

# CROSSJECT (+)

## Initiation of coverage

Opinion	BUY
Target price	12,1€
Potential	+43%

## Expanding product portfolio

We are initiating coverage of Crossject this morning with a BUY rating and a target price of €12,1. The company, which focuses on “supergenerics” (i.e. the combination of a generic drug with its Zeneo needle-free injection system), expects to launch its first product (MTX/Zeneo in rheumatoid arthritis) in mid-2017. With seven products under development, the company could potential proceed with launches every six months starting in mid-2017. Even if we have adopted an extremely conservative approach (only three products valued in our model at this point), we see upside potential of +43% compared to the last share price.

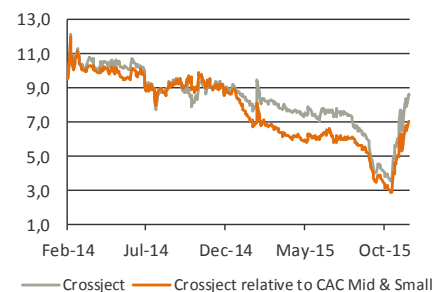
- Crossject’s different development projects target therapies where self-administration is the principal administration solution. Through its Zeneo single-use system, which enables needle-free injection of drugs, Crossject is offering a new form of delivery of generic drugs used in emergency or chronic treatments. The company’s strategy is entirely focused at present on the development of off-patent drugs in combination with its Zeneo system. The challenge here is to obtain new drugs (referred to as “supergenerics”) whose distinctive medical characteristics provide real advantages for patients and healthcare systems.
- Crossject has no fewer than seven “supergeneric” drugs under development that should come on the market over the next four years. Crossject’s approach involves the targeting of pathologies (principally acute) by providing a genuinely different manner of patient treatment. Treatments are currently being developed in seven indications: emergency treatment of allergic (or anaphylactic) shock, “chronic” treatment of rheumatoid arthritis and treatment of acute migraine, along with L15 (indication undisclosed) and a new portfolio of three products in the central nervous system area. With an initial filing expected over the coming month for approval at the end of 2016, we anticipate an accelerated pace of regional partnership agreements for the MTX/Zeneo combination in North America and Asia.
- One of the key points in the different valuations of the company’s products obviously remains the commercial partner. As of now, only the Epinephrine/Zeneo combination benefits from a worldwide commercial partnership. We expect regional distribution partnerships for each of the combinations under development, thereby leading to adjustments in our penetration rates depending on the distributor. We are currently extremely cautious in our model and use rather low potential market shares. We also do not include any values for the company’s three new products under development or for L15.
- We apply a probability of success of 75% to each of these products, a high level compared to the pharmaceutical sector but justified by the low development risk for a supergeneric. Our conservative approach (partially dependent on future distribution partnerships for MTX/Zeneo and Sumatriptan/Zeneo) nevertheless leads us to an upside of +43% compared to the last sale price. With cash of €6.5m, our sum of the parts valuation equals €12,1 per share, leading to our BUY rating.

in € / share	2014	2015e	2016e	2017e
diluted EPS	-0,65	-0,73	-0,72	-0,72
Chg 1 year	+0,0%	+12,5%	-1,6%	+0,0%
Revisions	n.s.	n.s.	n.s.	n.s.

ISIN	FR0011716265
Ticker	ALCJ-FR
DJ sector	Health Technology

Current Price	€8,5
Nb of shares (m)	6,7
diluted nb of shares (m)	7,3
Market cap (m€)	56
Float (m€)	32

	1m	3m	1 year
Absolute chg	+129,0%	+25,3%	-11,1%
Relative chg	+129,4%	+19,6%	-28,8%



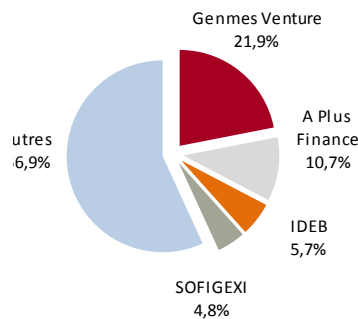
12/31/2013	2014	2015e	2016e	2017e
PE	n.s.	n.s.	n.s.	n.s.
EV/CA	n.s.	n.s.	n.s.	n.s.
EV/EBITDA	n.s.	n.s.	n.s.	n.s.
EV/EBITA	n.s.	n.s.	n.s.	n.s.
FCF yield	n.s.	n.s.	n.s.	n.s.
Yield	n.s.	n.s.	n.s.	n.s.
Net debt/EBITDA	n.s.	n.s.	n.s.	n.s.

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## Financial aspects

Shareholders	
Genmes Venture	21,9%
A Plus Finance	10,7%
IDEB	5,7%
SOFIGEXI	4,8%
Autres	56,9%



Next events  
Phase III expected for suma and epi T1-16

Data per share	2013	2014	2015e	2016e	2017e	2018e	2019e	2020e	2021e
published EPS	-0,27	-0,65	-0,73	-0,72	-0,72	1,10	2,99	5,47	8,44
<b>diluted EPS</b>	<b>-0,25</b>	<b>-0,60</b>	<b>-0,67</b>	<b>-0,66</b>	<b>-0,66</b>	<b>1,00</b>	<b>2,74</b>	<b>5,00</b>	<b>7,72</b>
<i>Var/consensus</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
Net asset	ns	ns	ns	ns	ns	ns	ns	ns	ns
Dividend	ns	ns	ns	ns	ns	ns	ns	ns	ns

Valuation ratios	2013	2014	2015e	2016e	2017e	2018e	2019e	2020e	2021e
P/E	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
VE/Revenue	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
VE/EBITDA	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
VE/EBITA adjusted	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
op. before BFR FCF yield	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
operational FCF yield	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Yield	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

EV (€m)	2013	2014	2015e	2016e	2017e	2018e	2019e	2020e	2021e
Share price in €		9,6	8,5	8,5	8,5	8,5	8,5	8,5	8,5
Capitalization	0	70	62	62	62	62	62	62	62
Net debt	-0,9	-10,8	-6,1	-4,5	-12,5	-20,0	-33,3	-69,8	-126,1
Minorities	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
Provisions	0,5	0,3	0,3	0,3	0,3	0,3	0,3	0,3	0,3
Others	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
<b>EV</b>	<b>0</b>	<b>59</b>	<b>56</b>	<b>58</b>	<b>50</b>	<b>42</b>	<b>29</b>	<b>-8</b>	<b>-64</b>

P&L (€m)	2013	2014	2015e	2016e	2017e	2018e	2019e	2020e	2021e
Revenue	1,1	1,7	2,0	2,0	4,3	53,6	93,9	139,5	186,1
<i>chg.</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>0,5</i>	<i>0,3</i>
EBITDA	-2,0	-4,0	-4,8	-4,8	-2,8	10,0	24,8	44,2	67,5
<b>EBITA adjusted</b>	<b>-2,6</b>	<b>-5,1</b>	<b>-6,0</b>	<b>-6,0</b>	<b>-4,0</b>	<b>8,8</b>	<b>23,7</b>	<b>43,0</b>	<b>66,3</b>
<i>chg.</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
EBIT	-2,6	-5,1	-6,0	-6,0	-4,0	8,8	23,7	43,0	66,3
Financial result	-0,2	-0,2	-0,2	-0,2	-0,2	-0,2	-0,2	-0,2	-0,2
Taxes	-0,6	-1,0	-0,9	-0,6	-0,6	-1,3	-3,5	-6,5	-9,9
Minorities	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
Net profit	-3,4	-6,3	-7,1	-6,8	-4,8	7,3	19,9	36,4	56,2
<b>Net profit adjusted</b>	<b>-3,4</b>	<b>-6,3</b>	<b>-7,1</b>	<b>-6,8</b>	<b>-4,8</b>	<b>7,3</b>	<b>19,9</b>	<b>36,4</b>	<b>56,2</b>
<i>chg.</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>

