EDISON

Crossject

Outlook

Adding asthma

Pharma & biotech

Crossject has developed a deep pipeline of products that are based on its proprietary needle-free injection system, Zeneo, across a variety of indications, with a focus on emergency-related areas. In addition to avoiding needles, Zeneo provides a simple and quick (~1/10th of a second) delivery of the drug. Recently, the company has added Zeneo Terbutaline for the acute treatment of exacerbations in severe asthmatics. This is a large market (~2.5m in the US) in need of better choices for patients.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/15	2.4	(6.7)	(0.85)	0.0	N/A	N/A
12/16	1.4	(7.3)	(0.85)	0.0	N/A	N/A
12/17e	2.9	(8.8)	(0.75)	0.0	N/A	N/A
12/18e	0.0	(12.0)	(1.03)	0.0	N/A	N/A

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

US partnership possible by year-end 2017

Crossject expects to license its lead product Zeneo Sumatriptan for the acute treatment of migraine in the US by YE17. Ease of use and fast onset should be key selling points for the product. Additionally, a tender process for US rights for Zeneo Midazolam for the acute treatment of epilepsy is expected to begin by year-end.

Entering the asthma attack market

Crossject recently announced the addition of Zeneo Terbutaline for the acute treatment of asthma exacerbations in severe asthmatics to its pipeline of emergency medicine products. There are 24.6 million asthmatics in the US, with 10% of them considered severe. While most rescue medications for those with asthma attacks are inhaled, Zeneo Terbutaline would have the advantage of a quicker onset of action and potentially a more convenient mode of administration. Regulatory filings are expected in 2020.

Manufacturing and clinical development delays

Due to anomalies in the production of ready-to-fill tubes at Crossject's plant in Dijon, the timeline for its ability to make clinical batches has been pushed back from Q217 to early 2018. As such, the clinical studies for the adrenaline, midazolam and sumatriptan products have been pushed back from 2017 to 2018 and their launch timelines affected as well (six to 12 months for most programs).

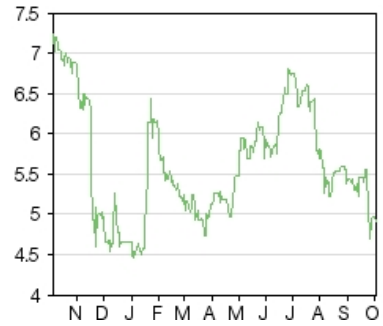
Valuation: €121m or €13.72 per share

We have increased our valuation for Crossject from €87.4m or €9.91 per basic share to €121m or €13.72 per basic share. This was almost entirely due to the inclusion of Zeneo Terbutaline in the pipeline and an increase in our expectations for Zeneo Naloxone and was mitigated by delayed launch timelines and a lower cash balance. As of H117, the company has a cash position of €6.1m and expects to receive an additional €5.9m by year-end 2018. Between now and projected profitability in 2020, we forecast a total funding need of €20m.

3 October 2017

Price	**€4.90**
Market cap	**€43m**
Net debt (€m) at 30 June 2017	2.9
Shares in issue	8.8m
Free float	72.3%
Code	ALCJ
Primary exchange	Euronext
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(9.8)	(26.9)	(32.3)
Rel (local)	(13.5)	(29.2)	(43.9)
52-week high/low		€7.2	€4.4

Business description

Crossject has several programmes in development based on its proprietary needle-free injection system, Zeneo. The first to market will be Zeneo Sumatriptan, which the company expects to be commercialised in 2020. Over the course of 2020 and 2021, Crossject expects to launch proprietary versions of six other products on its Zeneo platform.

Next events

Zeneo Sumatriptan partnership	Q417

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Edison profile page

Investment summary

Company description: A platform company with a deep pipeline

Crossject is a needle-free specialty pharmaceutical company that was founded in Dijon, France, in 2001 as a spinout from Fournier Laboratories (which has since been acquired by Abbott) and went public on the Paris exchange in 2014 in a €17m offering. It is a low overhead company with 60 employees.

Crossject has eight programmes in development, all using its proprietary needle-free injection system, Zeneo. The pipeline has been prioritised in favour of emergency products and with a focus on the US market. Key products include Zeneo Sumatriptan for the acute treatment of migraine, Zeneo Midazolam for the acute treatment of epileptic seizures and Zeneo Adrenaline for anaphylactic shock, with anticipated regulatory submissions in 2019. Crossject recently announced the addition of Zeneo Terbutaline for the treatment of severe asthma to its pipeline. The company already has a global partnership (for Zeneo Adrenaline) as well as regional partnerships in France, India and China (for Zeneo Methotrexate) and is currently focused on signing US partners, first for Zeneo Sumatriptan by the end of 2017 and then for Zeneo Midazolam.

Valuation: €121m or €13.72 per share

We have increased our valuation for Crossject from €87.4m or €9.91 per basic share to €121m or €13.72 per basic share. This is almost entirely due to the inclusion of Zeneo Terbutaline into the pipeline and an increase in our expectations for Zeneo Naloxone and was mitigated by delayed launch timelines and a lower cash balance. Zeneo Terbutaline has taken the place of Zeneo Apomorphine for Parkinson's disease, which is still alive but deprioritised (we now expect launch in 2022 instead of 2020). We had applied a lower probability of success for Zeneo Apomorphine as it does not treat an emergency related condition, which is where the company has been focused, so the impact of the de-emphasis is minimal. Also, much of our valuation is dependent upon successful launches in the US as pricing in Europe, according to company comments, will likely be a fraction of that in the US and in the rest of the world. Potential catalysts will likely include the announcement of additional partnerships for Crossject's various products, especially in the US.

