BRYAN, GARNIER & CO

INDEPENDENT RESEARCH

Shire PLC

A "rare" opportunity!

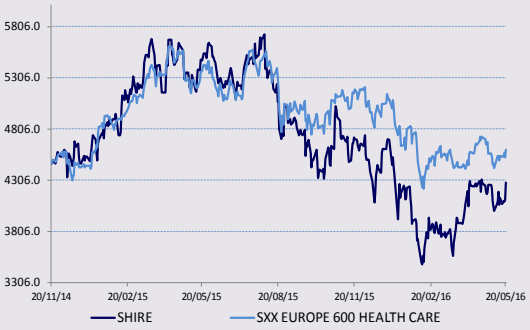
23rd May 2016

Healthcare

Fair Value 5900p (price 4,281p) **BUY**

Bloomberg	SHP LN
Reuters	SHP.L
12-month High / Low (p)	5,730 / 3,480
Market capitalisation (GBPm)	25,397
Enterprise Value (BG estimates GBPm)	29,649
Avg. 6m daily volume ('000 shares)	2,018
Free Float	87.0%
3y EPS CAGR	12.3%
Gearing (12/15)	14%
Dividend yields (12/16e)	0.42%

YE December	12/15	12/16e	12/17e	12/18e
Revenue (USDm)	6,100	6,796	7,604	8,362
EBIT(USDm)	2,785	3,078	3,538	3,989
Basic EPS (USD)	3.89	4.23	4.79	5.51
Diluted EPS (USD)	3.89	4.23	4.79	5.51
EV/Sales	6.27x	6.33x	5.46x	4.73x
EV/EBITDA	13.1x	13.3x	11.1x	9.4x
EV/EBIT	13.7x	14.0x	11.7x	9.9x
P/E	16.0x	14.7x	13.0x	11.3x
ROCE	16.3	12.4	14.0	16.0



We are initiating coverage of Shire with a BUY recommendation and a FV of GBp5,900 with the dawn of a transformative merger with Baxalta. Beyond the fact that we see significant upside (+40%), in our view the pressure on the share price caused by the current arbitrage strategies, and doubts as to the degree of value creation from the transaction have created a "rare" opportunity in that 1/ Shire ex-Baxalta is a strong growth story at an extremely affordable price (2017e PER 12-13x); and 2/ the planned merger should be earnings accretive as of 2017e.

- **So rare, my precious.** On a stand-alone basis, Shire is a growth story which is unparalleled in Europe. Firstly, from a quantitive perspective, EPS growth is expected to average nearly 11% in the 2015-2020e period (vs +8% for the big/specialty pharmas in Europe); but also at the qualitative level since this growth should be underpinned, in particular, by the company's growing exposure to rare diseases (well known for the pricing power it offers, in addition to strong resilience and a degree of immunity given the debate surrounding drug prices).

- **The merger with Baxalta will enhance an already-exceptional growth/risk profile;** our initial estimates of the EPS impact associated with the integration of this Baxter spin-off suggest that the transaction should be earnings accretive as of 2017e (+1%e then +4-5%e in the following years). In addition to the fact that the Hemophilia franchise should continue to grow despite competition from novel new therapies, in our view a portion of the consensus is underestimating the potential for the ImmunoGlobulin activites (and notably that of Hyqvia).

- **Initiation of coverage with a BUY recommendation and an ex-Baxalta FV of GBp5,900**. The earnings dynamic in our forecasts is more than positive…and yet 1/ the share price has fallen by more than 25% over 12m (vs –13% for the STOXX Europe 600 Healthcare); and 2/ the 2017e PER currently stands at a c.30% discount relative to the rest of the sector. Add to this the fact that the shares are trading below our worst case valuation and the opportunity looks more than compelling in our view!

