. Most people with IBS experience symptoms for an average of 8.1 days/month, had approximately two times as many days off work compared to the general population, and experienced more days in bed or felt less productive at work because of their symptoms. It is estimated that IBS costs USD 1.6 bn per year in health-related spending in the US alone.

Aemcolo/Relafalk targets bacterial overgrowth but without systemic side effects

The precise cause of IBS is not known. Factors that appear to play a role include: muscle contractions in the intestine, abnormalities in the nerves of the digestive system (poorly controlled signals between brain and intestines), inflammation of the intestines, severe infection (associated with a surplus of bacteria in the intestines called "bacterial overgrowth"), and changes in "good" bacteria in the gut (microflora). IBS patients are often treated with a range of antibiotics to reduce bacterial overgrowth. However, these often have systemic side effects and impact the microflora. Aemcolo has a wide spectrum of activity against the microbes implicated in bacterial overgrowth. Because it is non-absorbed, it should lack systemic side effects seen with current antibiotics with a low propensity to resistance.

Phase II IBS-D trial started in Q4 2017 which is enrolling patients in Europe

In Q4 2017, Cosmo started a phase II trial of Aemcolo/Relafalk in patients with IBS-D with the trial open in Belgium, Italy, Spain and Germany and recruiting is ongoing. The trial will recruit 342 patients at 25 sites and will randomize patients equally in three treatment arms, including placebo and two doses of Relafalk; 600 mg Relafalk twice daily and 600 mg Relafalk three times daily, for a treatment duration of 2 weeks. The trial will investigate the lasting treatment effects during a 3-months follow up period. The primary endpoint will be the percentage of patients who achieve adequate relief from both abdominal pain and diarrhea (a decrease of at least 30% in the weekly average pain score, and a 50% or more reduction in the number of days per week with diarrhea), based on patient-reported outcomes. The trial will also assess other outcomes such as bloating symptoms, frequency, feelings of urgency and impact on quality of life. On positive results, Cosmo is expected to start pivotal phase III development with an expected trial duration of 18 months. We assume first launches in the US and EU to occur in 2022.

Forecasts & Sensitivity Analysis

AEMCOLO / RELAFALK - FINANCIAL FORECASTS FOR TRAVELERS' DIARRHEA

INDICATION	TRAVELERS' DIARRHEA CAUSED BY NON-INVASIVE STRAINS OF ESCHERICHIA COLI (E.COLI)
DOSAGE	388 MG (TWO TABLETS) ORALLY TWICE DAILY (IN THE MORNING AND EVENING) FOR THREE DAYS: TOTAL OF 12 TABLETS PER TREATMENT
PRICING	3 DAYS TREATMENT PER PATIENT; US: USD 12.50/TABLET = USD 50/DAY = USD 150/TREATMENT; EU/ROW: EUR 4/TABLET = EUR 16/DAY = EUR 48/TREATMENT
STANDARD OF CARE	VALEANT'S XIFAXAN (RIFAXIMIN); BAYER'S CIPROBAY (CIPROFLOXACIN) WHICH IS AVAILABLE GENERICALLY
UNIQUE SELLING POINT	WELL TOLERATED ANTIBIOTIC WITH SHORTER TREATING PERIOD & LESS SUSCEPTABILITY TO ANTIBIOTIC RESISTANCE (WITHOUT A BLACK BOX WARNING)

7PS ANALYSIS

PATENT	EXPIRY: EU: 2028E (10 YEAR DATA EXCLUSIVITY); US: 2028 (NCE + QIDP EXCLUSIVITY); 4 GRANTED US PATENTS & 1 GRANTED EU PATENT EXPIRE IN MAY 2025
PHASE	EU TRIAL (NON-INFERIORITY VS CIPRO) & US TRIAL (SUPERIORITY VS PLACEBO) PRIMARY ENDPOINTS MET; APPROVED NOV 2018 IN US & EU; LAUNCH Q1 2019
PATHWAY	NORMAL REVIEW IN EU; EXPEDITED REVIEW IN US DUE TO QIDP (QUALIFIED INFECTIOUS DISEASE PRODUCT) DESIGNATION
PATIENT	WELL TOLERATED ANTIBIOTIC WITH FASTER TIME TO RECOVERY
PHYSICIAN	WELL TOLERATED ANTIBIOTIC WITH LESS PROPENSITY TO ANTIBIOTIC RESISTANCE
PAYER	COST EFFECTIVE ANTIBIOTIC DUE TO FASTER RECOVERY TIME AND ABSENCE OF ANTIBIOTIC RESISTANCE MAKING MANY CURRENT TREATMENTS REDUNDANT
PARTNER	EU (EX. ITALY) & AUS.: DR. FALK (BRANDED RELAFALK); US: (BRANDED AEMCOLO) NEW ONLINE DTC MODEL TARGETING TRAVELERS WITH OGILVY HEALTH & UPSCRIPTHEALTH

REVENUE MODEL

EUROPE / REST OF WORLD - SOLD BY DR. FALK	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
PATIENTS WITH TRAVELERS' DIARRHEA (75%)	12	12	13	13	13	13	13	14	14	14	14
GROWTH (%)	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
PERCENTAGE DIAGNOSED (%)	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
PATIENTS DIAGNOSED (MN)	3.6	3.7	3.8	3.8	3.9	3.9	4.0	4.1	4.1	4.2	4.2
PERCENTAGE TREATED (%)	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%
PATIENTS TREATED (MN)	2.6	2.6	2.6	2.7	2.7	2.8	2.8	2.8	2.9	2.9	3.0
PENETRATION (%)	0%	1%	4%	6%	7%	8%	9%	10%	11%	11%	6%
NUMBER OF PATIENTS (MN)	0.0	0.0	0.1	0.1	0.2	0.2	0.2	0.3	0.3	0.3	0.2
COST OF TREATMENT (EUR)	48	48	48	48	48	48	48	48	48	48	48
SALES (EUR MN)	**0**	**1**	**4**	**7**	**8**	**10**	**11**	**13**	**15**	**15**	**9**
CHANGE (%)			611%	60%	20%	17%	15%	13%	12%	2%	-39%
ROYALTY (%)	12%	12%	12%	12%	12%	12%	12%	12%	12%	12%	12%
ROYALTIES (EUR MN)	0	0	1	1	1	1	1	2	2	2	1
MANUFACTURING INCOME (%)	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
MANUFACTURING INCOME (EUR MN)	0	0	0	1	1	1	1	1	1	1	1
UPFRONT & MILESTONE PAYMENTS (EUR MN)											
COGS (%)	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
COGS (EUR MN)	0	0	0	0	0	0	0	0	0	0	0
R&D COSTS (EUR MN)	-2	0	0	0	0	0	0	0	0	0	0
PROFIT BEFORE TAX (EUR MN)	**-2**	**0**	**1**	**2**	**2**	**2**	**2**	**3**	**3**	**3**	**2**
TAX RATE (%)	0%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
TAXES (EUR MN)	0	0	0	0	0	0	0	-1	-1	-1	0
PROFIT (EUR MN)	**-2**	**0**	**1**	**1**	**1**	**2**	**2**	**2**	**2**	**3**	**2**

UNITED STATES - SOLD BY ARIES PHARMA	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
PATIENTS WITH TRAVELERS' DIARRHEA	10	10	10	11	11	11	11	11	11	12	12
GROWTH (%)	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
PERCENTAGE DIAGNOSED (%)	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
PATIENTS DIAGNOSED (MN)	5.1	5.1	5.2	5.3	5.4	5.5	5.5	5.6	5.7	5.8	5.9
PERCENTAGE TREATED (%)	80%	80%	80%	80%	80%	80%	80%	80%	80%	80%	80%
PATIENTS TREATED (MN)	4.1	4.1	4.2	4.2	4.3	4.4	4.4	4.5	4.6	4.6	4.7
PENETRATION (%)	0%	1%	4%	6%	8%	9%	10%	11%	12%	13%	12%
NUMBER OF PATIENTS (MN)	0.0	0.0	0.2	0.3	0.3	0.4	0.4	0.5	0.6	0.6	0.6
COST OF TREATMENT (EUR)	127	133	133	133	133	133	133	133	133	133	133
SALES (EUR MN) - BOOKED BY COSMO (ARIES PHARMA)	**0**	**3**	**20**	**34**	**46**	**53**	**59**	**66**	**73**	**77**	**75**
CHANGE (%)			509%	72%	35%	14%	13%	12%	11%	6%	-4%
COGS (%)	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
COGS (EUR MN)	0	0	-1	-2	-2	-3	-3	-3	-4	-4	-4
R&D COSTS (EUR MN)	-2	0	0	0	0	0	0	0	0	0	0
SG&A (%)		108%	49%	28%	21%	18%	16%	15%	13%	13%	13%
SG&A COSTS (EUR MN)	-2	-4	-10	-10	-10	-10	-10	-10	-10	-10	-9
PROFIT BEFORE TAX (EUR MN)											
TAX RATE (%)	0%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
TAXES (EUR MN)	0	0	-2	-5	-7	-8	-9	-11	-12	-13	-12
PROFIT (EUR MN)	**-3**	**0**	**7**	**18**	**27**	**32**	**37**	**43**	**48**	**51**	**49**