Financials

As of 30 June 2017, Crossject had €6.1m in cash and cash equivalents on hand, up from €2.6m as of year-end 2016 as well as €3.2m in long-term debt. It successfully completed a €5m rights offering in March 2017 and received a €1.7m payment from Bpifrance's Programme des Investissements d'Avenir (PIAVE). Crossject expects to receive an additional €5.9m by year-end 2018. Between now and projected profitability in 2020, we forecast a total funding need of €20m. This requirement would be mitigated somewhat by additional upfront payments from partners as well as milestone payments upon product approvals.

Sensitivities: Commercialisation risk prevails

As Crossject is focusing on well characterised and approved generic drugs, there should be very little clinical risk, with only positive bioequivalence and device usability studies likely needed in healthy volunteers. The main risk will come on the commercialisation front, as Crossject is completely dependent upon partners to market the products. In addition, Crossject is generally focused on areas that are heavily genericised with multiple dosage forms available. In the case of sumatriptan, there are oral, injectable (both with a needle and needle-free) and intranasal forms available. Making headway may be extremely difficult and will likely depend heavily on physician

and patient preference. However, Crossject diversifies the commercialisation risks and its dependence on any single product by having a deep product pipeline, with the total cost of developing each product estimated to be in the €4-6m range.

A productive platform

Crossject's proprietary needle-free injection platform, Zeneo, can be used for up to 200 drugs (both small molecule and biologic) that the company has identified, although currently the company is focusing mainly on acute treatments where ease of use and the speed of treatment is an important factor for patients. The current plan is for regulatory submissions to begin in the 2019 timeframe (see Exhibit 1), which is a delay from the previous expectation of 2018 due to production anomalies related to Crossject's ready-to-fill tubes.

Exhibit 1: Crossject pipeline

Product	Indication	Previous expectation for submission (EU)	Current expectation for submission (US/EU)	Notes
Sumatriptan	Acute migraine	H118	H119	Bioequivalence study expected to be completed in 2018
Midazolam	Acute epilepsy seizures	H218	H219	Bioequivalence study given regulatory go-ahead and expected to be completed in 2018
Epinephrine/adrenaline	Anaphylactic shock	H218	H219	Bioequivalence study expected to be completed in 2018
Methotrexate	Rheumatoid arthritis	H218	H120	Bioequivalence study completed
Hydrocortisone	Acute adrenal insufficiency	H218	H219	Bioequivalence study expected to be completed in 2018
Naloxone	Opioid overdose	H218	H219	Expect to confirm formulation and pre-stability studies and receive regulatory authorisation for bioequivalence studies
Terbutaline	Severe asthma	N/A	2020	Expect to confirm formulation and pre-stability studies
Apomorphine	Parkinson's disease	H119	2021	Expect to confirm formulation and pre-stability studies

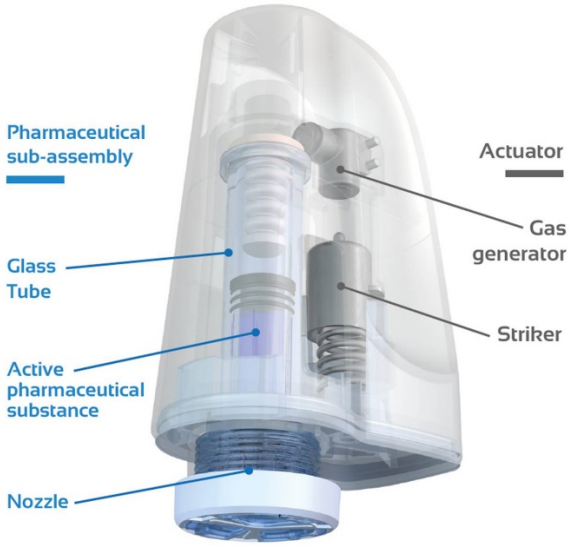
Source: Crossject, Edison Investment Research estimates

Broadly, Zeneo offers a number of advantages over conventional syringes:

- Greater compliance, as Zeneo has been designed to reduce human factor risk on self-administration. For example, there is less risk of going too deep or not deep enough – just place and push down.
- A very fast ~1/10th of a second injection, instead of a possibly prolonged push on the needle.
- Eliminates risk of needle injury during use and/or disposal. While there is no data on needle injuries among patients, the Centers for Disease Control (CDC) estimates that there are 385,000 needlestick injuries per year among hospital-based personnel alone.
- Avoids needle-phobia/aversion. The number of people with needle-phobia is unknown. Historically, 10%[1] of people were thought to be needle-phobic, however more recent data suggest an even higher prevalence. In a study of 400 travellers visiting a travel health clinic, 21.7%[2] indicated being afraid of injections. In a study of 177 patients at a general practice in Australia, 22.0% indicated a fear of needles and 20.5%[3] of those reported having fainted.
- In total, Zeneo allows for a very easy-to-use and simple injection process driving a greater acceptance of self-injection.

1 Hamilton J et al. *Journal of Family Practice*, 1995;41-169-75
2 Nir Y et al. *American Journal of Tropical Medicine and Hygiene*, 2003;68:341-4
3 Wright S et al. *Australian Family Physician*, 2009; Vol. 38, No. 3, March 2009

Exhibit 2: The Zeneo device



Source: Crossject

The device itself is disposable, pre-filled and single-use. It generally works in a similar fashion to other needle-free devices as it involves an energy source (gas), a volume of drug and a nozzle. However, unlike other systems, the gas to power the drug through the skin is generated at the time of injection through a controlled chemical process. This avoids the need for special storage and transportation of a pressurised system. In addition, unlike certain other needle-free technologies, such as powder-based injection systems, no reformulation of the reference product is needed, making both clinical development and commercial manufacturing cheaper and easier. It is also adaptable to various product viscosities and can be discharged subcutaneously, intramuscularly or intradermally. The mechanism was adapted from airbag systems technology and can be manufactured in a mass and low-cost fashion. It is covered by over 400 patents, with patent protection running into 2036.