Cash flow statement (€m)	2013	2014	2015e	2016e	2017e	2018e	2019e	2020e	2021e
Net income	-1,8	-4,3	-4,9	-4,8	-4,8	7,3	19,9	36,4	56,2
Amort.	0,6	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2
Others	-0,4	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
<b>op. before BFR FCF</b>	<b>-1,6</b>	<b>-3,2</b>	<b>-3,7</b>	<b>-3,6</b>	<b>-3,6</b>	<b>8,4</b>	<b>21,1</b>	<b>37,5</b>	<b>57,3</b>
Change in WCR	0,6	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
<b>operational FCF</b>	<b>-1,0</b>	<b>-3,2</b>	<b>-3,7</b>	<b>-3,6</b>	<b>-3,6</b>	<b>8,4</b>	<b>21,1</b>	<b>37,5</b>	<b>57,3</b>
Acquisitions/disposals	-1,1	-4,8	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0
Capital change	4,4	16,4	0,0	3,0	12,7	0,0	-6,7	0,0	0,0
Dividends	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
Others	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
<b>published FCF</b>	<b>2,3</b>	<b>8,5</b>	<b>-4,7</b>	<b>-1,6</b>	<b>8,1</b>	<b>7,4</b>	<b>13,4</b>	<b>36,5</b>	<b>56,3</b>

Balance sheet (€m)	2013	2014	2015e	2016e	2017e	2018e	2019e	2020e	2021e
Current assets	2,08	5,52	5,37	5,21	5,06	4,90	4,75	4,60	4,44
including intangible/goodwill	0,0	0,0	0,1	0,2	0,3	0,4	0,5	0,7	0,8
WCR	-0,9	-0,9	-0,9	-0,9	-0,9	-0,9	-0,9	-0,9	-0,9
Total equity	1,6	15,1	10,3	8,5	16,4	23,6	36,9	73,2	129,4
Minorities	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
Provisions	0,5	0,3	0,3	0,3	0,3	0,3	0,3	0,3	0,3
<b>Net debt</b>	<b>-0,9</b>	<b>-10,8</b>	<b>-6,1</b>	<b>-4,5</b>	<b>-12,5</b>	<b>-20,0</b>	<b>-33,3</b>	<b>-69,8</b>	<b>-126,1</b>

Financial ratios (%)	2013	2014	2015e	2016e	2017e	2018e	2019e	2020e	2021e
EBITDA/Revenue	n.s.	n.s.	n.s.	n.s.	n.s.	18,6%	26,4%	31,6%	36,2%
EBITA/Revenue	n.s.	n.s.	n.s.	n.s.	n.s.	16,5%	25,2%	30,8%	35,6%
NR adjusted/Revenue	n.s.	n.s.	n.s.	n.s.	n.s.	13,6%	21,2%	26,1%	30,2%
WCR /Revenue	ns	ns	ns	ns	ns	ns	ns	ns	ns
ROCE excl. Incorpor/ GW	ns	ns	ns	ns	ns	ns	ns	ns	ns
ROE adjusted	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Net debt/Total equity	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Net debt/EBITDA (en x)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

The information contained in this document has been derived from sources deemed to be reliable. However, we will not accept any liability in case of error or omission.

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## Introduction

Crossject, which was listed in 2014, straddles the boundary between a Biotech essentially specialising in generic drugs and a Medtech providing a genuinely innovative approach to self-injection. This innovation involves a single-use system called Zeneo, which allows needle-free drug administration. The injection takes place by sending the drug solution through one or several small orifices under high pressure.

The company's entire strategy at present is to develop the combination of off-patent drugs with its Zeneo system. The final goal here is to obtain a new product whose distinct medicinal properties offer a real advantage for the patient and healthcare systems.

Crossject's management is highlighting the fact that the company offers the advantage of promoting new drugs with attractive profitability but without the risk associated with discoveries. The pharmaceutical companies currently speak of "New Therapeutics Entities" or "Supergenerics". Crossject is development of portfolio of "supergeneric" products based on its needle-free injection system.

The company is targeting drugs used in chronic treatments such as methotrexate in rheumatoid arthritis and emergency treatments (a priority area) such as adrenaline in anaphylactic shock. We nevertheless believe that the company should maintain its development efforts in the emergency treatment area, where substantial differentiation compared to the competition should be easier to demonstrate.

The pipeline had up until recently been made up of four drugs: methotrexate in rheumatoid arthritis, adrenaline in the treatment of anaphylactic shock, sumatriptan in acute migraine and L15, whose indication has not yet been disclosed. Three new products in the central nervous system area have just been added.

*Value-added  
supergenerics*

MÉDICAMENT	INDICATION	PRÉ-CLINIQUE	CLINIQUE	DÉPÔT	AMM
Methotrexate	Polyarthrite rhumatoïde	Résultats positifs	→	2016 - EU	Fin 2016 Partenaire France
Adrénaline	Choc anaphylactique	→	S2 2015		Partenaire Monde
Sumatriptan	Migraine aiguë	→	S2 2015	2016 - EU	
L15	Possible obtention du statut orphelin				

*Seven products  
under development*

Source : Crossject

Crossject has received a refundable grant of €6.7m from Bpifrance to support these three new projects (apomorphine in the treatment of Parkinson's disease, midazolam in epilepsy and naloxone in painkiller overdoses). With sumatriptan, these new drugs could serve as the cornerstone of a genuine development platform in central nervous system emergencies.

In total, no fewer than seven drugs are under development and should come on the market over the next 3-4 years.

## 1 – Clear advantage in self-administration

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### 1.1 A technological rupture in self-administration

p.6

Self-administration: comfort for the patient ...

... and savings for healthcare systems

Safety enhanced by needle-free and single-use administration

Three forms of injection: intradermal, subcutaneous and intramuscular

### 1.2 Competition

p.7

Combinations in seven different indications with a focus on the CNS

Reduced development risk

Numerous possible combinations in chronic and emergency treatments

## 1 – Clear advantage in self-administration

Crossject's different development projects target therapies where self-administration is the principal administration solution. This approach obviously offers numerous advantages for both the patient and healthcare systems.

*Self-administration:  
comfort for the  
patient ...*

As concerns patients, the objective essentially remains an improvement in comfort and autonomy. The ability to self-administer their treatments "anywhere" also offers the advantage of being less costly for healthcare authorities, with limited visits to healthcare centres (hospitals, clinics etc.). Even if the safety of the different self-injection systems is well controlled at present, the real disadvantage of this approach involves a lack of compliance. The World Health Organization (WHO) estimates that one out of two patients with chronic diseases do not follow their treatment correctly and that 21% modify the prescribed therapeutic doses.

The challenge is therefore to enable the combination of comfort of administration and lower costs for healthcare systems with better treatment compliance in order to lead to better therapeutic outcomes.

### 1.1 A technological rupture in self-administration

Zeneo, the system developed by Crossject, meets this challenge by also contributing technological differentiation in the administration of the originator drug. This system competes directly with other self-administration systems such as pens or pre-filled syringes.

*... and savings for  
healthcare systems*

More specifically, the system involves a gas generator. The gas that propels the liquid is generated during the injection, which can be broken down into two phases. The first phase enables the product to pierce the skin and the second phase adjusts the injection to the desired depth. By adapting the intensity of the discharge, administration can either be intradermal, subcutaneous or intramuscular. The drug is in this manner 100% injected in 50ms.



Source: Crossject

## 1 – Clear advantage in self-administration

*Safety enhanced by needle-free and single-use administration*

Through this system, Crossject is seeking to differentiate itself from existing drugs administered through self-injection. We believe that its principal advantages are greater safety given its single use and absence of a needle, but also the certainty that 100% of the product will be administered (in contrast to administration using a syringe). We believe that this last aspect is of primordial importance in a therapeutic treatment programme (i.e. a chronic disease), but also as an emergency solution with the certainty of 100% administration. The second point is obviously the ergonomics offered by the system in order to boost its comfort of use. Different studies have linked poor treatment compliance with “needle phobia” (between 7% and 22% of the general population is in principle concerned here; Agras et al. 1969; APA; Bienvenu & Eaton, 1998; Costello, 1982). Even if there currently is no specific pharmaceutical-economic study evaluating the advantage of the Crossject system for healthcare systems, we believe that these highlighted factors constitute the entire interest of this innovative system.

The advantage of this system also involves the large range of drugs that can be used. The viscosity or the volume (between 0.1 and 0.6 ml) of the drug to be injected can be modified and fit in perfectly with the system. The system can consequently be adapted to small molecules and large proteins such as monoclonal antibodies. Regarding vaccinations and allergy treatments, Zeneo’s precise and standardised intradermal injection could allow reductions in the antigen doses and the elimination of adjuvants.

*Three forms of injection: intradermal, subcutaneous and intramuscular*

### 1.2 Competition

Zeneo is consequently used by patients who self-administer drugs, either regularly in the context of treatments of chronic diseases or in emergency situations. It therefore competes directly with traditional self-injectable treatments using syringes.