	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
GLOBAL SALES (EUR MN)	**0**	**4**	**24**	**41**	**55**	**63**	**71**	**79**	**88**	**92**	**84**
CHANGE (%)			525%	70%	32%	15%	13%	12%	11%	5%	-9%
GLOBAL PROFIT (EUR MN)	**-5**	**0**	**8**	**19**	**29**	**34**	**39**	**45**	**50**	**54**	**51**
CHANGE (%)	20%	-96%	-3596%	140%	48%	18%	16%	14%	13%	6%	-5%

WACC (%)	7%
NPV TOTAL PROFIT (CHF MN)	**243**
NUMBER OF SHARES (MN)	15.0
RISK ADJUSTED NPV PER SHARE (CHF)	**16**

SENSITIVITY ANALYSIS

		WACC (%)						
	CHF/SHARE	5.5	6.0	6.5	7.0	7.5	8.0	8.5
	120	23	23	22	22	21	20	20
	110	22	21	20	20	19	19	18
	100	20	19	18	18	17	17	16
PEAK SALES (EUR MN)	90	18	17	17	**16**	16	15	15
	80	16	15	15	14	14	14	13
	70	14	13	13	13	12	12	12
	60	12	11	11	11	10	10	10

ESTIMATES AS OF 3 JUNE, 2019

SOURCE: VALUATIONLAB ESTIMATES

AEMCOLO / RELAFALK - FINANCIAL FORECASTS IRRITABLE BOWEL SYNDROME WITH DIARRHEA (IBS-D)

INDICATION	IRRITABLE BOWEL SYNDROME PREDOMINANTLY WITH DIARRHEA (IBS-D)
DOSAGE	582 MG (3 TABLETS) THREE TIMES DAILY FOR 14 DAYS: TOTAL OF 126 TABLETS PER TREATMENT - TBD
PRICING	14 DAYS TREATMENT ASSUMED: US: USD 12.50/TABLET = USD 112.50/DAY = USD 1,575/TREATMENT; EU/ROW: EUR 4/TABLET = EUR 36/DAY = EUR 504/TREATMENT
STANDARD OF CARE	NOVARTIS' ZELNORM (TEGASEROD) HOWEVER NOT INDICATED FOR MEN; BAUSCH HEALTH'S XIFAXAN (RIFAXIMIN) APPROVED IN 2015
UNIQUE SELLING POINT	WELL TOLERATED AND EFFECTIVE ANTIBIOTIC WITH LIKELY SHORTER TREATMENT COURSE, LOW PROPENSITY TO ANTIBIOTIC RESISTANCE (WITHOUT BLACK BOX WARNING)

7Ps ANALYSIS

PATENT	EXPIRY: EU: 2028E (10 YEAR DATA EXCLUSIVITY); US: 2028 (NCE + QIDP EXCLUSIVITY); 4 GRANTED US PATENTS & 1 GRANTED EU PATENT EXPIRE IN MAY 2025
PHASE	PHASE II IN 342 PATIENTS WITH IBS-D STARTED IN Q4 2017 AND STILL ENROLLING; ASSUMING NORMAL REVIEW FIRST LAUNCHES EXPECTED IN 2022
PATHWAY	NORMAL REVIEW IN EU; EXPEDITED REVIEW IN US DUE TO QIDP (QUALIFIED INFECTIOUS DISEASE PRODUCT) DESIGNATION
PATIENT	WELL TOLERATED ANTIBIOTIC WITH FASTER TIME TO RECOVERY
PHYSICIAN	WELL TOLERATED ANTIBIOTIC WITH LESS SUSCEPTABILITY TO ANTIBIOTIC RESISTANCE
PAYER	COST EFFECTIVE ANTIBIOTIC DUE TO FASTER RECOVERY TIME AND ABSENCE OF ANTIBIOTIC RESISTANCE MAKING MANY CURRENT TREATMENTS REDUNDANT
PARTNER	EU (EXCL. ITALY) & AUSTRALIA: DR. FALK (BRANDED RELAFALK); US TO BE MARKETED BY ARIES PHARMA (BRANDED AEMCOLO)

REVENUE MODEL

EUROPE / REST OF WORLD - SOLD BY DR. FALK	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
NUMBER OF IBS PATIENTS (MN)	67	68	69	71	72	74	75	77	78	80	81
GROWTH (%)	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
IBS PATIENTS WITH IBS-D (%)	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
IBS PATIENTS WITH IBS-D (MN))	33	34	35	35	36	37	38	38	39	40	41
PATIENTS CONSULTING PHYSICIAN (%)	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
PATIENTS CONSULTING PHYSICIAN (MN)	10	10	10	11	11	11	11	11	12	12	12
PENETRATION (%)	0%	0%	0%	0%	1%	3%	5%	6%	7%	7%	4%
NUMBER OF PATIENTS (MN)	0.0	0.0	0.0	0.0	0.1	0.3	0.5	0.6	0.8	0.8	0.4
COST OF THERAPY PER DAY (EUR)	36	36	36	36	36	36	36	36	36	36	36
NUMBER OF TREATMENT DAYS	14	14	14	14	14	14	14	14	14	14	14
COST OF TREATMENT (EUR)	504	504	504	504	504	504	504	504	504	504	504
COMPLIANCE (%)	40%	40%	40%	40%	40%	40%	40%	40%	40%	40%	40%
SALES (EUR MN)	**0**	**0**	**0**	**0**	**11**	**56**	**102**	**127**	**153**	**169**	**86**
CHANGE (%)						410%	84%	25%	21%	10%	-49%
ROYALTY (%)	12%	12%	12%	12%	12%	12%	12%	12%	12%	12%	12%
ROYALTIES (EUR MN)	0	0	0	0	1	7	12	15	18	20	10
MANUFACTURING INCOME (%)	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
MANUFACTURING INCOME (EUR MN)	0	0	0	0	1	6	10	13	15	17	9
UPFRONT & MILESTONE PAYMENTS (EUR MN)	0	0	0	10	0	0	10	0	0	15	0
COGS (%)	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
COGS (EUR MN)	0	0	0	0	-1	-3	-5	-6	-8	-8	-4
R&D (%)	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
R&D COSTS (EUR MN)	-6	-10	-12	0	0	0	0	0	0	0	0
PROFIT BEFORE TAX (EUR MN)	**-6**	**-10**	**-12**	**10**	**2**	**9**	**27**	**22**	**26**	**44**	**15**
TAX RATE (%)	0%	0%	0%	20%	20%	20%	20%	20%	20%	20%	20%
TAXES (EUR MN)	0	0	0	-2	0	-2	-5	-4	-5	-9	-3
PROFIT (EUR MN)	**-6**	**-10**	**-12**	**8**	**1**	**8**	**22**	**17**	**21**	**35**	**12**

UNITED STATES - SOLD BY ARIES PHARMA	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
NUMBER OF IBS PATIENTS (MN)	37	38	39	39	40	41	42	43	43	44	45
GROWTH (%)	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
IBS PATIENTS WITH IBS-D (%)	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
IBS PATIENTS WITH IBS-D (MN))	18.5	18.9	19.3	19.7	20.1	20.5	20.9	21.3	21.7	22.1	22.6
IBS PATIENTS CONSULTING PHYSICIAN (%)	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
IBS PATIENTS CONSULTING PHYSICIAN (MN)	5.6	5.7	5.8	5.9	6.0	6.1	6.3	6.4	6.5	6.6	6.8
PENETRATION (%)	0%	0%	0%	0%	1%	3%	5%	7%	8%	9%	3%
NUMBER OF PATIENTS (MN)	0.0	0.0	0.0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.2
COST OF THERAPY PER DAY (EUR)	96	99	99	99	99	99	99	99	99	99	99
NUMBER OF TREATMENT DAYS	14	14	14	14	14	14	14	14	14	14	14
COST OF TREATMENT (EUR)	1,338	1,391	1,391	1,391	1,391	1,391	1,391	1,391	1,391	1,391	1,391
COMPLIANCE (%)	40%	40%	40%	40%	40%	40%	40%	40%	40%	40%	40%
SALES (EUR MN) - BOOKED BY COSMO (ARIES PHARMA)	**0**	**0**	**0**	**0**	**33**	**102**	**174**	**231**	**272**	**314**	**96**
CHANGE (%)						206%	70%	33%	18%	16%	-69%
UPFRONT & MILESTONE PAYMENTS (EUR MN)	0	0	0	0	0	0	0	0	0	0	0
COGS (%)	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
COGS (EUR MN)	0	0	0	0	-2	-5	-9	-12	-14	-16	-5
R&D (%)	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
R&D COSTS (EUR MN)	0	0	-2	0	0	0	0	0	0	0	0
SG&A (%)					185%	65%	32%	30%	25%	25%	25%
SG&A COSTS (EUR MN)	0	0	-4	-31	-62	-66	-56	-69	-68	-79	-24
PROFIT BEFORE TAX (EUR MN)	**0**	**0**	**-6**	**-31**	**-30**	**31**	**110**	**150**	**190**	**220**	**67**
TAX RATE (%)	0%	0%	0%	20%	20%	20%	20%	20%	20%	20%	20%
TAXES (EUR MN)	0	0	0	6	6	-6	-22	-30	-38	-44	-13
PROFIT (EUR MN)	**0**	**0**	**-6**	**-25**	**-24**	**25**	**88**	**120**	**152**	**176**	**54**