A quick treatment for migraines: Zeneo Sumatriptan

Migraines are a very common and debilitating ailment often lasting between four and 72 hours, with prevalence of around 13% in the US[4] and around 15%[5] in the EU, totalling over 100 million sufferers across the two regions. Sumatriptan was the first drug within the triptan class available for the treatment of migraines and has been the standard of care since. There are a number of different dosage forms available, including traditional injectable, needle-free, nasal, patch, oral tablet and oral melt (see Exhibit 3). The oral forms together dominate the market, accounting for over 95% of all doses according to Symphony Health. Injectable forms (both traditional and needle-free) are less than 3% of the market despite having a much faster onset of action, with migraine relief coming in a matter of minutes instead of a matter of hours.

4 Victor T et al., *Cephalalgia* 2010 Sep;30(9):1065-72

5 Stovner L et al., *Journal of Headache Pain* (2010) 11:289-299

Exhibit 3: Triptan competitive landscape for migraine

Drug	Brand	Route of administration	Time to peak concentration (Tmax)	Relief at 1 hour	Relief at 2 hours
Sumatriptan	Sumavel DosePro	Needle-free	12 minutes	70%	81-82%
Sumatriptan	Imitrex	Autoinjector pen	12 minutes	70%	81-82%
Sumatriptan	Zeneo Sumatriptan	Needle-free	N/A*	N/A*	N/A*
Sumatriptan	Imitrex	Nasal	N/A	38-46%	43-64%
Zolmitriptan	Zomig	Nasal	3 hours	60%	69-70%
Sumatriptan	Zecuity	Patch	1.1 hours	N/A	53%
Zolmitriptan	Zomig-ZMT	Oral melting tablet	3 hours	33-43%	63%
Rizatriptan	Maxalt-ZMT	Oral melting tablet	1.6-2.5 hours	38-43%	59-74%
Sumatriptan	Imitrex	Oral	2-2.5 hours	28-36%	50-62%
Sumatriptan + naproxen sodium	Treximet	Oral	1 hour	28%	57-65%
Zolmitriptan	Zomig	Oral	1.5 hours	35-45%	59-67%
Rizatriptan	Maxalt-ZMT	Oral	1-1.5 hours	38-43%	60-77%
Naratriptan	Amerge	Oral	2-3 hours	19-21%	50-66%
Almotriptan	Axert	Oral	1-3 hours	32-36%	55-65%
Frovatriptan	Frova	Oral	2-4 hours	12%	37-46%
Eletriptan	Relpax	Oral	1.5 hours	20-30%	47-77%

Source: FDA, Zogenix, Edison Investment Research. Note:*Zeneo Sumatriptan is expected to have the same profile as the currently marketed autoinjector pen and needle-free versions of sumatriptan.

The needle-free version of sumatriptan currently on the market, Sumavel DosePro, was originally developed by Zogenix and has been approved since 2009. It was launched in January 2010 by both Zogenix and Astellas as part of a co-promotion agreement. Astellas terminated the agreement in 2012, but then Mallinckrodt took up the product with a similar arrangement, which ended in early 2014. Eventually, Endo purchased the programme outright for $85m in April 2014. As Endo does not break out Sumavel DosePro sales, the last firm data point we have is the $31.7m in sales that Zogenix reported for 2013. The product had been doing well while Astellas was promoting the drug, but then flattened out after changing hands to Mallinckrodt and, now with Endo, is falling. Also as Endo announced it was eliminating its pain field salesforce at the end of 2016, Sumavel DosePro is currently not being detailed, potentially providing an opening for a new competitor.

From the point of view of providing fast relief for migraines, injectable forms are superior to the other various forms. And based on the initial launch trajectory of Sumavel DosePro, there is a market for needle-free injection products, though their success will likely depend on a quality partner. We currently assume approval in the US and EU in 2020 for Crossject's Zeneo Sumatriptan with pricing of €100 (which is approximately in line with Sumavel DosePro pricing) and €25 per dose, respectively. Peak sales are estimated at €73.0m in the US (8% peak penetration of the injectable triptan market) and €8.8m in the EU (12% peak penetration of the injectable triptan market). Our estimates for injectable market penetration are conservative due to its competitive nature and the fact that there is already a needle-free option. For both the US and EU we expect regional partnerships to help sell the products. For the US, we assume a €2m upfront/approval milestone and an additional €4m in commercial milestones with a 20% royalty. For the EU, we assume a €2m upfront/approval milestone with a 20% royalty. As a reference, Astellas paid $2m upfront and another $18m in milestones in exchange for a service fee of 45-55% of net sales of Sumavel DosePro to physicians who were in the Astellas target market (primary care physicians, obstetrician-gynaecologists, emergency physicians and urologists).

Helping to quickly stop epileptic seizures: Zeneo Midazolam

According to the CDC, 2.9 million people have active epilepsy in the United States. The prevalence of epilepsy in Europe is 3.4 million with 20-30% having more than one seizure per month.[6] The average seizure lasts less than two minutes[7] but the longer a seizure does last the harder it is to

6 Forsgren L. et al., *European Journal of Neurology* 2005 Apr;12(4)245-53

7 Alford E et al., *Journal of Pediatric Pharmacology and Therapeutics* 2015;20(4):260-289

stop with treatment and the greater the likelihood of complications. For seizures lasting 10-29 minutes, only 43% cease without treatment and once they reach 30 minutes in length only 7% cease without treatment, with 19% of affected patients dying.[8]

Optimally, the patient would be treated at home as the trip to the hospital can waste very valuable time. However, only one at-home treatment is approved in the US: a rectal gel version of diazepam, which is part of the benzodiazepine class along with midazolam.

