EDISON

Crossject

Pipeline update

L15 unmasked

Pharma & biotech

Recently, Crossject disclosed the identity of the product behind its L15 programme. L15 is its needle-free version of hydrocortisone, which Crossject will develop for the treatment of acute adrenal insufficiency, a potentially fatal condition. The company expects the commercial launch of the product in H118, although we believe peak sales will be a modest €9m as it is a niche market with little pricing power.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/14	1.7	(5.3)	(0.66)	0.0	N/A	N/A
12/15	2.4	(6.7)	(0.85)	0.0	N/A	N/A
12/16e	3.1	(5.4)	(0.62)	0.0	N/A	N/A
12/17e	3.0	(9.7)	(1.05)	0.0	N/A	N/A

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

Tackling a potentially fatal condition

Adrenal insufficiency is a condition where a patient is missing certain hormones like cortisol, which helps the body use sugar and protein for energy and helps it recover from stresses and infections. The condition has multiple causes including autoimmune disease, tuberculosis, congenital adrenal hyperplasia (CAH), benign pituitary tumours, brain injury or even over-use of steroids.

A relatively niche market

While most of Crossject's programmes focus on large indications like rheumatoid arthritis, migraine or epileptic seizures, acute adrenal insufficiency is relatively small. Based on prevalence data, we calculate almost 500,000 patients in the US and Europe. Approximately 30% of them carry an emergency kit with them, which will often include an anal suppository or a vial for intra-muscular injection.

RA product set to be commercialised in 2017

Crossject's lead programme is ZENEO Methotrexate for rheumatoid arthritis (RA), which is an autoimmune inflammatory arthritis that affects 1.3 million adults in the United States. The company expects it to be commercialised in Europe in H217 and in China sometime in 2017. It already has regional partnerships in France, India and China, and Crossject will likely sign additional agreements to commercialise the product in other regions.

Valuation

We are increasing our risk-adjusted valuation slightly to €81.9m or €12.07 per share, from €81.1m or €11.96 per share due to the inclusion of the ZENEO Hydrocortisone programme. As of 2015 year-end, the company had €5.2m in cash. It expects to receive an additional €3.1m in grants in 2016 and has also recently announced an equity line, which could provide up to ~€10m. Between now and projected profitability in 2018, we forecast a total funding need of €15m for all projects.

23 June 2016

Price	**€7.12**
Market cap	**€48m**

Net cash (€m) at 31 December 2015	5.2
Shares in issue	6.7m
Free float	72.3%
Code	ALCJ
Primary exchange	Euronext
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(12.4)	(22.2)	(5.7)
Rel (local)	(12.6)	(21.2)	7.1
52-week high/low		€11.06	€3.52

Business description

Crossject has several programmes in development based on its proprietary needle-free injection system, ZENEO. The first to market will be ZENEO Methotrexate, which the company expects to be commercialised in 2017. Over the course of 2018 and 2019, the company expects to launch proprietary versions of six other products on its ZENEO platform.

Next events

Launch of ZENEO Methotrexate	H217

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Edison profile page

Treating acute adrenal insufficiency

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 (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.[1] 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.[2]

Exhibit 1: Frequency of adrenal crisis (AC) based on patient responses to a survey

Number of AC	PAI (n=254)		SAI (n=190)	
	n	%	n	%
0	135	53.1	124	65.1
1	58	22.8	32	16.9
2	24	9.4	8	4.2
3	10	3.9	12	6.3
≥4	27	10.6	14	7.4

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

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 EU5, per company guidance. Our model assumes launch in H118, with peak penetration of 30% in both markets and total peak sales of €6m.

Valuation

We are increasing our risk-adjusted valuation slightly to €81.9m or €12.07 per share, from €81.1m or €11.96 per share, due to the inclusion of the ZENEO Hydrocortisone programme. We continue to exclude Crossject's naloxone and apomorphine products, because their expected launch is further out and visibility on them is limited. Potential catalysts will likely include the announcement of

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

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

additional partnerships for the various products as well as product approvals, which should start in earnest within the developed countries in H217.

Exhibit 2: Crossject valuation table

Product	Main Indication	Prob. of success	Launch year	WW Peak sales (€m)	Patent protection	Royalty	rNPV (€m)
Methotrexate	Rheumatoid Arthritis	60%	2017	€100	2034	20%	€18.4
Sumatriptan	Acute Migraine	60%	2018	€82	2034	20%	€14.1
Adrenaline	Anaphylactic shock	60%	2018	€133	2034	25% US/20% EU	€36.3
Midazolam	Acute epileptic seizures	60%	2018	€58	2034	20%	€8.3
Hydrocortisone	Acute Adrenal Crisis	60%	2018	€9	2034	20%	€0.8
Total							€77.9
Cash and cash equivalents (Q116e) (€m)							€3.91
Total firm value (€m)							€81.85
Total basic shares (m)							6.78
Value per basic share (€)							€12.07
Stock options (3/2016e, m)							0.62
Weighted average exercise price (€)							€2.68
Cash on exercise (€m)							€1.67
Total firm value (€m)							€83.52
Total number of shares							7.4
Diluted value per share (€)							€11.28