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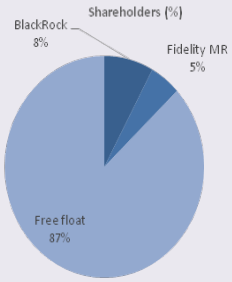

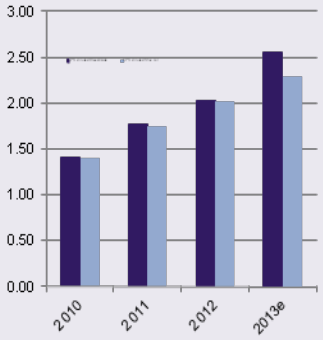

Company description

Shire is a specialty pharma with an increasing focusing on rare diseases

Simplified Profit & Loss Account (USDm)	2014	2015	2016e	2017e	2018e	2019e	2020e
Revenues	5,830	6,100	6,796	7,604	8,362	9,102	9,549
Change (%)	*-%*	*4.6%*	*11.4%*	*11.9%*	*10.0%*	*8.9%*	*4.9%*
Adjusted EBITDA	2,756	2,924	3,248	3,736	4,223	4,726	5,001
EBIT	2,593	2,785	3,078	3,538	3,989	4,452	4,677
Change (%)	*-%*	*7.4%*	*10.5%*	*14.9%*	*12.8%*	*11.6%*	*5.0%*
Financial results	(39.7)	(48.9)	(92.8)	(117)	(50.0)	(11.0)	(2.0)
Pre-Tax profits	2,553	2,736	2,985	3,421	3,939	4,441	4,675
Exceptionals	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tax	468	424	478	582	670	755	795
Net profit	2,088	2,310	2,508	2,839	3,270	3,686	3,880
Restated net profit	2,088	2,310	2,508	2,839	3,270	3,686	3,880
Change (%)	*-%*	*10.6%*	*8.6%*	*13.2%*	*15.2%*	*12.7%*	*5.2%*
Cash Flow Statement (USDm)							
Operating cash flows	4,165	2,368	1,528	1,962	2,464	2,916	3,159
Change in working capital	(63.9)	30.6	78.1	(16.2)	(15.1)	(14.8)	(8.9)
Capex, net	77.0	115	306	319	334	355	363
Financial investments, net	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Dividends	121	134	156	168	190	219	247
Other	(3,287)	(4,935)	319	(3,700)	(3,000)	(900)	0.0
Net debt	(2,187)	1,360	6,172	4,681	2,726	369	(2,188)
Free Cash flow	4,151	2,222	1,144	1,659	2,145	2,576	2,805
Balance Sheet (USDm)							
Tangible fixed assets	838	828	1,049	1,269	1,487	1,705	1,906
Intangibles assets	7,409	13,321	13,236	13,137	13,020	12,884	12,721
Cash & equivalents	3,037	222	1,528	(681)	(1,726)	(269)	2,288
current assets	2,146	2,034	2,372	2,631	2,873	3,110	3,253
Other assets	3,239	427	7,533	5,324	4,279	5,736	8,293
Total assets	13,632	16,610	24,191	22,362	21,659	23,435	26,174
L & ST Debt	850	1,581	7,700	4,000	1000	100	100
Others liabilities	4,119	5,199	5,459	5,734	5,992	6,243	6,395
Shareholders' funds	8,663	9,829	11,031	12,627	14,667	17,091	19,678
Total Liabilities	13,632	16,610	24,191	22,362	21,659	23,435	26,174
Capital employed	8,423	14,194	20,208	20,313	20,398	20,466	20,495
Ratios							
Operating margin	44.47	45.66	45.29	46.52	47.71	48.92	48.97
Tax rate	18.31	15.51	16.00	17.00	17.00	17.00	17.00
Net margin	35.82	37.87	36.90	37.34	39.10	40.50	40.63
ROE (after tax)	24.10	23.50	22.73	22.49	22.29	21.57	19.72
ROCE (after tax)	24.79	16.27	12.41	13.98	16.03	18.01	18.93
Gearing	(25.25)	13.84	55.95	37.07	18.59	2.16	(11.12)
Pay out ratio	5.80	5.82	6.21	5.92	5.82	5.94	6.37
Number of shares, diluted	591	593	593	593	593	593	593
Data per Share (USD)							
EPS	3.53	3.89	4.23	4.79	5.51	6.21	6.54
Restated EPS	3.53	3.89	4.23	4.79	5.51	6.21	6.54
% change	*-%*	*10.3%*	*8.5%*	*13.2%*	*15.2%*	*12.7%*	*5.2%*
BVPS	14.65	16.57	18.59	21.28	24.72	28.81	33.17
Operating cash flows	7.04	3.99	2.58	3.31	4.15	4.92	5.32
FCF	7.02	3.75	1.93	2.80	3.62	4.34	4.73
Net dividend	0.21	0.23	0.26	0.28	0.32	0.37	0.42

Source: Company Data; Bryan, Garnier & Co ests.