Exhibit 4: Profiles of acute treatments for epileptic seizures

	Time to response (in minutes)	Duration (in hours)
Lorazepam (iv)	3–10	12–24
Diazepam (rectal)	5–15	<1
Diazepam (iv)	1–5	<1
Midazolam (im)	5–10	<1
Midazolam (buccal)	5–10	<1
Midazolam (Zeneo, needle-free)	5-10 (expected)	<1 (expected)
Midazolam (iv)	10–30	12–2
Phenytoin (iv)	10–30	12–24
Fosphenytoin (iv)	10–30	12–24
Phenobarbitone (iv)	5–30	48–72

Source: Cherian A. et al., Annals of Indian Academy of Neurology 2009 Jul-Sep; 12(3): 140-153. Edison Investment Research

While rectal diazepam does work quickly (see Exhibit 4), it is not patient friendly as it involves injecting a liquid inside the rectum of a patient while they are having a seizure, which may be convulsive. Nevertheless, rectal diazepam achieved over $100m in sales before going generic in 2010.

In Europe, a buccal form of midazolam, known as Buccolam, is marketed by Shire. It is a liquid that needs to be inserted slowly into the space between the gum and cheek, again possibly not the most convenient way to administer a drug to someone with a convulsive seizure. According to EvaluatePharma, sales in 2016 were $39m, though Shire does not disclose sales specifically for that product, given its small size.

Crossject's Zeneo Midazolam should have a similar profile to intramuscular and buccal midazolam, with a 5-10 minute onset but short duration of action, ideal for home use. Given the quick and easy administration of midazolam via the Zeneo device, Crossject should have an advantage over the competition.

We currently assume approval in the US and EU in 2020 for the product, with pricing of €100 and €25 per dose, respectively (approximately the average price of Buccolam in Europe). Peak sales are estimated at €50.8m in the US (8% peak penetration) and €6.8m in the EU (12% peak penetration). Our penetration estimates are conservative due to the competitive nature of the market. We believe Crossject will require a marketing partner in the different regions. In terms of milestones, we model €2m upfront/approval milestones for EMA and FDA approval and a further €4m in commercial milestones. We estimate royalties of 20% for both the US and EU.

Breaking into the EpiPen market: Zeneo Adrenaline

An estimated 1.6%[9] of the US population has had an episode of anaphylactic shock (which could potentially be fatal), with allergic reactions to medication, food and insect stings being the most common reasons. This might be an underestimate as data suggests that just food allergy prevalence is 6% in children and 4% in adults.[10] Mylan currently dominates this market with its EpiPen product, which had over $1.1bn in 2016 US sales.

8 DeLorenzo R. et al., *Epilepsia* 1999 Feb;40(2):164-9

9 Wood R. et al., *The Journal of Allergy and Clinical Immunology* 2014 Feb;133(2):461-7

10 Dreborg S. et al., *Allergy, Asthma & Clinical Immunology* (2016) 12:11

A major issue with the EpiPen is that only a minority of patients and physicians know how to use it correctly. According to one study, just 18% of participants were able to perform all steps correctly (one of the major weaknesses being not keeping the EpiPen in place for the full 10 seconds recommended).[11] In another study, 32% of participants were able to, but only 18% of paediatricians were able to correctly demonstrate use of the device.[12]

In order to combat this, Sanofi launched Auvi-Q, an autoinjector that is voice-guided to help with compliance, in 2013. There was a manufacturing related recall in October 2015, but prior to this, it had achieved €113m in sales through the first nine months of 2015, up 52.4% on a constant currency basis over the prior year. This level of sales indicates that there is room in the market for a compliance and user friendly product, such as Zeneo Adrenaline, which is very easy to use and does not need to be held in place for 10 seconds as the product is injected in ~1/10th of a second.

Crossject currently has a worldwide commercial agreement with an undisclosed partner for this product. The partner will be responsible for all R&D expenses related to the product and will pay double-digit royalties and up to approximately $470m in milestones. Crossject received €1m upfront and will receive an additional €8m upon EMA and FDA approvals.

We currently assume approval in the US and EU in 2020 for the product, with pricing of €100 (which is a discount to both EpiPen and generic EpiPen) and €33 per dose, respectively. Peak sales are estimated at €127.3m in the US (8% peak penetration) and €5.8m in the EU (6% peak penetration). Our estimates are conservative due to the strength of the EpiPen brand, which has been able to withstand previous competitors. However, the egregious 500% price increase of Mylan's EpiPen over the last decade has outraged consumers and government officials and therefore provides a unique opportunity for competition due to the negative impact on branding. In terms of milestones, we model €8m upon EMA and FDA approvals (€3m and €5m, respectively) and a further €10m in commercial milestones. We estimate royalties of 25% in the US and 20% in the EU, where the product will be less profitable to the partner.

Rescue medication for severe asthmatics: Zeneo Terbutaline

The prevalence of asthma, a chronic inflammatory respiratory disease, is significant, affecting an estimated 18.4 million adults and 6.2 million children in the US[13] and 48.5 million adults and 14 million children in the EU.[14] Between 2002 and 2007, direct asthma-related healthcare costs in the US averaged $50.1bn annually.[15]

Severe asthmatics, accounting for approximately 5% to 10% of all patients with asthma, experience poor ongoing control of daily symptoms and abnormal lung function despite the use of second and third line controller medications, such as long-term beta2- agonists (LABAs), high doses of corticosteroids, and in some cases anti-immunoglobulin E (IgE) therapy.[16] Moreover, traditional markers of asthma severity are directly related to frequency of emergency department (ED) visits

11 Sicherer S. et al., *Journal of Pediatrics* 2012 Apr;160(4):651-6

12 Sicherer S. et al., *Journal of Pediatrics* 2000 Feb;105(2):359-362

13 CDC.

14 Olof Selroos et al*, National and regional asthma programmes in Europe; Asthma and allergy review;* 0: 1–10, (2014).

15 Barnett, S.B., and Numragambetov, T.A. Costs of asthma in the United States: 2002-2007. *Journal of Allergy and Clinical Immunology, 127(1),* 145-152.