The only truly needle-free system on the market at present was developed by the US company Zogenix. This system, called DosePro Technology, is also needle-free. However, in contrast to Zeneo, it is currently only used in the subcutaneous treatment of migraines. This sumatriptan-based treatment, called Sumavel DosePro, was launched in the United States in 2010 and in Europe in 2011 and was sold to Endo in May 2014 for a total of \$85m along with royalties on future product sales. Product sales equalled \$31.7m for the full year 2013.

Crossject’s approach involves the targeting of chronic or acute diseases by offering genuine differentiation in terms of patient treatment using generic drugs. Seven combinations are currently being developed in four areas:

1. Emergency treatment of allergic (or anaphylactic) shock
2. Chronic treatment of rheumatoid arthritis
3. Treatment of acute migraines
4. New portfolio involving the CNS and L15

*Combinations in seven different indications with a focus on the CNS*

## 1 – Clear advantage in self-administration

We believe that these new products can provide genuine added value in each indication being developed. Described by Teva as NTEs (New Therapeutic Entities), they are included among this company's speciality medicine programmes. Based on already known drugs, this process allows the targeting of populations seeking new treatments for their pathologies. Even if only the drug delivery method is modified, these NTEs enable the improvement of treatment effectiveness (better compliance). As such, we believe that the strategy based on portfolios of activities makes sense in order to enable the company to be viewed as a Specialty Pharma rather than a Medtech.

### NTE - a process to grow our pipeline

The NTE process generates new specialty products that:

- Address an unmet patient need
- Are based on a known molecule
- Are formulated, delivered, or used in a novel way

Products from NTE process:  
attractive risk/return profile

- Proven efficacy
- Lower development risk
- Shorter timelines
- Lower costs
- Significant returns



Source: Teva

The advantage for Crossject in developing a pharmaceutical form using Zeneo is to limit the development risk (drugs already known) and development costs (between €2-4m per project) and to reduce development times, which in principle average between 18-24 months on the European market and 36 months for the US market according to the company.

Products from NTE process have shorter development timelines and lower costs

Products from NTE process target an attractive space

NCE (New Chemical Entity) process = 10-15 years, \$1-2B



NTE process = 3-6 years, \$10-50M



- 505(b)(2) pathway in U
- Referencing safety & efficacy data of origina molecule



Source : Teva

Out of the some 900 injectable drugs currently on the market, Crossject estimates that around 100 products correspond to the specifications of the Zeneo system and therefore could be injected using this needle-free injection system as of today. These specifications take into account the technical aspects (viscosity of the injected drug, quantity to be injected etc. ) as well as the financial aspects (public sale price, estimated profitability of the system, competitive intensity).

### Short-term newsflow: first launch in 2017!

Among the seven pathologies listed above and in a short-term perspective, we anticipate the filing of a European approval application in rheumatoid arthritis at the beginning of 2016 and the launch of bioequivalence studies for adrenaline (allergic shock) and sumatriptan (acute migraine) and L15 (undisclosed indication) over the coming weeks. The company is in the process of completing arrangements with industrial sites, with certification by the European regulatory authorities (GMP certification) expected over the coming days. Following this, the company will have production capacity for 1.5 million units per year. This should be sufficient for the initial launches.

Reduced  
development risk

Numerous possible  
combinations in  
chronic and  
emergency  
treatments



## 2 – Allergic shock emergencies

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### 2.1 An emergency market

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An emergency situation that could be a public health issue in the United States  
A market dominated by Mylan's EpiPen

### 2.2 EMA conclusions that will indicate the design of the study

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A market totalling several billion dollars  
Ease of use is the principal advantage in this emergency treatment

### 2.3 Valuation

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A worldwide distribution partnership agreement has already been signed

## 2 – Allergic shock emergencies

As of today, only the allergic shock emergency indication has a worldwide commercial distribution partnership. Crossject signed an exclusive licence and supply contract covering the injection of epinephrine using the Zeneo system in 2013. The partner, whose name has not been disclosed, has taken responsibility for all the clinical expenses as well as the registration of the product. In return, it has obtained a worldwide licence for the product. For its part, Crossject is supplying all the elements needed for the clinical study and registration.

The financial terms of this agreement have been only partially disclosed. An upfront of €9m will be paid and accompanied by revenues and royalties on sales at variable rates depending on the country and the date of the sale.

### 2.1 An emergency market

Allergic (or anaphylactic) shock is a violent allergic reaction that leads to disruption in the blood flow. This leads to a state of shock, with a brutal drop in arterial pressure putting into danger the vital organs, notably the heart and the brain. The reaction can be rapid and violent and occur within five to 20 minutes. This acute pathology represents an emergency situation for the patient that requires an immediate solution.

Epinephrine (also called adrenaline) is the gold standard treatment for anaphylactic shock. The administration of this neurotransmitter is of primordial importance, as an incorrect dose can lead to the death of the patient. According to the American College of Allergy, Asthma & Immunology, it can be estimated that over 1.6% of the population has experienced anaphylactic shock, thereby indicating the importance of this market. The United States remains the principal market for this pathology (90% of worldwide sales). Following a few deaths, the different states have accelerated the adoption of laws designed to increase the awareness of this public health issue.

There are currently four pens on the market, EpiPen, Auvi Q, Anapen and Jext. The principal player nevertheless remains Mylan with its EpiPen, which reached \$1bn in sales in 2014.

The only difference between these four products involves the injection system. The latest entrant, Auvi Q by Sanofi, differs by offering vocal instructions for its use. In practical terms the retractable needle system orally guides the user as to the steps to take in the injection. As such, a third party can easily administer the product in an emergency situation. Nevertheless, the market remains dominated by EpiPen and winning significant market share requires substantial increases in marketing costs. For example, AUVI Q, which was launched in 2013, reached €72m in sales in 2014 and €113m for the first nine months of 2015.

Note that Sanofi halted production of the Auvi Q a few weeks ago and has recalled nearly a half million devices on the US and Canadian market. The recall was decided after Sanofi received around 20 reports of patients experiencing undesirable reactions following the use of the device. It would appear that the error came from the dose included in the injectable system. Out of the 2.8 million units distributed in North America, the recall involves 492,000 packs with two devices each. The financial impact of this recall for Sanofi is estimated at around €100m.

*An emergency situation that could be a public health issue in the United States*

*A market dominated by Mylan's EpiPen*

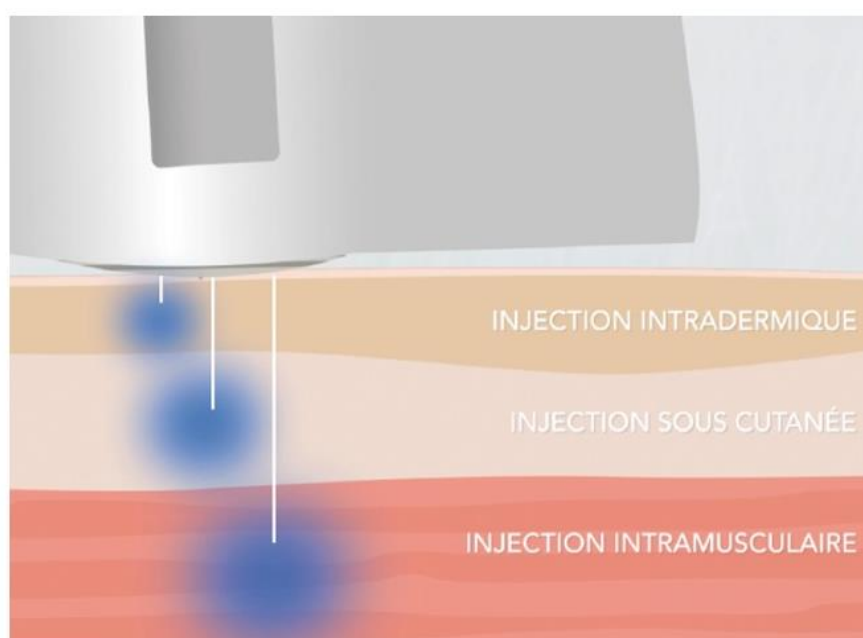
## 2 – Allergic shock emergencies

### 2.2 EMA conclusions that will indicate the design of the study

A recent study has indicated that only 16% of pen users performed the injection correctly in cases of severe allergic reactions (source: "Development and validation of educational materials for food allergy". J Pediatr 2012). The error generally comes for poor positioning of the device during the injection. Following a few serious incidents, the European healthcare authorities decided to conduct a full review of injectable pens in this indication based on the hypothesis that the effectiveness of injectable pens in intramuscular injections is questionable.