	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
GLOBAL SALES (EUR MN)	**0**	**0**	**0**	**0**	**44**	**158**	**276**	**358**	**425**	**483**	**182**
CHANGE (%)						256%	75%	30%	19%	14%	-62%
GLOBAL PROFIT (EUR MN)	**-6**	**-10**	**-18**	**-17**	**-23**	**32**	**110**	**137**	**173**	**211**	**66**
CHANGE (%)	200%	67%	82%	-8%	35%	-244%	238%	25%	26%	22%	-69%

WACC (%)	7%	
NPV TOTAL PROFIT (CHF MN)	**438**	
NUMBER OF SHARES (MN)	15.0	
NPV PER SHARE (CHF)	**29**	
SUCCESS PROBABILITY	35%	(PHASE II SUCCESS PROBABILITY)
RISK ADJUSTED NPV PER SHARE (CHF)	**10**	

SENSITIVITY ANALYSIS

		WACC (%)						
	CHF/SHARE	5.5	6.0	6.5	7.0	7.5	8.0	8.5
	60%	19	18	17	17	16	16	15
	55%	17	17	16	15	15	14	14
	50%	16	15	15	14	13	13	13
SUCCESS PROBABILITY	45%	14	14	13	13	12	12	11
	40%	13	12	12	11	11	10	10
	35%	11	11	10	**10**	9	9	9
	30%	9	9	9	8	8	8	8

ESTIMATES AS OF 3 JUNE, 2019

SOURCE: VALUATIONLAB ESTIMATES

Unique Selling Point

Aemcolo/Relafalk is a potent antibiotic that is delivered directly to the colon utilizing the MMX technology avoiding an impact on beneficial bacterial flora living in the upper portions of the gastrointestinal tract, with no systemic absorption, resulting in a better safety and tolerability profile than current antibiotics with a low propensity to bacterial resistance.

7P's Analysis

Patent: Six granted composition of matter and method of use patents protect Aemcolo until May 2025. In the EU, Relafalk will enjoy 10 years data exclusivity. In the US, Aemcolo is entitled to 5 years NCE (new chemical entity) exclusivity and an additional 5 years QIDP (qualified infectious disease product) designation in travelers' disease according to the GAIN Act, for a total of 10 years.

Phase: Aemcolo/Relafalk was approved for travelers' diarrhea in both the US and EU in November 2018. US launch through a novel online DTC business model directly targeting travelers is planned for June/July 2019, while Dr. Falk plans a traditional EU launch targeting physicians in Q3 2019. The phase II trial in IBS-D started in Q4 2017 and is currently enrolling patients. Pivotal phase III trials in IBS-D could start in 2020 with first launches in 2022.

Pathway: In the EU/ROW the compound is expected to have a normal review period (~10 months) for both indications based on two positive pivotal phase III trials in each indication. In the US, Aemcolo was granted QIDP (qualified infectious disease product) and Fast Track designations for travelers' diarrhea, which allows for 5 years additional market exclusivity in the US and expedited 6 months review. For IBS-D we assume a normal review period based on two positive pivotal phase III trials in the US.

Patient: Aemcolo/Relafalk provides patients with a convenient and well-tolerated antibiotic with no safety warnings and a faster time to recovery, which they could take on trip as a precaution.

Physician: Aemcolo/Relafalk broadens the physician's treatment options for travelers' diarrhea with a well-tolerated novel antibiotic with no warnings, a rapid time to recovery with a low propensity to bacterial resistance, an emerging problem with current antibiotic treatments.

Payer: Aemcolo/Relafalk provides a cost-effective treatment due to faster recovery time and the absence of antibiotic resistance, which makes current treatments redundant.

Partner: Dr. Falk acquired exclusive development and commercialization rights for the EU (excluding Italy), selected Eastern European countries & Australia for undisclosed terms. We assume Cosmo will receive royalties on sales in the low mid teen range. Cosmo will manufacture Aemcolo in return for a manufacturing fee. In the US, Cosmo will commercialize Aemcolo in TD through a novel online DTC business model targeting travelers directly. For other indications such as IBS-D, Cosmo can use Aries or seek a commercialization partner. Cosmo will seek further commercialization agreements to expand the compound's global reach.

Uceris / Cortiment - Ulcerative colitis

Product Analysis

Uceris sales peaked at EUR 149 mn - NPV of CHF 7 per share

Uceris/Cortiment sales in ulcerative colitis (induction of remission) have peaked at EUR 149 mn in 2017, due to an "at risk" launch of a generic version of Uceris by Actavis (Teva) in July 2018, somewhat offset by increasing EU/ROW sales by Ferring. We assume a yearly cost per patient of between USD 2,240 (US) and EUR 560 (EU/ROW), a US market penetration that peaked at ~6% and now to gradually decline by ~30% per year due to generic erosion despite patent protection in the US until 2031. We assume EU/ROW market penetration peaking at ~8% and 10-years data exclusivity until 2024. Our NPV amounts to CHF 106 mn, or CHF 7 per share, assuming Cosmo receives EUR 8 mn milestone payments (EU/ROW), tiered royalties on sales ranging from 12-14% (US) and ~21% (EU/ROW), a manufacturing fee of 10% (US) and 4% (EU/ROW), and a WACC of 7% (see detailed forecasts on page 62).

NOTE: There is substantial upside to our Uceris forecasts if Bausch Health were to win the appeal against Actavis' earlier non-infringement ruling by a US District Court.

Uceris under new threat from Actavis' "at risk" US generic

Uceris/Cortiment was Cosmo's second drug to reach the market using Cosmo's proprietary MMX colon delivery technology with a peak sales potential in ulcerative colitis that could have rivaled Lialda peak sales (USD 792 mn) before generics became available in the US. The drug is branded Uceris in the US and Cortiment outside the US where Ferring is largely responsible for commercialization. In the US, Bausch Health (formerly Valeant Pharmaceuticals) is responsible for the commercialization of Uceris. In early 2013, Uceris was approved and launched by Santarus, Cosmo's original US commercialization partner. Salix acquired Santarus in late 2013, and in 2015 Valeant (now Bausch Health) acquired Salix. Uceris was off to a flying start in the US triggering the consecutive acquisitions. However, wholesaler destocking issues and a lack of sufficient marketing effort by Bausch Health hampered the US uptake of Uceris in recent years. Cosmo unsuccessfully sought arbitration at the International Chamber of Commerce for termination of the license agreement with Bausch Health alleging breach of contract with a negative ruling in April 2018.

Actavis launches generic version of Uceris in US "at risk" of triple damages

In July 2018, a new threat emerged for Uceris peak sales potential. The FDA approved Actavis' (Teva) generic version of Uceris, with Actavis launching its generic version "at risk" and an authorized generic by Bausch Health shortly after. In November 2017, the US District Court for the District of Delaware ruled a non-infringement of Actavis' generic version of Uceris. In other words, the District Court decided Actavis' generic version of Uceris does not infringe Uceris' patents, which reach until 2031. Bausch Health appealed the District Court's ruling and the patent infringement trial is still in appeal. An appeal typically takes 12-18 months from the start until a ruling, which could come at earliest in H1 2019. Nevertheless, Actavis decided to launch "at risk" in the US, risking triple damages if the appeal court overturns the US District Court's initial ruling. Consequently, we have adjusted our Uceris US sales forecasts to decline by ~30% per year onwards assuming a worst-case scenario with Actavis winning the appeal.

International rollout by Ferring is well on its way with approval in 47 countries
Outside the US (except Japan and Asia) Ferring is responsible for selling Cortiment and has obtained approval in 47 countries, including the major EU countries, and several countries in South and North America and the Far East. Cosmo plans to out license the drug in Japan, an important market not yet included in our forecasts, to a local gastro-intestinal player. The Japanese regulatory authorities require clinical development to start from phase I.

Potential to become the preferred corticosteroid in ulcerative colitis
Ulcerative Colitis is a chronic relapsing-remitting illness for which there is no known cure, but with appropriate treatment patients can manage their symptoms. It is estimated that up to 30% of patients with mild or moderate ulcerative colitis do not respond sufficiently to aminosalicylate (5-ASA) drugs such as Lialda and require a different or add-on therapy. Patients refractive to 5-ASA treatment with typically receive a course of a systemically absorbed corticosteroid, which success may be limited by side effects. Uceris is the first convenient, oral, locally active corticosteroid, using Cosmo's proprietary MMX formulation of generic budesonide to be approved for induction of active, mild or moderate ulcerative colitis in the US. In the US, systemic corticosteroids such as prednisone are prescribed off-label for mild or moderate ulcerative colitis but have been used scarcely due to dreaded long-term side effects (e.g. "moon" face). Therefore, Uceris has the potential to supplant prednisone as an induction agent in the US due to improved safety and tolerability.