16 Moore, W. C., et al., (2007). Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institutes Severe Asthma Research Program. *Journal of Allergy and Clinical Immunology, 119*(2), 405-413.

and hospitalisation.[17] According to the CDC National Asthma Control Program, a reported 1.9 million ED visits and 479,300 hospitalisations in 2009 were attributed to asthma.[18]

Quick-relief or rescue medications, such as short-acting beta2-agonists (SABAs) and anticholinergics, can be administered in an outpatient setting to provide rapid relief during asthma exacerbations, which may include one or a combination of the following symptoms: coughing, wheezing, chest tightness, and trouble breathing. Rescue medications for asthma exacerbations are typically available in hydrofluoroalkane (HFA) inhalers. However, effectiveness of delivering the medication to the lungs is highly dependent on accurate technique.[19] Current guidelines for HFA inhalers include shaking the device for 5-10 seconds, expelling air fully from the lungs, holding the inhaler to the mouth according to device-specific orientation, pressing down on the canister and inhaling the medication, holding breath for about 10 seconds, and exhaling slowly for as long as possible. Although relatively simple, it can be difficult for a patient experiencing a severe exacerbation to comply.

Exhibit 5: Profiles of rescue medications for asthma attacks

	Mechanism	Time to response (in minutes)	Duration (in hours)
Albuterol sulfate (inhaled)	SABA	30	2.5-6
Levalbuterol tartrate (inhaled)	SABA	5.5-10.2	3-6
Terbutaline sulfate (oral)	SABA	30	4-8
Terbutaline sulfate (sc)	SABA	5	1.5-4
Terbutaline sulfate (Zeneo, needle-free)	SABA	5 (expected)	1.5-4 (expected)
Ipratropium bromide (inhaled)	Anticholinergics	15	2-4
Ipratropium bromide + albuterol sulfate (inhaled)	Anticholinergics + SABAs	15	4-5

Source: NIH, US National Library of Medicine, Edison Investment Research. Notes: SABAs = short-acting beta2-agonists, SI = subcutaneous injection, Time to response = 15% increase in forced expiratory volume in one second (FEV1).

While inhaled SABAs and anticholinergics are the cornerstone for outpatient treatment, subcutaneous injection of terbutaline sulfate delivers quick symptom relief (see Exhibit 5) by improving airflow. AstraZeneca's Bricanyl (terbutaline sulfate) solution for intravenous and subcutaneous injection (0.5 mg/ml) is marketed in the EU and Canada as a bronchodilator for asthmatic exacerbations and had $51m in sales according to Evaluate Pharma.

We currently assume approval in the US and EU in 2021 for Zeneo Terbutaline, with pricing of €100 and €40 per dose, respectively. Peak sales are estimated at €100.0m in the US (10% peak penetration) and €61.0m in the EU (10% peak penetration). Our penetration estimates are conservative due to the competitive and genericised nature of the market. We believe Crossject will require a marketing partner in the different regions. In terms of milestones, we model €1m upfront/approval milestones for EMA and FDA approval. We estimate royalties of 20% for both the US and EU.

Tackling the opioid crisis: Zeneo Naloxone

Crossject is also working on a needle-free naloxone, which is intended for the acute treatment of opioid overdose. Naloxone is an opioid antagonist that is able to reduce the respiratory and mental depression due to opioids and hence can be very useful in saving lives when available. The need is clear; according to the Drug Abuse Warning Network, in 2011 there were 258,482 emergency room visits in the United States due to heroin and another 488,004 due to nonmedical use of prescription

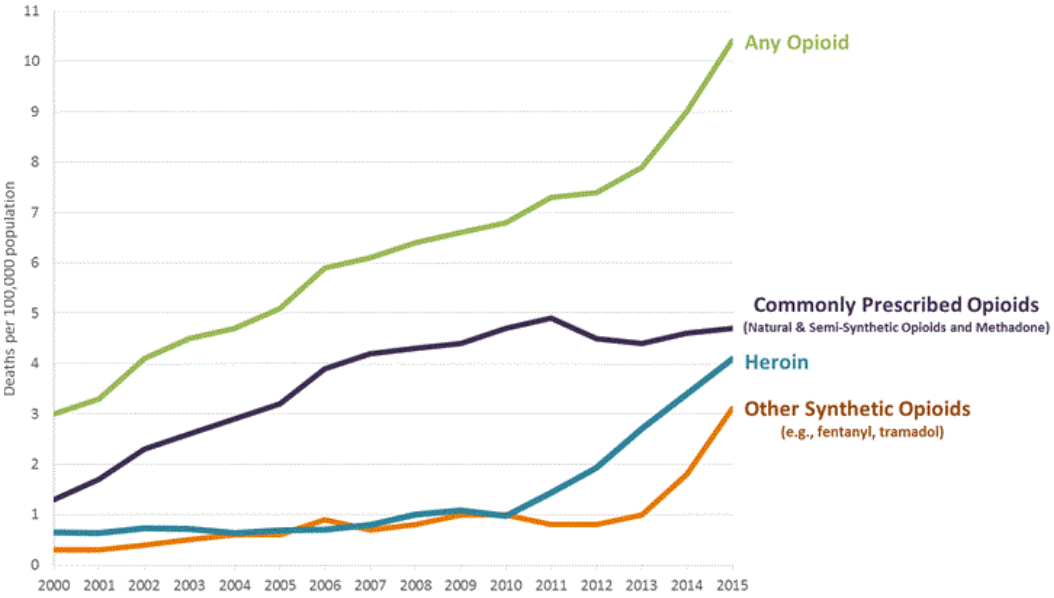
17 Griswald, S.K. et al., (2005). Asthma exacerbations in North American adults: Who are the "frequent fliers" in the emergency department. *CHEST, (127),* 1579-1586.