We are waiting for the EMA's conclusion to know the protocol for the launch of the study (new evaluation criteria?) recommended for a bioequivalence test. The bioequivalence study could potentially be conducted in comparison to an intramuscular injection. Misuse, the long time for preparation (ten seconds) and, most importantly, needles that do not guarantee the injection of the product in the muscle are obstacles to guaranteeing an immediate clinical response.

The Zeneo system consequently responds perfectly to these questions. As described above, the intensity of the administration discharge can be modified beforehand in order to assure the intramuscular injection of the product. This is not the case for the majority of injection pens (their needles are too short and the pens are difficult to use in emergency situations).



Source: Crossject

Zeneo's characteristics fit in perfectly with the needs of this emergency pathology. The system is easy to use and dosage errors are virtually non-existent for the patient or a third party. The ease of self-administration also reflects the fact that Zeneo adrenaline is immediately ready for use, in contrast to the EpiPen.

A market totalling several billion dollars

Ease of use is the principal advantage in this emergency treatment

## 2 – Allergic shock emergencies

### 2.3 Valuation

We estimate that a study will be launched at the beginning of 2016, with a potential launch of the product at the end of 2017. Given that the name of the distribution partner has not been disclosed, we estimate that the salesforce could be limited in certain zones.

In this specific approach that could be described as “in-town emergencies”, the treatment is simple. The patient is diagnosed as showing risks of allergic emergencies and receives a prescription for an emergency does to be administered in emergency situations. However, in the large majority of cases, the doses sold are replaced on expiration without having been used. As such, sales volumes are indexed to the population concerned and have no real connection with the number of emergencies.

As such, using a conservative approach, we have valued this product by estimating that potential sales of the Epinephrine/Zeneo combination would take a small portion of the total sales of epinephrine (the price of the Epipen is €40 in Europe and between \$100 and \$130 in the United States). We anticipate an EBIT margin of 35% starting in the fourth year of commercialisation, product capex equal to 2% of total sales and a WCR equal to 10% of total sales.

*A worldwide distribution partnership agreement has already been signed*

m€	2015	2016	2017	2018	2019	2020	2021	2022
Sales Epinephrine (m\$)	1800	1818	1836	1855	1873	1892	1911	1930
%		1%	1%	1%	1%	1%	1%	1%
in EUR (m€)	1636	1653	1669	1686	1703	1720	1737	1754
%			0,0%	1,0%	2,0%	3,0%	4,0%	4,0%
<b>SALES</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>17</b>	<b>34</b>	<b>52</b>	<b>69</b>	<b>70</b>
<b>EBIT</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>3</b>	<b>9</b>	<b>15</b>	<b>24</b>	<b>28</b>
				15%	25%	30%	35%	40%
<b>Partnership</b>	<b>0,0</b>	<b>0,0</b>	<b>0,0</b>	<b>1,3</b>	<b>4,3</b>	<b>7,7</b>	<b>12,2</b>	<b>14,0</b>
	50%	100%	50%	50%	50%	50%	50%	50%
Tax	0,0	0,0	0,0	-0,2	-0,6	-1,1	-1,7	-2,0
CAPEX		0	0,0	0,3	0,7	1,0	1,4	1,4
D&A	0	0	0	0	0	0	0	0
Working Capital	0,0	0,0	0,0	1,7	3,4	5,2	6,9	7,0
Var WC	0,0	0,0	0,0	1,7	1,7	1,8	1,8	0,1
<b>Free Cash Flow</b>	<b>0,0</b>	<b>0,0</b>	<b>0,0</b>	<b>-0,3</b>	<b>2,6</b>	<b>5,9</b>	<b>10,1</b>	<b>13,4</b>

Source : Invest Securities

## 3 – Chronic treatment of rheumatoid arthritis

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### 3.1 A rapidly evolving market

p.14

The rheumatoid arthritis market totals several billion dollars but is extremely crowded

Injections show a real advantage over oral administration

### 3.2 The advantages of MTX/Zeneo

p.15

First-line positioning for an active population

Two regional agreements already signed

### 3.3 Valuation

p.17

## 3 – Chronic treatment of rheumatoid arthritis

Crossject signed an exclusive licence and supply contract for the Zeneo/methotrexate combination with the Biodim pharmaceutical company in 2012. Under this regional agreement, Biodim has an exclusive licence in France for the product in the treatment of rheumatoid arthritis. Note that Crossject is assuming the development costs. Crossject will receive up to €1m per development milestone up until the commercialisation of the product. After this, the company will receive royalties on sales of the product on the French market at a rate that has not been disclosed but has been described by the company as significant. A second regional agreement in India was signed in the middle of 2015. With an application filing expected over the coming months for approval at yearend 2016, we anticipate an accelerated pace of signings of regional agreements with local players, principally on the US and Asian markets.

### 3.1 A rapidly evolving market

Rheumatology is one of the principal markets in the pharmaceutical universe in value terms. This market covers numerous pathologies such as rheumatoid arthritis, lupus etc. that manifest themselves in the form of joint pain and disabling inflammation. These chronic diseases are seeing strong growth and affect 52.5 million Americans according to the American College of Rheumatology.

Again according to the American College of Rheumatology, 1.3 million American adults suffer from a form of rheumatoid arthritis (two women for one man).

The exact aetiology of this disease is unknown, even if a genetic predisposition appears possible as well as environmental exposure. More specifically, rheumatoid arthritis is an auto-immune disease, i.e. the patient's own immune system synthesises antibodies that attack the synovial membrane of joints. As a result of this, the synovial membrane produces an excessive amount of liquid containing abnormal inflammatory enzymes that attack the joint. The evolution of this pathology can lead to a degradation of organs such as the lungs, the heart or the nerves. If the patient is not treated rapidly or if the treatment is inadequate, the patient's life expectancy can be reduced.

The goal of current treatments is to slow the progression of the pathology and the bone destruction. The guidelines recommend rapid medical treatment leading to combinations between different treatments.

The initial treatment involves non-steroid anti-inflammatory drugs and methotrexate. In case of failure and further evolution of the pathology, the basis of treatment remains methotrexate in combination with an anti-TNF or a JAK inhibitor in the United States. Those patients still presenting symptoms can be then treated with other therapeutic classes such as Orencia (Bristol-Myers), Actemra (Roche) or Rituxan (Biogen Idec / Roche).

The rheumatology market totals over \$40bn in value terms and should continue to grow over the coming years despite the arrival of generic versions of Humira. The market continues to be driven by anti-TNFs such as Enbrel (Amgen / Pfizer) and Humira (AbbVie), Remicade (JNJ, MRK), Simponi (JNJ, MRK) and Cimzia (UCB), followed by new entrants such as Xeljanz (Pfizer). Anti-TNFs consequently dominate the market, notably with Humira, which showed \$12.5bn in sales in 2014.

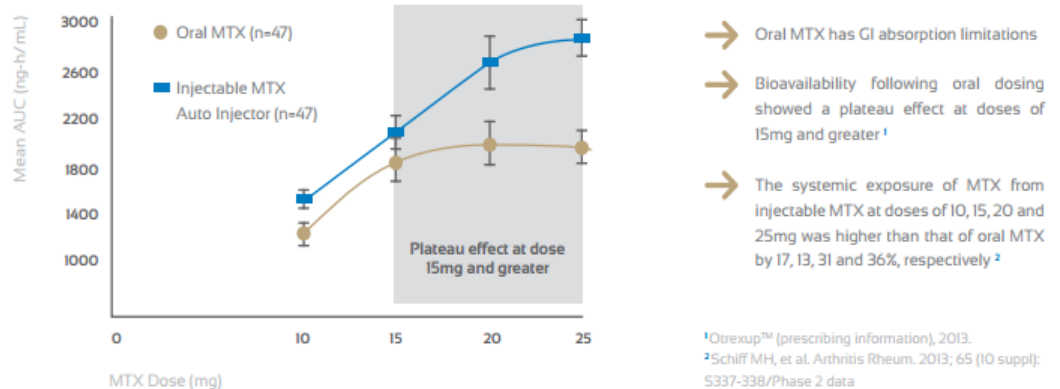
Crossject is currently targeting the generic version of methotrexate, which acts to inhibit the reduction in folic acid and the proliferation of tissue cells. It acts more specifically on actively proliferating tissue and is therefore used in certain cancers and auto-immune diseases. The goal in this case is to reduce the inflammation and suppress the immune system reactions.