Awareness of Uceris high thanks to widespread use of Astra Zeneca's Entocort EC
Outside the US, budesonide, given by enema, is used to treat ulcerative colitis patients. Due to the inconvenient administration, budesonide enema is not used extensively. Physicians are also familiar with a budesonide extended-release formulation for the small intestine, branded Entocort EC by AstraZeneca. This drug was approved globally for treating Crohn's disease, a type of inflammatory bowel disease that may affect any part of the gastrointestinal tract, but most commonly the last part of the small intestine (the terminal ileum). Entocort EC was on the brink of reaching USD 400 mn in sales just before the patent expired in 2011. Therefore, many physicians are aware of budesonide as an effective treatment for IBD, however, limited by side effects. Therefore, we believe Cortiment with its local activity, resulting in best in class efficacy, safety and tolerability is poised to capture a sizeable market share in patients who no longer respond to 5-ASA.

Maintenance of remission a potential to broaden the label and increase peak sales
Uceris/Cortiment may also be useful for maintenance therapy in ulcerative colitis in clinical remission. In an extended-use trial reported at the Digestive Disease Week in 2012, patients whose disease was in remission were randomly assigned to receive either Uceris/Cortiment 6 mg/day (n=122) or placebo for 12 months. Although the trial was not powered to show statistical significance, this exploratory efficacy analysis suggests that Uceris/Cortiment 6 mg was not significantly different from placebo in influencing probability of clinical relapse; 40.4% in the budesonide group vs. 60.1% in the placebo group. However, Uceris/Cortiment significantly prolonged the time to relapse. The median time to clinical relapse was more than 1 year in the Uceris/Cortiment group compared with 182 days in patients who received placebo. To maximize the potential of Uceris/Cortiment in ulcerative colitis and broaden the label with maintenance therapy, additional trials will be needed, which will depend on Bausch Health winning the appeal, otherwise the economics do not add up.

Forecasts & Sensitivity Analysis

UCERIS / CORTIMENT - FINANCIAL FORECASTS FOR ULCERATIVE COLITIS

INDICATION	INDUCTION OF REMISSION FOR PATIENTS WITH ACTIVE ULCERATIVE COLITIS OF MILD TO MODERATE SEVERITY
DOSAGE	A SINGLE 9 MG ORAL TABLET ONCE DAILY FOR UP TO 8 WEEKS
PRICING	8 WEEKS TREATMENT DURATION: US: USD 40/DAY = USD 2,240; EU: EUR 10/DAY = EUR 560
STANDARD OF CARE	GENERIC MESALAMINE /ASACOL (WARNER CHILCOTT) / LIALDA (COSMO) / ENTOCORT EC/ENEMA (ASTRAZENECA)
UNIQUE SELLING POINT	FIRST ORAL STEROID FOR ULCERATIVE COLITIS ON US MARKET - BETTER RESPONSE RATES THAN SALYCILATES, SAFER THAN SYSTEMIC STEROIDS (E.G. PREDNISON)

7Ps ANALYSIS

PATENT	EXPIRY SEP 2031; 12 GRANTED US PATENTS (COM, METHOD OF USE); 1 GRANTED EU PATENT (EP1183014); ACTAVIS GENERIC APPROVED & LAUNCHED "AT RISK" IN JUL 2018
PHASE	US: APPROVED JANUARY 2013 / EU: APPROVED OCTOBER 2014; LAUNCHED IN 22 COUNTRIES, APPROVED IN 47, PENDING REGISTRATION IN 13, FILINGS PLANNED FOR 29
PATHWAY	ESTABLISHED REGULATORY PATHWAY - "MMX" SUSTAINED RELEASE FORMULATION OF GENERIC BUDESONIDE
PATIENT	SIMPLE SINGLE ORAL TABLET VS ENTOCORT ENEMA (RECTAL ADMINISTRATION)
PHYSICIAN	HIGHER RESPONSE RATES THAN ASACOL, LIALDA AND ENTOCORT
PAYER	HIGHER PATIENT COMPLIANCE AND RESPONSE RATES LEAD TO LOWER TOTAL TREATMENT COSTS
PARTNER	FERRING GLOBAL RIGHTS EX-US; US: LICENSED TO BAUSCH HEALTH (FORMERLY VALEANT PHARMACEUTICALS)

REVENUE MODEL

EUROPE / REST OF WORLD - SOLD BY FERRING	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
NUMBER OF PATIENTS (MN)	1.2	1.2	1.3	1.3	1.3	1.4	1.4	1.5	1.5	1.6	1.6
GROWTH (%)	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
PATIENT WITH MILD-TO-MODERATE DISEASE (85%)	1.0	1.0	1.1	1.1	1.1	1.2	1.2	1.2	1.3	1.3	1.4
PENETRATION (%)	2%	3%	5%	7%	8%	8%	7%	3%	2%	1%	0%
NUMBER OF PATIENTS (MN)	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0
COST OF THERAPY PER YEAR (EUR)	560	560	560	560	560	560	560	560	560	560	560
SALES (EUR MN) - BOOKED BY FERRING	**15**	**22**	**37**	**49**	**58**	**64**	**53**	**27**	**14**	**7**	**4**
CHANGE (%)	12%	48%	66%	32%	18%	10%	-18%	-49%	-49%	-49%	-49%
ROYALTY (%)	21%	21%	21%	21%	21%	21%	21%	21%	21%	21%	21%
ROYALTIES (EUR MN)	3	5	8	10	12	13	11	6	3	2	1
MANUFACTURING INCOME (%)	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
MANUFACTURING INCOME (EUR MN)	1	1	2	2	3	3	2	1	1	0	0
UPFRONT & MILESTONE PAYMENTS (EUR MN)				8	8		8		8		
COGS (%)	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
COGS (EUR MN)	0	-1	-1	-1	-1	-2	-1	-1	0	0	0
PROFIT BEFORE TAX (EUR MN)	**3**	**5**	**9**	**19**	**21**	**15**	**20**	**6**	**11**	**2**	**1**
TAX RATE (%)	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
TAXES (EUR MN)	-1	-1	-2	-4	-4	-3	-4	-1	-2	0	0
PROFIT (EUR MN)	**3**	**4**	**7**	**16**	**17**	**12**	**16**	**5**	**9**	**1**	**1**

UNITED STATES - SOLD BY BAUSCH HEALTH (FORMERLY VALEANT)	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
NUMBER OF PATIENTS (MN)	1.1	1.1	1.1	1.2	1.2	1.3	1.3	1.3	1.4	1.4	1.5
GROWTH (%)	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%	3%
PATIENT WITH MILD-TO-MODERATE DISEASE (85%)	0.9	0.9	1.0	1.0	1.0	1.1	1.1	1.1	1.2	1.2	1.2
PENETRATION (%)	4%	2%	2%	1%	1%	1%	0%	0%	0%	0%	0%
NUMBER OF PATIENTS (MN)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
COST OF THERAPY PER YEAR (EUR)	1,904	1,979	1,979	1,979	1,979	1,979	1,979	1,979	1,979	1,979	1,979
SALES (EUR MN) - BOOKED BY BAUSCH HEALTH	**82**	**53**	**38**	**27**	**20**	**14**	**10**	**7**	**5**	**4**	**3**
CHANGE (%)	-28%	-36%	-28%	-28%	-28%	-28%	-28%	-28%	-28%	-28%	-28%
ROYALTY (%) - 12% UP TO USD 120 MN, 14% ABOVE	11%	12%	12%	12%	12%	12%	12%	12%	12%	12%	12%
ROYALTIES (EUR MN)	9	6	5	3	2	2	1	1	1	0	0
MANUFACTURING INCOME (%)	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
MANUFACTURING INCOME (EUR MN)	8	5	4	3	2	1	1	1	1	0	0
UPFRONT & MILESTONE PAYMENTS (EUR MN)	0	0	0	0	0	0	0	0	0	0	0
COGS (%)	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
COGS (EUR MN)	0	0	0	0	0	0	0	0	0	0	0
PROFIT BEFORE TAX (EUR MN)	**17**	**11**	**8**	**6**	**4**	**3**	**2**	**2**	**1**	**1**	**1**
TAX RATE (%)	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
TAXES (EUR MN)	-3	-2	-2	-1	-1	-1	0	0	0	0	0
PROFIT (EUR MN)	**14**	**9**	**7**	**5**	**3**	**2**	**2**	**1**	**1**	**1**	**0**

	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
GLOBAL SALES (EUR MN)	**97**	**75**	**75**	**77**	**78**	**78**	**63**	**35**	**19**	**11**	**6**
CHANGE (%)	-23%	-23%	0%	2%	2%	0%	-19%	-45%	-44%	-43%	-41%
GLOBAL PROFIT (EUR MN)	**16**	**13**	**13**	**20**	**21**	**14**	**18**	**6**	**10**	**2**	**1**
CHANGE (%)	-29%	-19%	1%	50%	2%	-31%	25%	-65%	57%	-80%	-42%

WACC (%)	7%
NPV TOTAL PROFIT (CHF MN)	**106**
NUMBER OF SHARES (MN)	15.0
NPV PER SHARE (CHF)	**7**

SENSITIVITY ANALYSIS

		WACC (%)						
	CHF/SHARE	5.5	6.0	6.5	7.0	7.5	8.0	8.5
	300	15	15	14	14	20	20	20
	250	12	12	12	12	17	17	16
	200	10	10	10	9	13	13	13
PEAK SALES (EUR MN)	150	7	7	7	**7**	10	10	10
	100	5	5	5	5	7	7	7
	50	2	2	2	2	3	3	3
	0	0	0	0	0	0	0	0

SOURCE: VALUATIONLAB ESTIMATES

Unique Selling Point

Uceris is the first oral, locally acting, corticosteroid approved in the US for ulcerative colitis. It is a convenient once a day treatment for induction of remission in mild-to-moderate disease utilizing Cosmo's MMX technology. The safe side effect profile, due to its local mode of action, is an additional USP with the potential to be used in longer-term maintenance of remission.