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1. Investment Case

Why the interest now?

The reason for writing now

The stock has significantly underperformed the STOXX 600 Europe Healthcare over the last twelve months (-25% vs -13%) despite the fact that 1/ Shire benefits from one of the most attractive growth profiles within the European pharma sector; 2/ the merger with Baxalta should result in value creation. Add to this the fact that our DCF valuation derives a FV of 5,900GBp and the buying opportunity looks compelling in our view, especially since the shares are trading at levels below our worst case valuation.

Cheap or Expensive?

Valuation

The current multiples point to an abnormally high discount relative to the sector average (c.40% based on the 2017^{e} ex-Baxalta PER), whereas 1/ we are forecasting growth far higher than for the peers, and 2/ we believe the fortcoming merger will be accretive on earnings as of 2017e. Add to this the fact that our DCF valuation derives a FV of GBp5,900, and you have a compelling BUY opportunity in our view.

When will I start making money?

Catalysts

In addition to the traditional quarterly reporting in which we shall be paying particular attention to Vyvanse's growth, we shall notably be watching for 1/ the FDA's response regarding the market launches for lifitegrast, and then SHP465; and 2/ the announcement of the finalisation of the Baxalta acquisition (due mid-2016).

What's the value added?

Difference from consensus

Our view may diverge from that of other analysts on at least three points: 1/ we believe that the arrival of new therapies in Hemophilia A will only have a limited impact on Baxalta's EPS; 2/ we are perhaps a little more optimistic on the sales potential for Hyqvia in primary immunodeficiency (PID) and its impact on the Group's margins; and 3/ we are, however, more cautious than the consensus on the ramp-up of lifitegrast (probably because we expect the FDA label to be limited to the treatment of the symptoms).

Could I lose money?

Risks to our investment case

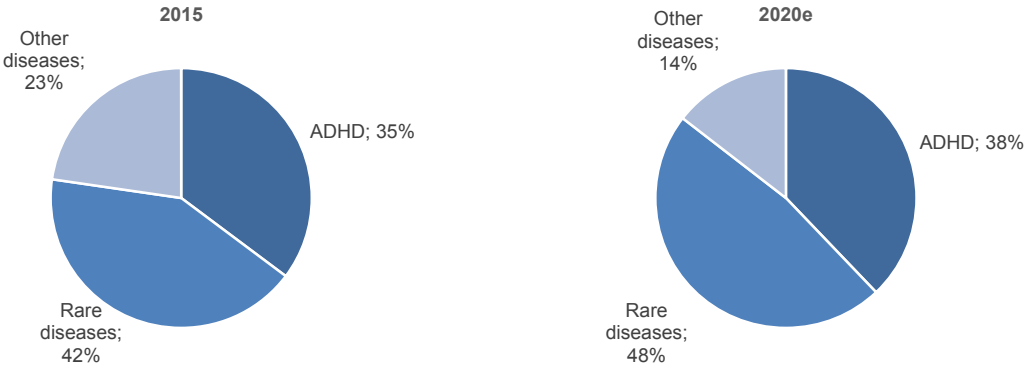
In addition to possible disappointment on quarterly results, in our view the main short-term risks to our valuation are mainly 1/ rejection of the requests for lifitegrast and SHP465 regulatory approval; 2/ a clinical failure for SHP607.

Please see the section headed "Important information" on the back page of this report.

2. Why invest now?

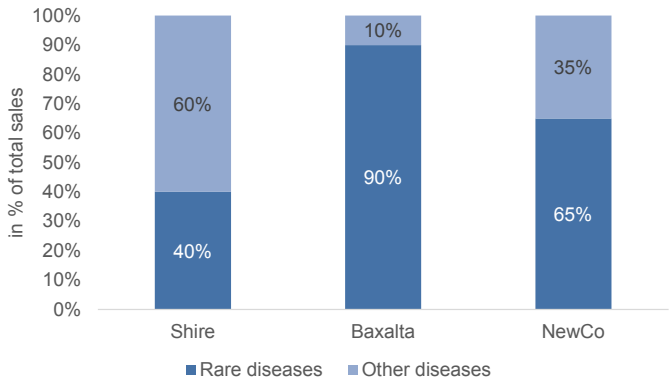
Shire's name has long been associated with that of Vyvanse and attention deficit hyperactivity disorder (ADHD) but a strategic shift has taken place with the realisation of multiple acquisitions and business development transactions (Dyax, NPS, ViroPharma, to mention but a few). The highly likely merger with Baxalta will only accelerate the dilution of this franchise within the business mix (desirable within a context where all the products in this area are expected to be generic early in the next decade), resulting in **an entity much more oriented towards rare diseases with a far more diversified, de-risked profile and generating a higher level of profitability** than in the past. In a context where some pharmaceutical companies are reporting disappointing ramp-ups which are falling well short of consensus expectations (Entresto from Novartis being just one example), we would recommend pharamaceutical positioning biased towards stocks with significant exposure to this type of segment, where the unmet medical need is so considerable that marketing approval is often granted.