*The rheumatoid arthritis market totals several billion dollars but is extremely crowded*

## 3 – Chronic treatment of rheumatoid arthritis

Initially administered orally, a patient takes 7.5mg once per week (or 2.5mg three times per week), with this dose potentially doubled based on the clinical result. The Wegrzyn study showed that injections provide greater effectiveness than oral administration. This study effectively showed that oral administration led to a relatively early plateau effect in contrast to injections.

Injectable MTX Value Proposition = Increased Bioavailability



Source : Crossject

The subcutaneous injection of methotrexate is significantly more effective than oral administration for the same dose, without an increase in side effects.

### 3.2 The advantages of MTX/Zeneo

Methotrexate is therefore the cornerstone of long-term treatment of a patient suffering from rheumatoid arthritis. Serving as first-line treatment, every patient suffering from rheumatoid arthritis undergoes this treatment.

As noted above, there are two routes of administration: oral and injectable. Oral administration, which could appear more comfortable for the patient, has the disadvantage of having more limited effectiveness than administration by injection, as well as side effects that nevertheless remain minor (the most common being nausea). As such, with greater effectiveness and equivalent side effects, it is recommended to use the injectable route of administration.

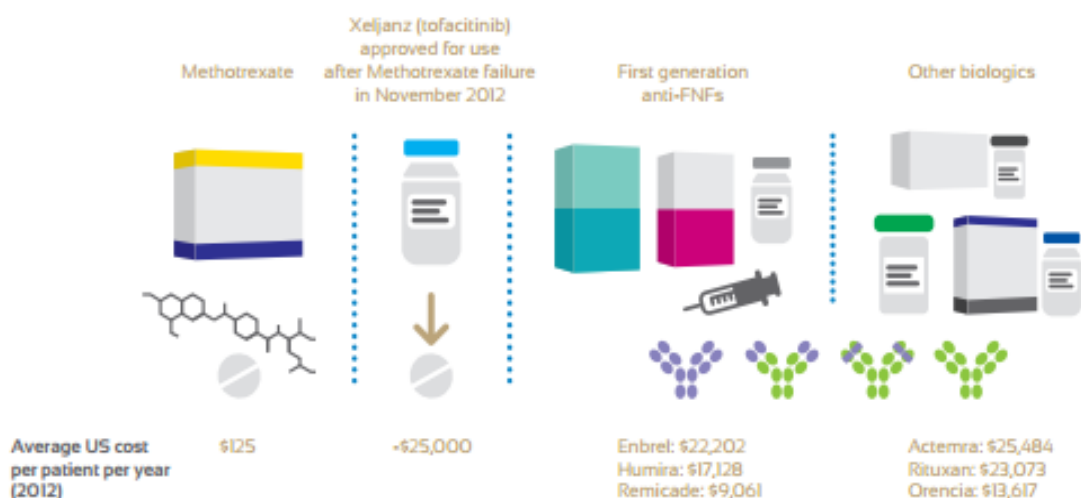
The MTX/Zeneo combination has the advantage of having equivalent effectiveness as the subcutaneous injectable route of administration without patient apprehension regarding the injection of a drug through the use of a needle.

This route of administration therefore combines good effectiveness with comfort of use for the patient.

Injections show a real advantage over oral administration

First-line positioning for an active population

### 3 – Chronic treatment of rheumatoid arthritis



Source: Datamonitor Healthcare, US Redbook, Pfizer Media briefing, November 2012

Additionally, Crossject is emphasising the importance of administering a dose fixed for the patient, thereby reducing the risk of error. The system is locked for a fixed dose, pre-filled, disposable and configured for a specific route of administration. The injection is secured to avoid any abusive use and guarantees a very short duration of injection (1/10 of a second). Even if MTX/Zeneo will be logically offered in five doses (7.5mg, 10mg, 15mg, 20mg and 25mg), thereby covering a large part of prescriptions in rheumatoid arthritis, we nevertheless believe that these dosages could potentially be a slight commercial handicap. In effect, MTX doses can be rapidly modified for the same patient as a function of the evolution of the pathology, but also between one patient and another. This “fixed dose” could very well be more constraining for medical prescriptions than the oral route.

**We do not view MTX/Zeneo as direct competition for oral MTX treatments, but instead as more an alternative solution prior to the shift to anti-TNFs. The real competition would therefore be the traditional intramuscular and subcutaneous routes.**

Crossject published the bioequivalence results for MTX/Zeneo, the only study required by the European authorities, in H2 2014. This mono-centric bioequivalence study was conducted using 52 subjects. The results showed equivalence for the Zeneo administration systems compared to needle-based injections based on the validation of the principal endpoints of the study. Zeneo delivered the planned dose of methotrexate (25 mg). In contrast to studies underway in the United States involving intramuscular administration, development in Europe is based on subcutaneous administration. The principal reason for this difference involves a legal battle between two players on the US market. In order to avoid regulatory problems and penetrate the market more rapidly, Crossject has decided to concentrate on the development of the intramuscular form.

The goal here is to develop a generic version of syringes pre-filled with MTX offering the advantages of the Zeneo system. This combination would potentially improve treatment compliance compared to traditional injections.

Two regional agreements have been signed for the commercialisation of MTX/Zeneo, one on the French market with Biomid and the other on the Indian market with Sayre Therapeutics. The registration filing for the latter agreement is planned for H1 2017. The contract signed with Sayre Therapeutics for India should involve royalties ranging between 20% and 40% of sales.

*Two regional agreements already signed*



## 3 – Chronic treatment of rheumatoid arthritis

### 3.3 Valuation

We are assuming a price of €25 on the European market and \$120 on the US market, with these two markets remaining the principal markets for this product. With a filing expected at the beginning of 2016 and a partner already found for the French market, we anticipate initial sales starting in 2017, possibly supported by new partnerships on the European market.

	2016	2017	2018	2019	2020	2021	2022
<b>US</b>							
Population	317	320	323	327	330	333	337
prevalence AR	0,6%	0,6%	0,6%	0,6%	0,6%	0,6%	0,6%
% sous MTX	50%	50%	50%	50%	50%	50%	50%
% avec EI ou admin. inject	30%	30%	30%	30%	30%	30%	30%
% patients actifs	30%	30%	30%	30%	30%	30%	30%
Pop cible US (m)	0,1	0,1	0,1	0,1	0,1	0,1	0,1
Utilisation par patient par an	52	52	52	52	52	52	52
Marché en volume	4,5	4,5	4,5	4,6	4,6	4,7	4,7
Taux de pénétration %			1%	2%	4%	6%	8%
Unités vendues			0,0	0,1	0,2	0,3	0,4
Prix			109	109	109	109	109
<b>Ventes US (m€)</b>			<b>5,0</b>	<b>10,0</b>	<b>20,2</b>	<b>30,6</b>	<b>41,2</b>
<b>EU-5</b>							
Population	321	324	327	331	334	337	341
prevalence AR	0,6%	0,6%	0,6%	0,6%	0,6%	0,6%	0,6%
% sous MTX	50%	50%	50%	50%	50%	50%	50%
% avec EI ou admin. inject	30%	30%	30%	30%	30%	30%	30%
% patients actifs	30%	30%	30%	30%	30%	30%	30%
Pop cible US (m)	0,1	0,1	0,1	0,1	0,1	0,1	0,1
Utilisation par patient par an	52	52	52	52	52	52	52
Marché en volume	4,5	4,6	4,6	4,6	4,7	4,7	4,8
Taux de pénétration %		2%	4%	6%	8%	10%	10%
Unités vendues		0,1	0,2	0,3	0,4	0,5	0,5
Prix		25	25	25	25	25	25
<b>Ventes EUR (m€)</b>		<b>2,3</b>	<b>4,6</b>	<b>7,0</b>	<b>9,4</b>	<b>11,8</b>	<b>12,0</b>
<b>ROW</b>				<b>1,7</b>	<b>3,0</b>	<b>4,2</b>	<b>5,3</b>
				10%	10%	10%	10%
<b>Ventes totales (m€)</b>	<b>0,0</b>	<b>2,3</b>	<b>9,6</b>	<b>18,7</b>	<b>32,6</b>	<b>46,7</b>	<b>58,5</b>
<b>EBIT</b>	<b>-2,0</b>	<b>-1,0</b>	<b>-0,5</b>	<b>3</b>	<b>8</b>	<b>14</b>	<b>20</b>
				15%	25%	30%	35%
Versement Biomid	0,5	0,5					
<b>Partenaire</b>	<b>-1,5</b>	<b>-0,5</b>	<b>-0,5</b>	<b>1,4</b>	<b>4,1</b>	<b>7,0</b>	<b>10,2</b>
				50%	50%	50%	50%
Impots	0,0	0,0	0,1	-0,2	-0,6	-1,0	-1,4
CAPEX	0	0	0	0,4	0,7	0,9	1,2
D&A	0	0	0	0	0	0	0
WC	0,0	0,5	0,9	1,4	1,9	2,4	2,4
Change in WC	0,0	0,5	0,5	0,5	0,5	0,5	0,0
<b>Free Cash Flow</b>	<b>-1,5</b>	<b>-0,8</b>	<b>-0,4</b>	<b>1,1</b>	<b>3,7</b>	<b>6,5</b>	<b>10,0</b>

Source : Invest Securities

The information contained in this document has been derived from sources deemed to be reliable. However, we will not accept any liability in case of error or omission.