7P's Analysis

Patent: Uceris/Cortiment is patent protected until 2020 by the MMX composition of matter (COM) patent (US7431943; EP1183014). Additional granted COM and method of use patents (e.g. US8895064, US9737489) should extend protection up to 2031. The active ingredient, the anti-inflammatory corticosteroid budesonide, is generically available. In July 2018, Actavis (Teva) launched “at risk” a generic version of Uceris, after receiving FDA approval and winning a non-infringement case in the US District Court. Bausch Health appealed the non-infringement case, which may overturn the initial ruling with the potential to receive “triple damages” from Actavis.

Phase: In January 2013, the FDA approved Uceris, shortly followed by the EMA (branded Cortiment in EU/ROW) and has been launched in the US and EU, respectively. Due to its safe side effect profile, Uceris could potentially be developed for maintenance treatment in mild-to-moderate ulcerative colitis. Additional clinical trials are needed for maintenance.

Pathway: Approved for induction of remission in patients with active mild-to-moderate ulcerative colitis. A bridging trial would be needed to gain approval for maintenance of remission in patients with active mild-to-moderate disease.

Patient: Uceris provides mild-to-moderate ulcerative colitis patients a convenient, once daily, fast and locally acting treatment for active disease. In particular, for those patients who no longer respond to standard mesalamine (5-ASA) treatment could benefit, without the long-term side effects seen with mainstay systemic corticosteroids.

Physician: In particular in the US, physicians now have another effective treatment to induce remission of mild-to-moderate disease, without having to use systemic corticosteroids with their dreaded (long-term) side effects. Patient compliance and efficacy could improve. Outside the US AstraZeneca’s Entocort, a cumbersome enema formulation of budesonide for treating ulcerative colitis is available, however, with a modest uptake.

Payer: A more effective treatment with few side effects that leads to less flares, hospitalizations, and surgery should reduce ulcerative colitis costs considerably, as drug costs are only a small portion of overall treatment costs (e.g. hospitalization, surgery, inability to work).

Partner: In the US, Cosmo receives tiered royalties of 12% up to annual Uceris sales of USD 120 mn and 14% above, and a manufacturing fee of 10% of net sales (all manufacturing at Cosmo) from Bausch Health. Ferring sells Cortiment (brand name outside the US) in the rest of the world (except Japan and Asia) with Cosmo receiving tiered royalties of 12-15% and a net manufacturing fee of 7% and undisclosed milestones. Cosmo expects to out license the drug to a specialty company for Japan and Asia.

Lialda / Mezavant - Ulcerative colitis

Product Analysis

Lialda/Mezavant sales peaked at USD 792 mn - NPV of CHF 5 per share

Sales of Lialda by Shire peaked at USD 792 mn in 2016 and are now in free fall due to US generic competition. The launch of a generic version of Lialda in the US by the Indian generic manufacturer Zydus adversely impacted Lialda sales. As a result, we base our forecasts and valuation on the amount of Lialda tablets Cosmo ships to its partners, in particular to Shire in the US. Lialda revenues for Cosmo largely consist of manufacturing fees from Shire, which will not be affected as much as the expected sales erosion caused by expected price drops of 30% in 2018 and again in 2020. Our NPV amounts to CHF 75 mn or CHF 5 per share, accounting for declining sales in the next ten years and a WACC of 7% reflecting the low Swiss interest environment.

Generic erosion has only a minor impact on Cosmo revenues

The approval of Lialda/Mezavant in 2007 was the first validation of Cosmo's proprietary MMX colon delivery technology. It was also the company's first prescription drug to reach the market. Lialda/Mezavant contains generic mesalamine, in a novel oral tablet formulation that utilizes the company's MMX technology. It was the first convenient once a day formulation of mesalamine on the market with the highest amount of mesalamine per tablet, which significantly reduces the frequency of dosing (once instead of 3-4 times a day) and the pill burden (2-4 tablets instead of 6-16) compared to competitor mesalamine products, which led to its success and validating Cosmo's MMX development approach.

Early licensing agreement funded other research projects at far better terms

Lialda/Mezavant was globally out-licensed to Giuliani and Shire Pharmaceuticals in 2001, in the early stage of Cosmo's existence and clinical development of the drug. This was in line with the company's strategy to share the risk and not to overstretch its financial reach. As a result, the licensing terms were rather poor with royalties on sales of 3.5% (with a cumulative cap of USD 95 mn on global sales - the US and EU cumulative cap of USD 80 mn was reached in 2014) and a manufacturing fee of 3%. Shire has rights to manufacture up to 20% of Lialda/Mezavant capacity, but this has proven difficult and Shire has not succeeded. This highlights Cosmo's manufacturing expertise and state-of-the-art facilities. On the positive side, Lialda/Mezavant's cash flows were used to fund other MMX projects such as Uceris, Rifamycin SV and MethyleneBlue and allowed the company to take on more risk over time by out-licensing these projects at a later stage of development with significantly better economics, and building an own direct US sales presence with Aries.

Stellar rise of Lialda thanks to its best-in-class profile but generics spoil the party

In 2007, Lialda/Mezavant was initially approved for induction of remission in patients with active, mild-to-moderate ulcerative colitis, followed by maintenance treatment in 2011. The convenient once a day dosing, with considerably less tablets, has been the key driver of growth and market penetration, achieving peak sales of USD 792 mn in 2016. Lialda was expected to enjoy protection for a few more years until 2020 when the MMX composition of matter patent would expire. However, after years of patent battles, the last legal barrier between Shire and a generic version of Lialda fell and the FDA approved a generic from the Indian generic manufacturer Zydus Cadila in June 2017. Zydus, which launched its generic, acquired “first-to-file” rights providing 6 months exclusivity. In FY 2018, Lialda manufacturing and royalty income declined by 18% to EUR 20.7 mn due to the launch of Zydus' generic in the US, which was partially offset by an increase in royalty income in Europe (Giuliani) and Japan (Nogra Pharma).

Limited impact for Cosmo and negligible effect on Cosmo's investment case

We do not expect other generics to enter the market until the MMX patent expiry in 2020, and only a few after this period. Given that Zydus is the only company that has performed clinical trials on Lialda, others may have difficulty of convincing the FDA to approve their generic versions before the MMX patent expiry. This class of drugs has proven extremely difficult to manufacture. For instance, there are still no generics for Shire's own ulcerative colitis drug Pentasa (mesalamine) that lost patent protection a decade ago. Therefore, we do not believe there will be many generic offerings post 2020, limiting the typical generic sales erosion decline. Cosmo is less affected as Lialda revenues are largely manufacturing fees from Shire, which are expected to decline less than pricing and sales. Given the relevant size of Lialda revenues for Cosmo, the impact is negligible for the company's investment case.

LIALDA / MEZAVANT - FINANCIAL FORECASTS FOR ULCERATIVE COLITIS

INDICATION	INDUCTION AND MAINTENANCE OF REMISSION FOR PATIENTS WITH ULCERATIVE COLITIS FO MILD TO MODERATE SEVERITY
DOSAGE	2.4 GRAMS/DAY (MAINTENANCE) OR 2.4-4.8 GRAMS/DAY (INDUCTION)
PRICING	US: 2 TABLETS PER DAY FOR 120 DAYS = USD 1,473 PER PATIENT; EU/ROW 2 TABLETS PER DAY FOR 120 DAYS = EUR 454 PER PATIENT
STANDARD OF CARE	GENERIC MESALAMINE / ASACOL (WARNER CHILCOTT)
UNIQUE SELLING POINT	ONLY ONCE-A-DAY DOSING (2-4 TABLETS), OTHER MESALAMINES REQUIRE 3-4 TIMES A DAY DOSING (6-16 TABLETS)

7PS ANALYSIS

PATENT	EXPIRY 2020 ("MMX" FORMULATION PATENT (USPTO: 7,431,943 - JUNE 2020)); INDIAN COMPANY ZYDUS RECEIVED US FDA APPROVAL FOR ITS GENERIC IN JUNE 2017
PHASE	LAUNCHED IN THE US BY SHIRE IN 2007 AND ROLLED OUT LATER IN THE EU; WE EXPECT NOGRA PHARMA TO LAUNCH IN JAPAN IN 2018
PATHWAY	ESTABLISHED REGULATORY PATHWAY - "MMX" SUSTAINED RELEASE FORMULATION OF GENERIC MESALAMINE
PATIENT	CONVENIENT ONCE-A-DAY DOSING SCHEDULE AND LOWER PILL LOAD COMPARED TO COMPETITORS
PHYSICIAN	BETTER PATIENT COMPLIANCE DUE TO ONCE-A-DAY DOSING SCHEDULE POTENTIALLY ENHANCING EFFICACY
PAYER	COST EFFECTIVE TREATMENT DUE TO IMPROVED PATIENT COMPLIANCE AND EFFICACY
PARTNER	US: SHIRE PHARMACEUTICALS I EU: GIULIANI SPA / LEHNER SA (SHIRE HAS EXCLUSIVE SELLING RIGHTS) I JAPAN: NOGRA PHARMA