Fig. 1: Shire stand-alone – Change in business mix (2015-2020e)



Source: Bryan, Garnier & Co. ests.

Fig. 2: Shire + Baxalta – Percentage of sales in rare diseases (2015)



Source: Bryan, Garnier & Co. ests.

In Shire's case, we would point to three medications worthy of particular attention, in terms of both their intrinsic potential and the approach of value-creating catalysts: 1/ DX-2930 for hereditary angioedema (HAE); 2/ Natpara in hypoparathyroidism, and 3/ Gattex for short bowel syndrome (SBS). That said, in our view there are also two other BUs which are likely to be particularly important

in terms of building the Shire of the future: 1/ Neurosciences, in which Vyvanse will continue to play a leading role; and 2/ Ophthalmology, which continues to see rapid development and for which we are awaiting the market launch of a first therapeutic candidate (lifitegrast in dry eye disease, for which we expect a green light from the FDA early in the Q3 16).

Beyond this simple change in mix, however, we expect **Shire to be amongst the few pharmaceutical companies capable of maintaining double-digit EPS growth through to the end of this decade…while the merger with Baxalta should only bolster this growth profile.** Our initial estimates of the EPS impact associated with the integration of this Baxter spin-off point to significant earnings enhancement from this business combination as of 2017e (+1%e then +4-6%e in the following years), making it attractive from both a strategic and financial perspective.

Fig. 3: BG Estimates vs Consensus (2015-2019^{e})

SHIRE	**2015**	**2016e**	**2017e**	**2018e**	**2019e**
Total revenues (in USDm)	6,416	7,117	7,937	8,706	9,457
% growth y-o-y	4.6%	10.9%	11.5%	9.7%	8.6%
% Δ vs Bloomberg consensus	0.0%	-0.9%	-0.2%	-0.7%	-1.2%
Bloomberg consensus	6,416	7,185	7,952	8,768	9,567
% growth y-o-y	4.6%	12.0%	10.7%	10.3%	9.1%
Reported diluted EPS (in USD)	**3.89**	**4.23**	**4.79**	**5.51**	**6.21**
% growth y-o-y	10.3%	8.5%	13.2%	15.2%	12.7%
% Δ vs Bloomberg consensus	0.0%	-0.3%	-1.5%	-2.2%	-3.9%
Diluted EPS Bloomberg consensus	3.89	4.24	4.86	5.64	6.46
% growth y-o-y	10.3%	8.8%	14.6%	16.0%	14.7%
BAXALTA	**2015**	**2016e**	**2017e**	**2018e**	**2019e**
Total revenues (in USDm)	6,230	6,825	7,465	7,964	8,247
% growth y-o-y	2.0%	9.6%	9.4%	6.7%	3.6%
% Δ vs Bloomberg consensus	0.0%	2.6%	4.5%	3.3%	-1.0%
Bloomberg consensus	6,230	6,650	7,144	7,709	8,329
% growth y-o-y	2.0%	6.7%	7.4%	7.9%	8.0%
Reported diluted EPS (in USD)	**2.08**	**2.25**	**2.52**	**2.82**	**2.89**
% growth y-o-y	-14.1%	8.1%	12.1%	12.0%	2.4%
% Δ vs Bloomberg consensus	0.0%	1.7%	2.0%	3.3%	3.3%
Diluted EPS Bloomberg consensus	2.08	2.21	2.47	2.74	2.80
% growth y-o-y	-14.1%	6.3%	11.7%	10.6%	2.4%

Source: Bloomberg; Bryan, Garnier & Co ests.