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## 4 – Headache, the asset with the strongest potential

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### 4.1 A market evangelised by Zogenix

p.19

A market with considerable volume ...  
...and very few therapeutic options

### 4.2 Bioequivalence study to be launched over the coming weeks

p.20

Development programme to be accelerated in 2016  
No partnership agreement as of yet

### 4.3 Valuation

p.21

We anticipate sales on the order of €85m

## 4 – Headache, the asset with the strongest potential

The second type of acute pathology involves the treatment of migraine. Crossject is developing sumatriptan in conjunction with its Zeneo system. This combination will consequently compete directly with the only needle-free treatment at present, Sumavel DosePro by Zogenix, which was acquired by Endo last year. This first entrant reached full year sales of \$31.7m in 2013.

### 4.1 A market evangelised by Zogenix

The American Medical Association estimates that over 26 million persons in the United State suffer from migraine. The diagnosis of migraine is essentially based on the symptoms of the pathology, i.e. a violent headache lasting for several hours often accompanied by nausea or vomiting, with sensitivity to light and noise.

There are different forms of migraine. 92 million persons are potentially subject to migraine and only 45% of them are in principle diagnosed. 50% of diagnosed patients show a severe form of the pathology. These patients are the target of Zeneo Sumatriptan.



Source: Crossject

This pathology remains extremely debilitating for patients. The frequency of severe migraine attacks generally increases over time. The WHO defines migraine as one of the 20 most debilitating pathologies. As noted above, migraine in the broadest sense of the term is poorly diagnosed, thereby leading to a lack of medical treatment.

Patients suffering from severe migraine during an attack have few therapeutic options. The principal treatments include triptans and NSAIDs, as well as some painkillers such as opiate derivatives. Triptans are considered to be first-line treatment. More precisely, sumatriptan is a selective antagonist of 5-hydroxytryptamine-1 (5HT<sub>1d</sub>) vascular receptors without effect on the other sub-types of 5HT receptors (5HT<sub>2</sub> to 5HT<sub>7</sub>). These 5HT<sub>1d</sub> vascular receptors induce vasoconstriction. The dilatation of these vessels is in principle responsible for migraine in humans.

Triptans are generally reserved for patients suffering severe attacks.

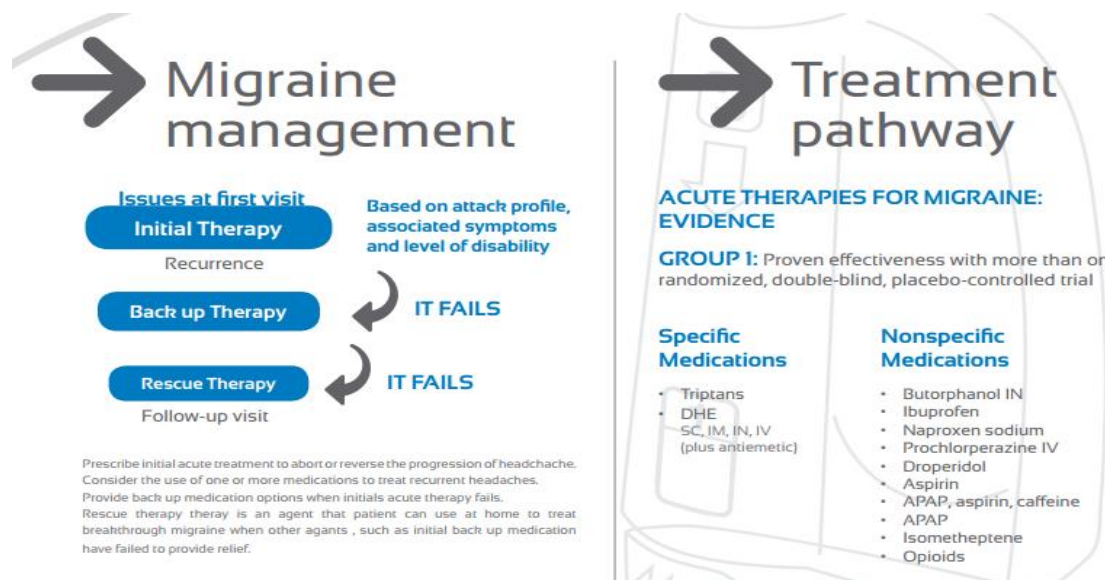
*A market with considerable volume ...*

*...and very few therapeutic options*

## 4 – Headache, the asset with the strongest potential

### 4.2 Bioequivalence study to be launched over the coming weeks

Zeneo principally targets severe migraine and patients with facial algia. Different routes of administration of sumatriptan exist: inhalation, oral administration, injections. In its oral form (the most commonly used at present), sumatriptan has severe side effects and the time of action can reach two hours.



Source : Crossject

In the United States, Crossject has entered into discussions with the FDA in connection with a Pre-IND (Pre-investigational New Drug Application) procedure. The launch of the bioequivalence study of Zeneo Sumatriptan is expected over the coming days. The clinical study will be conducted by Parexel, a CRO (Contract Research Organisation), in South Africa and involve 72 eligible patients. The goal of this study is to demonstrate that administration using the Zeneo needle-free injection system in the treatment of facial algia and severe migraine produces the same effects as administration using an injection pen.

Development programme to be accelerated in 2016

No partnership agreement as of yet

## 4 – Headache, the asset with the strongest potential

### 4.3 Valuation

*We anticipate sales on the order of €85m*

With a bioequivalence study slated to begin soon, we anticipate launch in Europe and the United States in 2018. The price of the treatment should be around \$70 on the US market and €35 in Europe, with a market share of 3% and average use of one and a half times per month. Crossject does not have any specific partner in this indication at present. We are currently assuming the same form of distribution, i.e. through regional partners. Our model as such is clearly dependent on a future partnership that could lead us to adjust our estimated market penetration. As with the other products, our approach remains extremely conservative.