Source: Edison Investment Research

Financials

As of year-end 2015, Crossject had €5.2m in cash and cash equivalents on hand. The company expects to receive an additional €3.1m in grants in 2016 and recently announced an equity line from Kepler Cheuvreux, which could provide ~€10m. The terms are that Kepler Cheuvreux has committed to subscribe over the next 24 months to a maximum of 1.2m shares at a 7% discount. Between now and expected profitability in 2018, we project a total funding need of €15m for Crossject and have modelled this via an illustrative long-term debt. This need would be mitigated somewhat by additional upfront payments from partners, as well as milestone payments on product approvals. With the addition of L15/ZENEO Hydrocortisone R&D expenses, we now expect a total of €10.5m in R&D expenses in 2016 and 2017 (versus €9m previously) and an additional €9m in SG&A (unchanged from our previous note).

Exhibit 3: Financial summary

	2014	2015	2016e	2017e	2018e
Year end 31 December	French GAAP	French GAAP	French GAAP	French GAAP	French GAAP
PROFIT & LOSS					
Revenue	1,744	2,370	3,100	3,000	14,830
Cost of Sales	0	(0)	0	0	0
Gross Profit	1,744	2,369	3,100	3,000	14,830
R&D Expenses	(2,421)	(3,077)	(3,721)	(6,800)	(7,820)
SG&A and Other Expenses	(3,388)	(4,808)	(4,354)	(4,702)	(6,079)
EBITDA	(4,066)	(5,516)	(4,975)	(8,502)	931
Operating Profit (before GW and except.)	(5,108)	(7,013)	(4,975)	(8,502)	931
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)	(4,975)	(8,502)	931
Net Interest	(36)	(19)	(400)	(1,200)	(1,199)
Other	(160)	299	0	0	0
Profit Before Tax (norm)	(5,334)	(6,720)	(5,375)	(9,702)	(268)
Profit Before Tax (FRS 3)	(5,304)	(6,732)	(5,375)	(9,702)	(268)
Tax	968	1,045	1,116	2,040	2,346
Deferred tax	0	0	0	0	0
Profit After Tax (norm)	(4,366)	(5,675)	(4,259)	(7,662)	2,078
Profit After Tax (FRS 3)	(4,336)	(5,687)	(4,259)	(7,662)	2,078
Average Number of Shares Outstanding (m)	6.7	6.7	6.9	7.3	7.6
EPS - normalised (€)	(0.66)	(0.85)	(0.62)	(1.05)	0.27
EPS - FRS 3 (€)	(0.65)	(0.86)	(0.62)	(1.05)	0.27
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets	5,521	5,936	7,521	8,726	9,642
Intangible Assets	2,327	2,330	2,330	2,330	2,330
Tangible Assets	888	1,727	3,313	4,518	5,433
Other	2,305	1,878	1,878	1,878	1,878
Current Assets	12,853	7,943	7,112	8,245	9,407
Stocks	0	761	761	761	761
Debtors	1,926	1,991	1,991	1,991	1,991
Cash	10,927	5,139	4,307	5,440	6,603
Other	0	52	52	52	52
Current Liabilities	(2,907)	(3,261)	(3,261)	(3,261)	(3,261)
Creditors	(2,907)	(3,261)	(3,261)	(3,261)	(3,261)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	(982)	(1,820)	(6,820)	(16,820)	(16,820)
Long term borrowings	0	0	(5,000)	(15,000)	(15,000)
Other long term liabilities	(982)	(1,820)	(1,820)	(1,820)	(1,820)
Net Assets	14,484	8,797	4,552	(3,111)	(1,032)
CASH FLOW					
Operating Cash Flow	(3,163)	(4,796)	(3,845)	(6,867)	3,163
Net Interest	0	0	0	0	0
Tax	0	0	0	0	0
Capex	(4,770)	(1,805)	(2,000)	(2,000)	(2,000)
Acquisitions/disposals	0	0	0	0	0
Financing	17,873	0	0	0	0
Dividends	0	0	0	0	0
Other	0	483	0	0	0
Net Cash Flow	9,940	(6,118)	(5,845)	(8,867)	1,163
Opening net debt/(cash)	(2,468)	(10,927)	(5,139)	693	9,560
HP finance leases initiated	0	0	0	0	0
Exchange rate movements	0	0	0	0	0
Other	-1481	330	13	0	0
Closing net debt/(cash)	(10,927)	(5,139)	693	9,560	8,397

Source: Crossject accounts, Edison Investment Research

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