18 CDC.

19 Biswas, R., Hanania, N. A., & Sabharwal, A. (2017). Factors Determining In Vitro Lung Deposition of Albuterol Aerosol Delivered by Ventolin Metered-Dose Inhaler. *Journal of Aerosol Medicine and Pulmonary Drug Delivery, 30*(4), 256-266.

opioids. In 2014, approximately 28,000 people died from opioid overdose and more than half those deaths were from prescription opioids.[20]

Exhibit 6: Overdose deaths involving opioids in the US, 2000-15



Source: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2016

Due to the exponential rise in opioid related mortality, naloxone kits are now available without prescription in over 40 states (naloxone has no side effects in people without opioids in their system) and in two states (Virginia and Vermont) a naloxone prescription is required to be prescribed to patients receiving opioid prescriptions who are at a high risk of overdose. They are available in traditional intramuscular, intramuscular/subcutaneous auto-injector and intranasal forms, all of which work within six to eight minutes of administration, with pricing ranging from $20 to $2,000 per dose, depending on the brand. The CDC recommends expanding access and use of naloxone to prevent overdose deaths.

Due to the recent success of the Narcan nasal spray (from Adapt Pharma and Opiant), which had over $25m in sales in H117 with pricing similar to what we have assumed for Zeneo Naloxone, we have increased our estimates for the product as well as the pace of market growth. Our model assumes a 60% probability of success, a launch in 2020, with peak penetration of 12% in the US (formerly 8%) and 8% in the EU. We assume a price of €100 per dose in the US and €33 in the EU. Our peak sales for the product is currently €34m (previously €14m). In light of the success of the Narcan spray, our peak sales estimates may be conservative.

Treating acute adrenal insufficiency: Zeneo Hydrocortisone

Adrenal insufficiency is a life-threatening condition that has multiple causes, including autoimmune disease, congenital adrenal hyperplasia (CAH), removal of the pituitary gland as well as certain medications, infections and surgeries. Patients with the condition are missing certain hormones like cortisol, which helps the body use sugar and protein for energy and helps it recover from stresses and infections. Hence, key symptoms of the disease are fatigue, weakness, weight loss, abdominal pain and dizziness when standing up.

Patients are generally classed with primary or secondary adrenal insufficiency. Primary adrenal insufficiency, also known as Addison's disease, results from disease intrinsic to the adrenal cortex

[20] Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths — United States, 2010–2015. MMWR Morb Mortal Wkly Rep 2016;65:1445–1452.

(such as CAH), which is situated along the perimeter of the adrenal gland and mediates the stress response through hormone secretion. It is primarily an autoimmune related disorder though tuberculosis can cause the condition as well. Secondary adrenal insufficiency is caused by a malfunctioning pituitary gland (often due to a benign tumour) or a lack of responsiveness of the adrenal glands to the hormones released by the pituitary gland. According to the EMA, prevalence is around 450 cases per million with approximately 34-38% being the primary form of the disease.[21] This suggests almost 500,000 sufferers in the US and Europe.

Treatment for both the primary and secondary forms is hormone replacement therapy through the use of hydrocortisone, fludrocortisone and prednisolone. This therapy is generally effective though sometimes patients will have acute attacks, which are often referred to as an adrenal crisis (AC). The incidence rate of these acute attacks is 6.3 crises per 100 patient years. Due to the threat of an acute attack, 29.6% of patients carry an emergency kit with emergency suppositories or intramuscular doses of steroid hormones.[22]

Crossject is targeting the emergency kit market, as Zeneo Hydrocortisone is capable of delivering the emergency dose in a single step in ~1/10th of a second. We assume the introduction of a more patient-friendly delivery mechanism would increase the penetration of emergency kits from 30% to 40% with an initial cost of €100 per dose in the US and €60 in the EU, per company guidance. Our model assumes launch in 2020, with peak penetration of 30% in both markets and total peak sales of €9m.

Rheumatoid arthritis relief: Zeneo Methotrexate

RA is an auto-immune inflammatory arthritis that affects 1.3 million[23] adults in the United States. Internationally, the prevalence rate is between 0.4-1.3% according to the CDC. Methotrexate is generally recommended as the first-line therapy for these patients and comes in both oral and injectable forms. Although the vast majority of patients (~80%[24]) in the United States take the oral version, the injectable version has shown greater bioavailability and dose response than the oral version (oral methotrexate exposure plateaus at doses of 15mg and above) due to absorption issues that the injectable version bypasses.[25]

We currently assume a 30% chance of success and a launch in 2021. We attribute a lower chance of success as methotrexate has previously been de-emphasised by the company (it had been its lead program) as it has decided to focus on acute rather than chronic medicines. Assumed pricing for the product is €100 per dose in the US and €20 per dose in the EU. Peak sales are estimated at €82.2m in the US (2% peak penetration of the methotrexate market) and €17.8m in the EU (6% peak penetration of the methotrexate market). We assume greater penetration in the EU market as injectable methotrexate in general has garnered greater acceptance in that market, while in the US injectable methotrexate is only ~20% of the market.

We do not expect Crossject to market Zeneo Methotrexate by itself and the company has already signed local partnership deals with Biodim for France, with Sayre for India and with Xi'an Xintong for China. Crossject will receive €1m per pre-commercialisation milestone from Biodim and €3m for Chinese approval from Xi'an Xintong. Sayre milestones for India are unknown. For the US, we expect a partner to pay a total of €2m upfront/approval and an additional €10m in commercial based milestones. For both the US and EU markets we have assumed a 20% royalty.

21 Charmandari, E et al. Adrenal Insufficiency *The Lancet* 2014, Volume 383, Issue 9935, 2152-2167.

22 Hahner S et al., Epidemiology of adrenal crisis in chronic adrenal insufficiency *European Journal of Endocrinology* (2010) 162 597-602.