	2015	2016	2017	2018	2019	2020	2021	2022
<b>US</b>								
Total population US (m)	314	317	320	323	327	330	333	337
Prevalance migraine	16%	16%	16%	16%	16%	16%	16%	16%
Prevalence de modéré à sévère	8%	8%	8%	8%	8%	8%	8%	8%
Utilisation de sumatriptan	40%	40%	40%	40%	40%	40%	40%	40%
Population cible	1 561 150	1 576 762	1 592 529	1 608 455	1 624 539	1 640 785	1 657 192	1 673 764
Utilisation par patient	18	18	18	18	18	18	18	18
Marché en volume	28 100 705	28 381 712	28 665 529	28 952 184	29 241 706	29 534 123	29 829 464	30 127 759
Taux de pénétration			0,0%	1,0%	1,5%	2,0%	2,5%	3,0%
Volume (en m)	0,0	0,0	0,0	0,3	0,4	0,6	0,7	0,9
Prix unitaire	58	58	58	58	58	58	58	58
<b>Ventes US en m€</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>17</b>	<b>26</b>	<b>34</b>	<b>44</b>	<b>53</b>
<b>EUROPE</b>								
Total population US (m)	318	321	324	327	331	334	337	341
Prevalance migraine	16%	16%	16%	16%	16%	16%	16%	16%
Prevalence de modéré à sévère	8%	8%	8%	8%	8%	8%	8%	8%
Utilisation de sumatriptan	40%	40%	40%	40%	40%	40%	40%	40%
Population cible	1 580 547	1 596 352	1 612 316	1 628 439	1 644 723	1 661 170	1 677 782	1 694 560
Utilisation par patient	18	18	18	18	18	18	18	18
Marché en volume	28 449 837	28 734 336	29 021 679	29 311 896	29 605 015	29 901 065	30 200 076	30 502 076
Taux de pénétration			0,0%	1,0%	1,5%	2,0%	2,5%	3,0%
Volume (en m)	0,0	0,0	0,0	0,3	0,4	0,6	0,8	0,9
Prix unitaire	35	35	35	35	35	35	35	35
<b>Ventes EUR en m€</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>10</b>	<b>16</b>	<b>21</b>	<b>26</b>	<b>32</b>
<b>VENTES totales</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>27</b>	<b>41</b>	<b>55</b>	<b>70</b>	<b>85</b>
<b>EBIT</b>	<b>0</b>	<b>-2</b>	<b>-1</b>	<b>7</b>	<b>12</b>	<b>19</b>	<b>28</b>	<b>34</b>
			15%	25%	30%	35%	40%	40%
<b>Partenaire</b>	<b>0,0</b>	<b>-2,0</b>	<b>-1,0</b>	<b>3,4</b>	<b>6,2</b>	<b>9,7</b>	<b>14,0</b>	<b>17,0</b>
	50%	100%	100%	50%	50%	50%	50%	50%
Impots	0,0	0,0	0,0	-0,5	-0,9	-1,4	-2,0	-2,4
CAPEX		0	0,0	0,5	0,8	1,1	1,4	1,7
D&A	0	0	0	0	0	0	0	0
BFR	0,0	0,0	0,0	2,1	4,1	5,5	7,0	8,5
Variation BFR	0,0	0,0	0,0	2,1	2,1	1,4	1,5	1,5
<b>Free Cash Flow</b>	<b>0,0</b>	<b>-2,0</b>	<b>-1,0</b>	<b>1,4</b>	<b>4,1</b>	<b>8,0</b>	<b>12,0</b>	<b>14,8</b>

Source : Invest Securities

## 5 – An expanding pipeline

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### 5.1 Midazolam could be the first product in this new series

p.23

Midazolam in epilepsy

Potential competition with the Pfizer drug

### 5.2 Apomorphine in Parkinson's disease

p.24

Emergency unblocking in Parkinson's disease

With a price 10x higher, the target population would appear to be active persons

### 5.3 Naloxone in opioid overdoses

p.25

A change in the treatment of pain

Un Launch anticipated at the end of 2019 / beginning of 2020

## 5 – An expanding pipeline

In addition to the “L15” development programme, which targets emergency situations in an as yet undisclosed pathology (discussions underway with the healthcare authorities concerning the status of this drug), Crossject recently announced an expansion of its development pipeline, notably through three products targeting neurological emergencies: i) midazolam in severe epileptic seizures, ii) apomorphine in Parkinson’s disease and iii) naloxone in opioid overdoses. Through this “new” pipeline, the company is seeking to present a coherent profile with marketing synergies.

The expansion in the development profile has led to Crossject receiving a €6.7m reimbursable three-year grant in the framework of the Investments for the Future programme managed by Bpifrance.

### *Midazolam in epilepsy*

#### **5.1 Midazolam could be the first product in this new series**

Midazolam (Buccolam) is a solution injected during prolonged acute convulsive seizures in children older than six months (three months in hospital settings). The goal is not to cure the pathology, but instead to prevent the appearance of its symptoms. An epileptic seizure is a therapeutic emergency given that it can very rapidly lead to irreversible brain damage. The rapid control of convulsions and their systemic consequences is therefore of primordial importance. The injection is currently made on the buccal level.

If the seizure is not controlled, it can lead to central nervous system damage in the child. A prolonged seizure can therefore degenerate into status epilepticus. However, these seizures can also become more and more frequent and longer. In this case, the treatment must be able to be administered rapidly by a third party with the correct dosage.

The clinical alternative to injections is currently rectal diazepam, which has obvious disadvantages in cases of seizures in adolescents.

A prospective study compared midazolam (0.2mg/kg in intramuscular injection) to diazepam (0.3mg/kg in IV) in terms of effectiveness and onset of action in children suffering epileptic seizures lasting longer than ten minutes [39]. The effectiveness rate was identical, but the intramuscular injection of midazolam led to a significantly more rapid end of the seizure (8 min vs. 11 min) (source: “Status epilepticus in adults and children; N. Engrand”. The advantage of midazolam is consequently a very short duration of action (less than one minute) accompanied by substantial effectiveness.

Midazolam/Zeneo fits in perfectly with these parameters. Intramuscular administration by a third party is facilitated by the Zeneo system, with the certainty of administering the correct dose. The example of a child suffering a seizure in school is an extremely good example of the interest of a simplified form of action. In this case, rapid action can be taken before the arrival of medical help in order to limit potential damage.

### *Potential competition with the Pfizer drug*

Note that even if seemingly more expensive than Buccolam (four syringes should cost €86 vs. €3 for six injectable doses of Buccolam), the cost of the healthcare systems would be potentially less. In effect, the cost of treatment of patients in emergency rooms along with their transportation would be higher in connection with treatment with Buccolam. This remains on one of the key points in terms of the pharmaco-economy highlighted by the pharmaceutical companies distributing the drug.

Pfizer appears to be developing an old-style pen that could be used in outside the hospital setting or as an outpatient. We have very few details concerning this programme, which does not enter into the company’s core business.

The combination consequently targets epileptic seizures. By ending epileptic seizures in less than two minutes, the injection of midazolam allows the stabilisation of the patient’s condition prior to the arrival of the emergency services while restoring their autonomy. According to Datamonitor, 1.9 million persons in Europe and 2.2 million persons in the United States suffer from epilepsy. We anticipate registration of the combination in the intramuscular form at the end of 2017 and commercial launch in H2 2018.

## 5 – An expanding pipeline

### 5.2 Apomorphine in Parkinson's disease

Parkinson's disease is a chronic degenerative neurological disorder caused by dysfunction on the level of the neurons, which no longer secrete the dopaminergic neurotransmitter, thereby leading to different forms of difficulties in movement. This lack of dopamine on the level of the brain causes motor disorders. There are two phases of the pathology, referred to as On/Off, corresponding to periods without symptoms and periods with symptoms. Around 50% of patients will experience flare-ups in OFF periods. However, their intensity varies from one patient to another.

The different treatments (drug or surgical) are designed to treat the symptoms of the pathology, i.e. by increasing dopamine or limiting its degradation. The treatment of patients with Parkinson's depends on their age as well as the evolution of the disease.

More specifically, Crossject should target apomorphine, a dopaminergic agonist (synthesised molecule very similar to dopamine) that reproduces the effect of the neurotransmitter. As an agonist of dopamine, apomorphine acts to stimulate the organism's nerve cells. This action reduces the symptoms of Parkinson's disease.

The drug is administered by subcutaneous injection and is generally used as a second-line treatment after oral treatments.

Subcutaneous administration principally serves to "unblock" a patient experiencing freezing or motor block.

Like the other pathologies, we believe that the combination of the Zeneo system with apomorphine offers a genuine advantage. As this freezing blocks the patient's movements, the system must be easy to use.

In theory, the target population could be very large. However, the price of the Crossject combination should be significantly higher than apokin with subcutaneous injection. Compared to the current price of €2, we estimate that the price of the combination should be 10x higher, i.e. around €20. As such, Crossject will essentially target active persons suffering only occasional freezing episodes who seek a simple and fast acting system. This population would therefore be potentially less affected by the disease. Consequently, Crossject's approach should not directly compete with injection pumps, which principally target patients suffering from slight numerous freezing episodes. The real advantage of this combination using the subcutaneous route is the complete and rapid absorption of the product. Subcutaneous administration enables the product to reach the brain in less than ten minutes, thereby enabling a rapid effect on the Parkinson's symptoms. We anticipate a registration filing at the end of 2018 for a potential launch in H2 2019.

Apomorphine/Zeneo can therefore be viewed as an emergency treatment for persons in the "off" phase of Parkinson's disease (80% of this population). During these "off" episodes, patients are suddenly unable to move without taking a dopamine agonist. Easy to use, precise and rapid, the injection of apomorphine using the Zeneo system allows the restoring of the quality of life of patients and addresses an important medical need given the current absence of a satisfactory solution (particularly for active persons suffering only occasional episodes). The market for Parkinson's disease treatment could equal over \$2.6bn worldwide by 2020.