REVENUE MODEL

BASED ON SHIPPED TABLETS	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
SHIRE SALES (USD MN)	279	237	141	120	102	87	74	63	53	45	38
GROWTH (%)	-51%	-15%	-41%	-15%	-15%	-15%	-15%	-15%	-15%	-15%	-15%
SHIRE PRICE PER TABLET (USD)	1.23	1.23	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86
CHANGE (%)	-30%	0%	-30%	0%	0%	0%	0%	0%	0%	0%	0%
NUMBER OF TABLETS SHIPPED BY COSMO (MN)	226	192	163	139	118	100	85	73	62	52	45
CHANGE (%)	-35%	-15%	-15%	-15%	-15%	-15%	-15%	-15%	-15%	-15%	-15%
COSMO PRICE PER TABLET (EUR)	0.082	0.082	0.082	0.082	0.082	0.082	0.082	0.082	0.082	0.082	0.082
COSMO MANUFACTURING INCOME (EUR MN)	18	16	13	11	10	8	7	6	5	4	4
CHANGE (%)	-23%	-15%	-15%	-15%	-15%	-15%	-15%	-15%	-15%	-15%	-15%

	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
GLOBAL SALES (EUR MN)	237	209	125	106	90	76	65	55	47	45	38
CHANGE (%)	-51%	-12%	-41%	-15%	-15%	-15%	-15%	-15%	-15%	-4%	-15%
GLOBAL PROFIT (EUR MN)	18	16	13	11	10	8	7	6	5	4	4
CHANGE (%)	-23%	-15%	-15%	-15%	-15%	-15%	-15%	-15%	-15%	-15%	-15%

WACC (%)	7%
NPV TOTAL PROFIT (CHF MN)	75
NUMBER OF SHARES (MN)	15.0
NPV PER SHARE (CHF)	5

ESTIMATES AS OF 3 JUNE, 2019

SOURCE: VALUATIONLAB ESTIMATES

With Zydus' recent launch of its FDA approved generic version of Lialda in the US, we have based our revenue forecasts for Lialda on tablets shipped by Cosmo to Shire and partners. In 2019, we expect a 15% decline in the number of tablets shipped to Shire. We expect Shire to offer wholesalers a 30% price discount for Lialda to mitigate Zydus' price discount. Once more generics enter the market in 2020, we expect another price cut of 30% and an annual 15% decline in tablet shipments. We calculate an NPV of CHF 75 mn or CHF 5 per share for Lialda based on sales forecasts until 2028.

Ulcerative Colitis Market

The ulcerative colitis market value is around USD 3 bn and is expected to grow to USD 6.6 bn in 2022. The 5-ASA market is worth around USD 1.7 bn due to the lack of new branded treatments. Mainstay drugs are largely generically available. The market is set to grow due to the increased use of new, expensive, "last resort" biologic therapies (e.g. Humira, Simponi) and the launch of Uceris, a new oral, locally acting formulation of the off-patent corticosteroid budesonide. Ulcerative colitis is a costly disease. The combined direct (medication, hospitalization, surgery) and indirect cost (inability to work) is estimated to be between USD 8-15 bn per year in the US, and EUR 12.5-29 bn per year in Europe.

ULCERATIVE COLITIS - KEY FACTS	
MARKET SIZE	USD ~3BN, 5-ASA MARKET USD ~1.7 BN
PREVALENCE	~3 MN GLOBALLY, ~1 MN US, ~1.1 MN EU/ROW (114-505 CASES PER 100,000 INDIVIDUALS/YEAR
INCIDENCE	6.3 - 24.3 CASES PER 100,000 OF INDIVIDUALS PER YEAR
UNDERLYING CAUSE	UNKNOWN - INFLAMMATION AND ULCERS ALONG THE LINING OF THE LARGE INTESTINE (COLON) AND RECTUM THOUGHT TO BE RELATED TO ABNORMAL IMMUNE RESPONSE IN THE GASTROINTESTINAL TRACT, POSSIBLY ASSOCIATED WITH FOOD OR BACTERIA, E.G. ESCHERICHIA COLI - STRESS (NOT A CAUSE) INCREASES SEVERITY OF ATTACK
SYMPTOMS	- HALLMARK SYMPTOM IS RECURRENT ATTACKS OF BLOODY DIARRHEA (15-20 PER DAY) - SPASTIC RECTUM AND ANUS - ABDOMINAL PAIN, CRAMPING AND SOUNDS - IRRITABILITY, FEVER, WEIGHT LOSS, ANOREXIA, NAUSEA AND VOMITING
DRUG CLASS (KEY BRANDS)	MILD DISEASE (40-55% OF PATIENTS) - ANTISPASMODICS (TINCTURE OF BELLADONA) - ANTIDIARRHEALS (IMMODIUM) - ANTIBIOTICS (METRONIDAZOLE, AMPICILLIN, CIPROFLOXIN) - 5-ASA COMPOUNDS (SULFAZINE, MESALAMINE, PENTASA, ASACOL HD, APRISO, LIALDA) MODERATE DISEASE (30-35% OF PATIENTS): - CORTICOSTEROIDS (UCERIS, PREDNISONE, PREDNISOLONE, HYDROCORTISONE) SEVERE DISEASE (15-25% OF PATIENTS): - THIOPURINE (IMMUNOSUPPRESSANT) / METHOTREXATE - LAST RESORT DRUGS - ANTI-TNF (REMICADE, HUMIRA, SIMPONI) - LAST RESORT DRUGS - SURGERY - LAST RESORT THERAPY
MAJOR PLAYERS (KEY BRANDS)	- WARNER CHILCOTT (ASACOL HD) - SHIRE / GUILIANI / COSMO PHARMA (LIALDA / MESAVANT) - BAUSCH HEALTH (APRISO) - ASTRAZENECA (ENTOCORT ENEMA) - BAUSCH HEALTH / FERRING / COSMO PHARMA (UCERIS / CORTIMENT) - ABBVIE (HUMIRA) - JOHNSON & JOHNSON (REMICADE, SIMPONI)

SOURCE: VALUATIONLAB, NIH, CCFA, NEJM, ASG, WORLD GASTROENTEROLOGY ORGANIZATION

Ulcerative colitis affects an estimated 3 million people globally with around 1 mn patients in the US and 1.1 mn in the EU. The disease is a form of inflammatory bowel disease (IBD) that affects the inside lining of the large intestine (colon) and rectum and includes characteristic ulcers or open sores. The cause of ulcerative colitis is unknown. People with this condition have problems with the immune system, but it is not clear whether immune problems cause the illness. Although stress and certain foods can trigger symptoms, they do not cause ulcerative colitis. This disease may affect any age group, although there are peaks at ages 15-30 and then again at ages 50-70. The main symptom of active disease is usually constant diarrhea mixed regularly with blood. Ulcerative colitis is an intermittent disease with periods (weeks) of exacerbated symptoms and periods that are relatively symptom-free.

There are four stages of disease severity:

1) **Mild disease**, in which the patient has fewer than four stools daily, with or without blood and no systemic signs of toxicity. There may be mild abdominal pain or cramping. There is a constant feeling of the need to empty the bowel accompanied by involuntary straining efforts, pain and cramping.

2) **Moderate disease**, which correlates with more than four stools daily, but with minimal signs of toxicity. Patients may display anemia, moderate abdominal pain and low-grade fever.
3) **Severe disease**, which correlates with more than six bloody stools a day or observable massive and significant bloody bowel movement and evidence of toxicity (fever, rapid heart rate, anemia, elevated erythrocyte sedimentation rate)
4) **Fulminant disease**, with more than ten bowel movements daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion required and colonic expansion. The inflammation extends beyond the lining of the intestine and can lead to colonic perforation. Unless treated, fulminant disease can be fatal.

Colonoscopy with biopsy is the best test to confirm the diagnosis. Colonoscopy is also used to screen people with ulcerative colitis for colon cancer. Ulcerative colitis increases the risk of colon cancer. Patients with ulcerative colitis should be screened with colonoscopy about 8-12 years after being diagnosed and have follow-up colonoscopy every 1-2 years.

Drug treatment aims to induce remission followed by prevention of disease relapse
Because the cause of ulcerative colitis is unknown there is no cure. The primary aim of drug treatment is to induce remission initially (relieve symptoms and healing of the lining of the colon), followed by maintenance drugs to prevent a relapse of the disease. The drugs used to induce and maintain a remission somewhat overlap, but the treatments are different. Physicians use a stepped approach according to the severity of disease.