23 Helmick C et al., *Arthritis & Rheumatology* 2008 Jan;58(1):15-25

24 DiBenedetti et al., *Rheumatology and Therapy* 2015 June; Vol 2, Issue 1, pp 73-84

25 Schiff M et al., *Annals of the Rheumatic Diseases* 2014;0:1-3

Improving Parkinson's disease symptoms

Apomorphine is a dopamine agonist and is used to treat/manage sudden and unexpected bouts of hypomobility associated with Parkinson's disease (PD). According to the Parkinson's Disease Foundation, the prevalence of Parkinson's is one million people in the US, with 7-10 million people worldwide suffering from the disease. Once patients are on standard PD drug treatments for four to five years, they experience bouts of hypomobility, including the inability to rise from a chair, speak or walk. Often these can be treated by changing their treatment regimen. However, according to BlueShield of Northeastern New York, approximately 12,000 patients have severe hypomobility that requires apomorphine, which reverses symptoms in 7-14 minutes. As a month's supply is typically ~$2,000, this could be a potentially lucrative market. Our model assumes launch in 2022 (previously 2020 but its spot was taken by Zeneo Terbutaline in the schedule as it is more in line with the acute treatment focus) with peak penetration of 8% in the US and 6% in the EU, and total peak sales of €53m. We have assigned a 30% chance of success as its profile is similar to that of methotrexate. It is a non-emergency product that will use a disproportionate amount of manufacturing resources due to the need of multiple dosage strengths and has been de-emphasised by the company.

Sensitivities

As Crossject is focusing on well-characterised and approved generic drugs, there should be very little clinical risk for any one of its programmes. All that will likely be needed will be bioequivalence and device usability studies. The main risk will come on the commercialisation front as Crossject, at least at this point, is completely dependent upon partners to market the products and will need partners for each product in each region. Also, as we have seen, there is manufacturing risk although this is likely more a function of timing rather than ultimate viability. In addition, Crossject is generally focused on areas that are heavily genericised, with lots of different dosage forms for the product it is putting onto the Zeneo platform. In the case of sumatriptan, there are oral, injectable (both with a needle and needle-free) and intranasal forms available. Making headway may be extremely difficult and will likely depend heavily on simply physician and patient preference. Pricing/reimbursement will be another issue, as pricing outside the US is likely to be challenging, leading to minimal market opportunity for its products. In the US, on the reimbursement front, Crossject products will likely be placed in "Tier 3" with higher co-pays and need for prior authorisation. This would limit the opportunity for its products. However, Crossject does not depend on any one of its products to be extremely successful in order for it to be successful as a company, due to its deep pipeline, with the total cost of developing each product estimated to be in the range of €4-6m.

Valuation

We have increased our valuation for Crossject from €87.4m or €9.91 per basic share to €121m or €13.72 per basic share. This is due to the inclusion of Zeneo Terbutaline in the pipeline and an increase in our expectations for Zeneo Naloxone and was mitigated by delayed launch timelines and a lower cash balance. Zeneo Terbutaline has taken the place of Zeneo Apomorphine for Parkinson's disease, which is still alive but deprioritised. We had applied a lower probability of success for Zeneo Apomorphine as it did not treat an emergency related condition, which is where the company has been focused, so the impact of the de-emphasis is minimal. Also, much of our valuation is dependent upon successful launches in the US as pricing in Europe, according to company comments, will likely be a fraction of that in the US and in the rest of the world. Potential

catalysts will likely include the announcement of additional partnerships for Crossject's various products, especially in the US.

Exhibit 7: Crossject valuation table

Product	Main indication	Prob. of success	Launch year	WW peak sales (€m)	Patent protection	Royalty	rNPV (€m)
Methotrexate	Rheumatoid Arthritis	30%	2021	100	2036	20%	8.5
Sumatriptan	Acute Migraine	60%	2020	82	2036	20%	13.5
Adrenaline	Anaphylactic shock	60%	2020	133	2036	25% US/20% EU	34.8
Midazolam	Acute epileptic seizures	60%	2020	58	2036	20%	9.5
Hydrocortisone	Acute Adrenal Crisis	60%	2020	9	2036	20%	0.7
Naloxone	Opioid overdose	60%	2020	34	2036	20%	6.1
Terbutaline	Severe Asthma	60%	2021	161	2036	20%	34.5
Apomorphine	Parkinson's disease	30%	2022	53	2036	20%	10.5
Total (€m)							**118.1**
Net cash (H117) (€m)							2.86
Total firm value (€m)							**120.91**
Total basic shares (m)							8.81
Value per basic share (€)							**13.72**
Stock options (m)							0.62
Weighted average exercise price (€)							2.68
Cash on exercise (€m)							1.67
Total firm value (€m)							122.58
Total number of shares (m)							9.4
Diluted value per share (€)							12.99

Source: Edison Investment Research

Financials

As of 30 June 2017, Crossject had €6.1m in cash and cash equivalents on hand, up from €2.6m as of year-end 2016 as well as €3.2m in long-term debt. Based on the recent results, we have increased our operating spending estimates by approximately €2m per year in 2017 and 2018 (principally due to higher R&D expenditures). The company successfully completed a €5m rights offering in March 2017, and received a €1.7m payment from Bpifrance's PIAVE. It also expects to receive an additional €5.9m by year-end 2018. Between now and projected profitability in 2020, we forecast a total funding need of €20m. This requirement would be mitigated somewhat by additional upfront payments from partners as well as milestone payments upon product approvals.