*Emergency unblocking in Parkinson's disease*

*With a price 10x higher, the target population would appear to be active persons*



## 5 – An expanding pipeline

### 5.3 Naloxone in opioid overdoses

The “pain” market takes numerous forms ranging from backaches to neuropathic pain. It would appear that nearly 10% of adults in the United States suffer from moderate to severe pain and that over half of the population suffers chronic pain.

The market is estimated at a little over \$13bn, with moderate growth (including the opiates market) and \$6bn for chronic pain. Nevertheless, population aging, more specific diagnosis and treatment of chronic pain along with the arrival of a new class of drugs should favour growth on this market.

In an extremely fragmented market, we can estimate that Endo remains the principal player. The goal of the healthcare authorities at present is to diversify treatments in order to reduce addiction to opioids.

Opioids are substances derived from poppies or synthetic analogues with similar effects. Opioids can cause heavy dependence and withdrawal symptoms when persons stop taking the product. Additionally, this class of drugs has extremely serious undesirable effects that can lead to respiratory depression in users.

Naloxone (an opioid antagonist) is administered as an antidote in response to overdoses. Different routes of administration exist for this product: intravenous, intramuscular, subcutaneous or intranasal. The market still remains essentially hospital-based, even if the drug is already distributed in pharmacies in a few countries.

The combination of Naloxone and the Zeneo system obviously offers the advantage of rapid, easy and effective administration of the product in response to an overdose. The product acts to reverse the effects of the opioid overdose prior to receiving complete medical care and therefore serves as a transaction action to save the life of the victim.

Several countries have begun to adopt an approach focusing on prevention by distributing kits in specialised centres (Scotland, United States). The WHO is recommending the use of an entire range of therapeutic options in order to fight against opioid addiction and is supporting countries that establish these types of treatment programmes.

Crossject is responding to this challenge by development a combination that is easy to use for persons unfamiliar with the injection of drugs. We anticipate the launch of a bioequivalence study before the end of 2016 for registration in the subcutaneous form at the end of 2018 / beginning of 2019. This would suggest initial sales at the end of 2019 / beginning of 2020. The price of Hospira’s Evzio is currently \$317 per injection. According to the company, 70,000 to 100,000 persons die each year due to an overdose of opioids, including in the framework of analgesic treatment. The prevalence of exposure to opioids in the United States equals around 2% of the population. In Europe, this percentage is less than 0.67 %.

**We have not taken into account for the moment any potential sales for this new asset class: midazolam in epileptic seizures in children, apomorphine in Parkinson’s disease and naloxone in opioid overdoses. We believe that our current valuation of the company already offers a free option concerning this new pipeline, which depending on clinical results could significantly boost the valuation of Crossject.**

*A change in the treatment of pain*

*Launch anticipated at the end of 2019 / beginning of 2020*

## 6 – Positive momentum and strong undervaluation - BUY

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### 6.1 Summary of the different projects

p.27

A valuation that should rise with the announcements of partnerships and registrations

A highly cautious approach suggesting upside potential of +43%

Three products valued out of the seven under development

### 6.2 Valuation by peer comparisons

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Peer comparisons that do not make much sense

## 6 – Positive momentum and strong undervaluation - BUY

“Supergenerics” improve patient treatment. Be it in terms of comfort, higher effectiveness of the treatment or reduction in undesirable side effects associated with oral administration, each indication currently being developed by Crossject offers an advantage.

Additionally, as set out above, the time and cost of product development is reduced. Given their status as injectable generic drugs, clinical studies are more rapid (two to three years between the feasibility study and the obtaining of marketing authorisation according to the company), with by definition low risk of failure.

The Zeneo technology is currently protected by 31 patent families corresponding to 403 patents, with patent protection running through 2035. Depending on the different indications, we estimate that the EBIT margin for this type of products should equal between 30% and 50% of sales. This high profitability is principally attributable to the type of market addressed (either mass market or specific targets). Most importantly however, Crossject should be able to charge a premium for its supergeneric based on the Zeneo system compared to standard generics prices.

As highlighted above, Zeneo benefits from substantial product extension potential. The new portfolio under development is the best example of this. Crossject consequently has received a reimbursable grant payable based on clinical development, with reimbursement as a function of future sales. The €6.5m received by way of Bpifrance will also enable the company to assure more steps in Zeneo production process on the industrial scale in-house. In particular, Crossject will assure 100% of the pre-assembly of Zeneo devices in-house.

### 6.1 Summary of the different projects

One of the key points in the different product valuations remains the commercial partner. The company is principally targeting regional distribution partners at present. Sales of each product are therefore very highly linked to the choice of partner. We remain highly cautious in our approach at this point by assuming rather low potential market shares and not including any value for the three new products under development by the company or for L15.

Besides we apply corporate costs representing around 5% of the global EBIT as well as tax loss carry forward corresponding at 0,9m€.

We apply a probability of success of 75% to each of these products, a high level compared to other development projects in the sector but justified by the low development risk associated with a supergeneric. We assume a WACC of 11.6% reflecting a risk premium of 6.1% and a risk-free rate (3-month average OAT rate) of 0.9%.

Our conservative approach (depending in part on the distribution partnerships to be found for MTX/Zeneo and Sumatriptan/Zeneo) nevertheless leads us to a target price of €12,1 per share, corresponding to upside of +43% compared to the last sale price.

*A valuation that should rise with the announcements of partnerships and registrations*

*A highly cautious approach suggesting upside potential of +41%*

## 6 – Positive momentum and strong undervaluation - BUY

Three products valued out of the seven under development



### 6.2 Valuation by peer comparisons

It is extremely difficult to value the company using the peer comparison method, as the company represents a unique case in Europe. We list below an assortment of companies that we believe presenting very few comparison with Crossject.

In general, we see two companies that could be reasonably compared with Crossject: Bioject, a US company that, in contrast to Crossject, is only a pen distributor, and Injex, a UK company that is also developing needle-free injection systems but is focusing essentially on four areas: diabetes, dental, veterinary and beauty.

Peer comparisons that do not make much sense

Company Name	TEV/Total Revenues LTM - Latest	TEV/EBITDA LTM - Latest	TEV/EBIT LTM - Latest	P/Diluted EPS Before Extra LTM - Latest	P/TangBV LTM - Latest	NTM TEV/Forward Total Revenue (Capital IQ)	NTM TEV/Forward EBITDA (Capital IQ)	NTM P/E (Capital IQ)	NTM Forward (Capital IQ)
Bioject Medical Technologies Inc. (OTCPK:BJCT)	2,2x	-	NM	NM	NM	-	-	-	-
Etropal AD (BUL:5EO)	3,5x	31,9x	79,1x	NM	4,5x	-	-	-	-
Vigmed Holding AB (publ) (OM:VIG)	50,2x	NM	NM	NM	5,4x	5,45x	NM	NM	NM
Unilife Corporation (ASX:UNS)	12,9x	NM	NM	NM	NM	7,26x	NM	NM	NM
Retractable Technologies, Inc. (AMEX:RVP)	2,6x	NM	NM	20,6x	3,1x	-	-	-	-
Centenial Surgical Suture, Ltd. (BSE:531380)	0,5x	5,6x	7,1x	8,2x	0,6x	-	-	-	-
Well Lead Medical Co., Ltd. (SHSE:603309)	15,4x	87,1x	106,5x	91,1x	11,3x	-	-	-	-
Antares Pharma Inc. (NasdaqCM:ATRS)	3,8x	NM	NM	NM	3,0x	2,70x	-	-	NM
Revolutions Medical Corporation (OTCPK:RMCP)	7,8x	NM	NM	NM	NM	-	-	-	-
Synergetics USA, Inc.	-	-	-	-	-	1,91x	14,65x	25,73x	-

Source : Invest Securities

The information contained in this document has been derived from sources deemed to be reliable. However, we will not accept any liability in case of error or omission.

## Notes

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**Notes**

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## 5 years relative and absolute change in share value



## CONFLICT SCREEN

	Corporate Finance	Treasury stocks holding	Prior communication	Analyst's personal interest	Liquidity contract	Listing sponsor	Research contract
<b>Crossject</b>	No	No	Yes	No	No	No	Yes

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