Prescription drugs used to treat UC include:
Aminosalicylates (5-ASAs): This class of anti-inflammatory drugs is typically used to treat mild-to-moderate ulcerative colitis symptoms (induction of remission) and help prevent relapses (maintenance). They include sulfasalazine and oral formulations of mesalamine.
Corticosteroids: Also known as steroids, drugs such as prednisone, methylprednisolone, and hydrocortisone also reduce inflammation and are used to treat moderate-to-moderate ulcerative colitis (induction of remission). Corticosteroids suppress the immune system and are not recommended for long-term use because of severe side effects.
Immune modifiers: These drugs, such as azathioprine are used to help decrease corticosteroid usage. They lessen the inflammatory response caused by ulcerative colitis by working on the body's immune system.
Biologic therapies: Biologic therapies, such as the tumor necrosis factor-alpha (TNF-alpha) inhibitors, are the newest class of drugs used for people with moderate-to-severe ulcerative colitis who do not respond to conventional therapy. Biologic drugs are administered by injection or infusion and are very expensive.

New market entrants and increased diagnosis expected to spark market growth
The expanding number of diagnosed prevalent cases of ulcerative colitis should drive the underlying market growth. Cosmo's **Uceris/Cortiment** should boost growth in the mild-to-moderate segment. The uptake of two premium-priced TNF-alpha inhibitors (Abbvie/Eisai's **Humira** (adalimumab) and Johnson&Johnson/Merck&Co's **Simponi** (golimumab)), and two novel therapies, Takeda's anti-integrin inhibitor **Entyvio** (vedoluzumab) and Pfizer's oral Janus-activated kinase (JAK) inhibitor **Xeljanz** (tofacitinib – approved May 2018 by FDA) should primarily drive growth in the moderate-to-severe market segment.

Income Statement

COSMO PHARMACEUTICALS											SHARE PRICE (CHF) 97.60
IFRS											
INCOME STATEMENT (EUR MN)	2018	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
PRODUCT SALES (INCL. PARTNER SALES)	341	324	435	726	1,045	1,391	1,648	1,801	1,841	1,750	1,403
CHANGE (%)	-44%	-5%	34%	67%	44%	33%	19%	9%	2%	-5%	-20%
PRODUCT REVENUES (ARIES PHARMA / DISTRIBUTORS)	7	10	69	118	236	420	625	810	921	960	701
CHANGE (%)	331%	43%	608%	73%	100%	78%	49%	30%	14%	4%	-27%
TOTAL MANUFACTURING FOR THIRD PARTIES:	38.515	32	30	27	27	29	32	32	33	34	24
CHANGE (%)	-16%	-16%	-9%	-8%	-3%	11%	9%	0%	3%	1%	-29%
1) MANUFACTURING OF MMX PRODUCTS	27.515	22	19	17	16	19	22	22	23	23	14
CHANGE (%)	-24%	-19%	-13%	-12%	-5%	18%	14%	1%	5%	1%	-42%
2) MANUFACTURING OF GENERICS AND SPECIALTY DRUGS	7.775	7	7	7	7	7	7	7	7	7	7
CHANGE (%)	-6%	-10%	0%	0%	0%	0%	0%	0%	0%	0%	0%
3) RELATED SERVICES	2.280	2	2	2	2	2	2	2	2	2	2
CHANGE (%)	216%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
4) OTHER REVENUES FROM SALES	0.945	1	1	1	1	1	1	1	1	1	1
CHANGE (%)	17%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
CONTRACT MANUFACTURING & OTHER (EUR MN)	11	10	10	10	10	10	10	10	10	10	10
LICENCE AND UPFRONT FEES AND MILESTONES	6	1	30	18	18	0	33	5	8	15	0
ROYALTIES TO COSMO	15	17	43	99	145	176	183	172	154	118	123
CHANGE (%)	-24%	17%	149%	132%	46%	22%	4%	-6%	-11%	-23%	4%
TOTAL REVENUES (COSMO)	66	60	171	263	426	626	873	1,020	1,116	1,126	848
CHANGE (%)	-4.1%	-8.1%	183.7%	53.8%	61.8%	47.0%	39.5%	16.8%	9.4%	0.9%	-24.7%
COGS	-22	-24	-26	-28	-35	-46	-58	-68	-74	-77	-63
CHANGE (%)	0%	8%	9%	9%	22%	32%	26%	17%	10%	3%	-18%
GROSS PROFIT	44	36	145	235	391	580	815	952	1,042	1,050	785
CHANGE (%)	-6%	-17%	299%	62%	67%	48%	41%	17%	9%	1%	-25%
MARGIN (%)	66.4%	60.3%	84.7%	89.2%	91.9%	92.7%	93.4%	93.4%	93.4%	93.2%	92.6%
R&D	-10	-17	-21	-12	-11	-11	-12	-12	-13	-13	-14
CHANGE (%)	15%	67%	19%	-44%	-11%	5%	5%	4%	4%	4%	4%
S,G&A	-51	-22	-59	-89	-160	-165	-184	-219	-233	-239	-190
CHANGE (%)	9%	-57%	174%	50%	80%	3%	11%	19%	6%	2%	-20%
AS % OF REVENUES	77.2%	35.8%	34.7%	33.8%	37.6%	26.4%	21.0%	21.5%	20.9%	21.2%	22.4%
OTHER OPERATING INCOME / (EXPENSES)	1	1	1	1	1	1	1	1	1	1	1
NET OPERATING EXPENSES	-82	-62	-105	-128	-205	-221	-252	-298	-319	-328	-266
CHANGE (%)	7%	-25%	70%	22%	59%	8%	14%	18%	7%	3%	-19%
SHARE OF RESULT OF ASSOCIATES	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5
EBIT	-22.074	-7	60	129	216	399	616	716	791	793	577
CHANGE (%)	54%	-67%	-929%	115%	67%	85%	54%	16%	11%	0%	-27%
MARGIN (%)	-33.6%	-12.1%	35.2%	49.2%	50.7%	63.8%	70.5%	70.2%	70.9%	70.4%	68.0%
EBITDA	-18	-2	65	135	222	406	623	724	800	802	587
CHANGE (%)	63%	-86%	-2801%	106%	64%	83%	53%	16%	10%	0%	-27%
MARGIN (%)	-26.8%	-4.0%	38.3%	51.3%	52.1%	64.8%	71.3%	71.0%	71.7%	71.2%	69.2%
NET FINANCIAL INCOME / (EXPENSES)	5	-4	-4	-4	-4	-4	5	5	5	5	5
PROFIT BEFORE TAXES	-17	-11	56	125	212	395	620	721	796	798	582
CHANGE (%)	-44%	-35%	-592%	123%	69%	87%	57%	16%	10%	0%	-27%
TAXES	-1	-1	-2	-2	-30	-67	-111	-131	-147	-148	-105
TAX RATE (%)	-3.4%	-5.6%	2.8%	1.3%	14.3%	17.0%	17.8%	18.2%	18.5%	18.6%	18.1%
NET PROFIT/(LOSS)	-18.057	-12	54	124	181	328	510	590	649	650	476
CHANGE (%)	-42%	-33%	-553%	127%	47%	81%	55%	16%	10%	0%	-27%
MARGIN (%)	-27.5%	-20.0%	31.9%	47.0%	42.6%	52.4%	58.4%	57.8%	58.2%	57.7%	56.2%
PROFIT/(LOSS) PER SHARE (IN EUR)	-1.20	-0.80	3.63	8.23	12.09	21.86	33.96	39.29	43.26	43.30	31.75
PROFIT/(LOSS) PER SHARE (IN CHF)	-1.36	-0.91	4.11	9.31	13.67	24.72	38.40	44.43	48.92	48.97	35.90

ESTIMATES AS OF 3 JUNE, 2019 SOURCE: VALUATIONLAB ESTIMATES STIMATES

FY 2019 guidance:

- **Traditional contract manufacturing & other revenue** EUR 10 mn
- **Products manufacturing** EUR 26 mn
- **Royalties** EUR 10 mn
- **License fees, up-front fees and milestones** EUR 1 mn
- **Aries US sales** EUR 13 mn
- **Total Revenues** **EUR 60 mn**
- **Operating Expenses** EUR 72 mn
- **Operating loss** **EUR 12 mn**

Ratios & Balance Sheet

COSMO PHARMACEUTICALS SHARE PRICE (CHF) 97.60

IFRS

RATIOS	2018	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
P/E		-107.6x	23.8x	10.5x	7.1x	3.9x	2.5x	2.2x	2.0x	2.0x	2.7x
P/S		21.5x	7.6x	4.9x	3.0x	2.1x	1.5x	1.3x	1.2x	1.1x	1.5x
P/NAV		3.0x	2.7x	2.1x	1.6x	1.2x	0.8x	0.6x	0.5x	0.4x	0.3x
EV/EBITDA		-558.5x	20.7x	10.0x	6.1x	3.3x	2.2x	1.9x	1.7x	1.7x	2.3x

PER SHARE DATA (CHF)	2018	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
EARNINGS	**-1.36**	**-0.91**	**4.11**	**9.31**	**13.67**	**24.72**	**38.40**	**44.43**	**48.92**	**48.97**	**35.90**
CHANGE (%)	-44%	-33%	-553%	127%	47%	81%	55%	16%	10%	0%	-27%
CASH	**15.88**	**13.88**	**18.50**	**28.36**	**44.76**	**61.84**	**109.11**	**164.01**	**224.63**	**285.43**	**329.99**
CHANGE (%)	41%	-13%	33%	53%	58%	38%	76%	50%	37%	27%	16%
DIVIDENDS	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
PAYOUT RATIO (%)	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
NET ASSET VALUE	**33.53**	**32.62**	**36.73**	**46.04**	**59.70**	**84.43**	**122.83**	**167.26**	**216.18**	**265.15**	**301.05**
CHANGE (%)	-8%	-3%	13%	25%	30%	41%	45%	36%	29%	23%	14%