Exhibit 8: Financial summary

€000s	2014	2015	2016	2017e	2018e
Year end 31 December	French GAAP	French GAAP	French GAAP	French GAAP	French GAAP
PROFIT & LOSS					
Revenue	1,744	2,370	1,427	2,900	0
Cost of Sales	0	(0)	0	0	0
Gross Profit	1,744	2,369	1,427	2,900	0
R&D Expenses	(2,421)	(3,077)	(4,384)	(6,856)	(7,884)
SG&A and Other Expenses	(3,388)	(4,808)	(2,630)	(2,841)	(3,068)
EBITDA	(4,066)	(5,516)	(5,587)	(6,797)	(10,953)
Operating Profit (before GW and except.)	(5,108)	(7,013)	(7,291)	(8,695)	(10,953)
Intangible Amortisation	0	0	0	0	0
Other	(0)	0	0	0	0
Exceptionals	0	0	0	0	0
Operating Profit	(5,108)	(7,013)	(7,291)	(8,695)	(10,953)
Net Interest	(36)	(19)	(38)	(104)	(1,058)
Other	(160)	299	(429)	(1)	0
Profit Before Tax (norm)	(5,334)	(6,720)	(7,329)	(8,799)	(12,010)
Profit Before Tax (FRS 3)	(5,304)	(6,732)	(7,758)	(8,800)	(12,010)
Tax	968	1,045	1,095	2,057	2,365
Deferred tax	0	0	0	0	0
Profit After Tax (norm)	(4,366)	(5,675)	(6,234)	(6,742)	(9,645)
Profit After Tax (FRS 3)	(4,336)	(5,687)	(6,663)	(6,743)	(9,645)
Average Number of Shares Outstanding (m)	6.7	6.7	7.3	9.0	9.4
EPS - normalised (€)	(0.65)	(0.85)	(0.85)	(0.75)	(1.03)
EPS - FRS 3 (€)	(0.65)	(0.86)	(0.91)	(0.75)	(1.03)
Dividend per share (c)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets	5,521	5,936	9,252	9,549	10,005
Intangible Assets	2,327	2,330	2,506	2,579	2,579
Tangible Assets	888	1,727	5,636	5,621	6,077
Other	2,305	1,878	1,109	1,349	1,349
Current Assets	12,853	7,943	4,997	12,291	7,189
Stocks	0	761	398	885	885
Debtors	1,926	1,991	1,966	2,886	2,886
Cash	10,927	5,139	2,634	8,520	3,418
Other	0	52	0	0	0
Current Liabilities	(2,907)	(3,261)	(3,321)	(3,292)	(3,292)
Creditors	(2,907)	(3,261)	(2,566)	(3,292)	(3,292)
Short term borrowings	0	0	(755)	0	0
Long Term Liabilities	(982)	(1,820)	(4,645)	(12,213)	(17,213)
Long term borrowings	0	0	(3,235)	(8,235)	(13,235)
Other long term liabilities	(982)	(1,820)	(1,409)	(3,978)	(3,978)
Net Assets	14,484	8,797	6,284	6,334	(3,311)
CASH FLOW					
Operating Cash Flow	(3,163)	(4,796)	(4,403)	(5,917)	(8,296)
Net Interest	0	0	0	0	0
Tax	0	0	0	0	0
Capex	(4,770)	(1,805)	(6,065)	(1,805)	(1,805)
Acquisitions/disposals	0	0	0	0	0
Financing	17,873	0	3,961	6,803	0
Dividends	0	0	0	0	0
Other	0	483	(252)	872	0
Net Cash Flow	9,940	(6,118)	(6,759)	(47)	(10,101)
Opening net debt/(cash)	(2,468)	(10,927)	(5,139)	1,357	(284)
HP finance leases initiated	0	0	0	0	0
Exchange rate movements	0	0	0	0	0
Other	(1,481)	330	264	1688	0
Closing net debt/(cash)	(10,927)	(5,139)	1,357	(284)	9,817

Source: Crossject accounts, Edison Investment Research

Contact details	Revenue by geography
Crossject 6, rue Pauline Kergomard 21000 Dijon France +33 3 80 54 98 50 www.crossject.com	N/A

Management team

CEO: Patrick Alexandre	Chief Commercial Officer: Olivier Giré
Patrick Alexandre is a co-founder of the company. He has been the driving force in the development of Crossject's technology since its inception in 1997 when it was a research effort at Fournier Laboratoires. He has over 15 years' experience in the pharmaceutical industry. He also has 10 years' industrial R&D experience in the steel industry and graduated as an engineer from Supelec.	Olivier Giré joined Crossject in 2016 to define and deploy the company's commercial strategy. He has over 20 years' experience in the pharmaceutical industry, leading commercial affiliates and distributor networks for specialty pharma companies such as Ipsen, Amdipharm (now Concordia) and Exeltis, and negotiated over 40 business development deals. He is an EDHEC graduate.
Chief Supply and Manufacturing Officer: Henri de Parseval	**Quality and Regulatory Director: Isabelle Liebschutz**
Henri de Parseval has 17 years of experience in supply chain management with several international groups. He leads the industrialization of Crossject's manufacturing supply chain. Prior to joining Crossject, he created the supply chain of an innovative railway safety system implementation for a major mining group's projects. During his career Henri has developed expertise in managing strategic partnerships, purchasing and material flow management. He graduated from Ecole Nationale des Arts et Métiers ParisTech.	Isabelle Liebschutz joined Crossject in 2013. She is in charge of the development, approval and effective execution of quality and regulatory affairs. Previously, she had worked for five years in formulation and development at Fournier Laboratories and seven years as a quality assurance manager for transdermal systems manufacturing at Fournier/Solvay Group for European and US markets. She graduated from Montpellier University of Pharmacy.

Principal shareholders	(%)
Gemmes Venture	19
A Plus Finance	4
SNPE	4
IDEB	3
AutoControle	2

Companies named in this report

Abbott (ABT), Antares (ATRS), Zogenix (ZGNX), Astellas (4503), Mallinckrodt (MNK), Endo (ENDP), Mylan (MYL), Sanofi (SNY), Shire (SHPG), Opiant (OPNT)

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