BALANCE SHEET (EUR MN)	2018	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
NET LIQUID FUNDS	**211**	**184**	**245**	**376**	**594**	**821**	**1,448**	**2,176**	**2,981**	**3,787**	**4,378**
TOTAL ASSETS	**560**	**534**	**595**	**726**	**944**	**1,170**	**1,797**	**2,526**	**3,330**	**4,137**	**4,728**
TOTAL SHAREHOLDERS' EQUITY	**445**	**433**	**487**	**611**	**792**	**1,120**	**1,630**	**2,219**	**2,868**	**3,518**	**3,995**
- CHANGE IN %	-6%	-3%	13%	25%	30%	41%	45%	36%	29%	23%	14%
- RETURN ON EQUITY	-4%	-3%	11%	20%	23%	29%	31%	27%	23%	18%	12%
TOTAL EQUITY	**445**	**433**	**487**	**611**	**792**	**1,120**	**1,630**	**2,219**	**2,868**	**3,518**	**3,995**
FINANCIAL DEBT	**158**	**142**	**128**	**115**	**104**	**93**	**84**	**76**	**68**	**61**	**55**
EMPLOYEES	306	275	248	223	201	181	163	146	132	119	107
- CHANGE IN %	*2%*	*-10%*	*-10%*	*-10%*	*-10%*	*-10%*	*-10%*	*-10%*	*-10%*	*-10%*	*-10%*

CASH FLOW STATEMENT (EUR MN)	2018	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
PROFIT / (LOSS) BEFORE TAXES	-17	-11	56	125	212	395	620	721	796	798	582
DEPRECIATION & AMORTIZATION	4	5	5	6	6	7	7	8	8	9	10
OTHER NON-CASH ITEMS	3	0	0	0	0	0	0	0	0	0	0
CASH FLOWS FROM OPERATING ACTIVITIES	**-10**	**-7**	**61**	**131**	**218**	**402**	**627**	**728**	**804**	**807**	**591**
CASH FLOWS FROM INVESTING ACTIVITIES	-72	-20	0	0	0	0	0	0	0	0	0
FREE CASH FLOW	**-82**	**-27**	**61**	**131**	**218**	**402**	**627**	**728**	**804**	**807**	**591**
CASH FLOWS FROM FINANCING ACTIVITIES	144					-175					
NET FOREIGN EXCHANGE DIFFERENCES	3										
CHANGE IN LIQUID FUNDS	**62**	**-27**	**61**	**131**	**218**	**227**	**627**	**728**	**804**	**807**	**591**

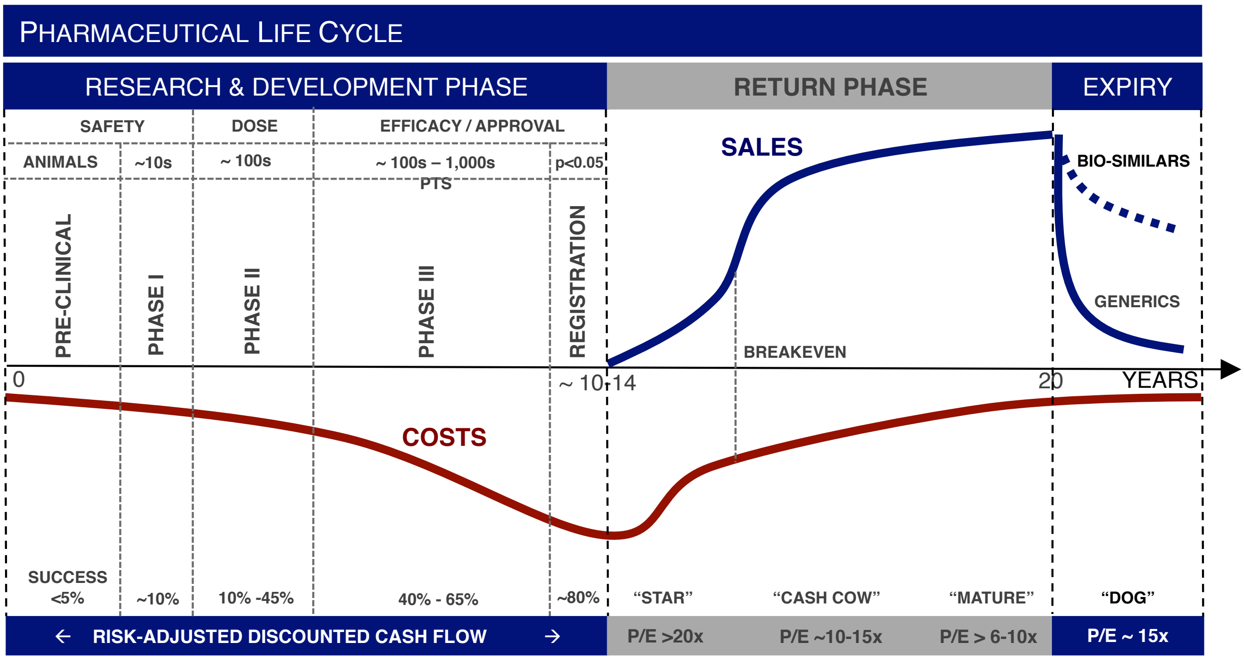
ESTIMATES AS OF 3 JUNE, 2019 SOURCE: VALUATIONLAB ESTIMATES

As of 6 May 2019, Cosmo has a net cash position of EUR 348 mn (including the EUR 175 mn convertible bond). The convertible bond financing was initially aimed to build up a commercial infrastructure and to scale up the new AI business. This is no longer necessary following the global Medtronic distribution agreement that provides substantial marketing muscle for the AI business. The substantial cash position is targeted to expand Cosmo's product offering through external transactions.

APPENDIX

Pharmaceutical life cycle

To determine the value of a prescription (bio)pharmaceutical compound, it is critical to understand its life cycle. Fortunately, all compounds follow the same life cycle. The clock starts ticking after the compound is patented, providing 20 years of protection from generic competition. Market exclusivities can extend this protection period. The average Research & Development Phase takes 10-14 years, leading to an effective Return Phase of 6-10 years. The Development Phase has 3 distinct Phases, focused on safety (Phase I), dose (Phase II) and efficacy/clinical benefit (Phase III). The compound is filed for registration/approval at the FDA (US) or EMA (EU). The Return Phase is characterized by a star, cash cow, and mature phase. After patent expiry (or loss of market exclusivity) generic manufacturers may copycat the branded prescription drug, at significantly lower costs, leading to a sales and earnings implosion of the branded drug.



SOURCE: VALUATIONLAB

Success probabilities & royalties

In our risk-adjusted NPV calculations, we use standardized success probabilities based on historical clinical success rates. The success rate increases as the project progresses through development. Sales and earnings forecasts are based on the clinical and competitive profile of the compound. The more advanced the compound is, the more accurate the forecasts become as the target market can be defined. We conservatively exclude projects that lack Phase IIa proof-of-concept data in our valuations.

SUCCESS PROBABILITIES & ROYALTIES

DEVELOPMENT STAGE	AIM	WHAT / WHO	SUCCESS PROBABILITY (%)	COSTS (USD MN)	ROYALTIES (%)
PRE-CLINICAL	SAFETY & PHARMACOLOGY DATA	LAB TESTS / ANIMALS - NO HUMANS!	< 5	3	
PHASE I	SCREENING FOR SAFETY	HEALTHY VOLUNTEERS (10'S)	5-15	3	< 5
PHASE IIA	PROOF-OF-CONCEPT	PATIENTS WITH DISEASE (10'S)	10-20		
PHASE II	ESTABLISH THE TESTING PROTOCOL	PATIENTS WITH DISEASE (100'S)	15-35	5	5-15
PHASE IIB	OPTIMAL DOSAGE	PATIENTS WITH DISEASE (100'S)	20-45	5-10	
PHASE III	EVALUATE OVERALL BENEFIT/RISK	PATIENTS WITH DISEASE (1,000'S)	40-65	> 20-1,000	10-25
REGULATORY FILING	DETERMINE PHYSICIAN LABELING	CLINICAL BENEFIT ASSESSMENT	80-90		
APPROVAL	MARKETING AUTHORIZATION	PHYSICIANS FREE TO PRESCRIBE	100		15-30

SOURCE: VALUATIONLAB, TUFTS, FDA, EMA, CLINICALTRIALS.GOV

Important Research Disclosures

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Our financial analyses are based on the "Directives on the Independence of Financial Research" issued by the Swiss Bankers Association in January 2008.

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Risk Analysis

Speculative	less than 1 year cash and breakeven beyond 1 year
High Risk	profitable within 2 years and 1 approved product/key indication (patent expiry > 5 years)
Medium Risk	profitable and/or sales from at least 2 marketed products/key indications (patent expiry > 5 years)
Low Risk	profitable and sales from >2 marketed products/key indications (patent expiry > 5 years)

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