Fig. 4: Main catalysts for Shire and Baxalta (2016)

Period	Compound	Indication	Event
Shire			
Q2 16	Baxalta	Rare diseases	Approval of the merger by Shire's shareholders (27 May)
Q2 16	SHP607 (premiplex)	Retinopathy of prematurity	Phase II top line results
Q2 16	SHP610	San Filippo A disease	Phase II top line results
Q3 16	Lifitegrast	Dry eye disease	Approval by the FDA - PDUFA date: July 22, 2016
Q4 16	Natpara	Hypoparathydroidism	European approval
H1 17	SHP465	ADHD	Approval by the FDA after a class 2 resubmission
Baxalta			
H1 16	BAX335	Hemophilia B	Two-year clinical data
H2 16	20% IGSC	Primary immunodeficiency	Approval in the US and Europe
H2 16	Onivyde	Pancreatic cancer	European approval as a second-line option
H1 17	Adynovate	Hemophilia A	Approval in Europe, pediatric US label expansion
2017	Adynovate	Hemophilia A	Data from the PUPs and PROPEL studies
2017	Onivyde	Pancreatic cancer	Phase III results as a first-line option
2017	Hyqvia	CIDP	Phase III results and approval
2017	Calaspargase pegol	Acute lymphoblastic leukemia	Phase III results and approval

Source: Company Data; Bryan, Garnier & Co ests.

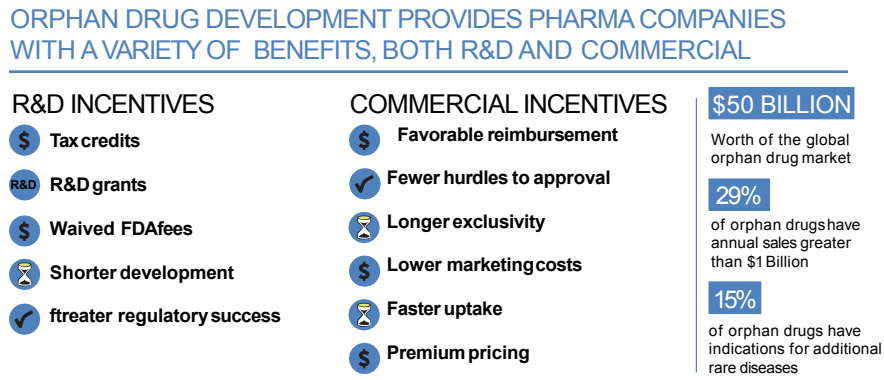
Last but not least, the stock has significantly underperformed and this makes **Shire one of the few medium-term/long-term quality growth plays currently offering a very low valuation (PE 2017e ex-Baxalta: 12x vs 17x for the European big pharma segment)**.

3. So rare! My precious…

- **What is a rare disease and why positioning in this segment?**

Rare diseases are traditionally defined based on a prevalence rate of fewer than 230,000 patients across the 27 European countries, and 200,000 in the United States (and, based on this classification, more than 7,000 diseases would be concerned). However, rare diseases should not be confused with orphan diseases; the latter are conditions for which there are no real remedial therapies, meaning that a disease can be orphan without being rare (like Alzheimer or Parkinson's disease)… although, inversely, a rare disease is frequently orphan.

Fig. 5: Orphan drugs – The key points



Source: NCBI, FDA

A higher ROI thanks to 1/ real price leverage; 2/ a shorter time-to-market; and 3/ a longer commercial exploitation period

Generally speaking, the ROI of an orphan drug tends to be higher than that of a more traditional medication. At first glance, this affirmation is not necessarily obvious but is explained by considerable differences in business model behind the development and marketing of medications addressing this type of pathology:

- **These medications often benefit from higher prices** than more traditional products. The alternative therapies are often more limited while the medical needs are frequently substantially unmet (probably because the large pharmaceutical companies have tended to neglect this segment in the past); and, in the absence of price leverage and other incentives, the pharmaceutical companies would certainly have abandoned this segment in view of the high development costs involved in addressing a fairly limited pool of patients (which would have been a disaster from a societal perspective). Admittedly, the price of drugs (and particularly those of anticancer drugs) is now an issue across the various US political classes, and will certainly result in sector volatility in the coming months…but we expect orphan drugs to remain relatively unscathed given the low number of patients involved and the scale of the unmet clinical need in often debilitating/life-threatening diseases.

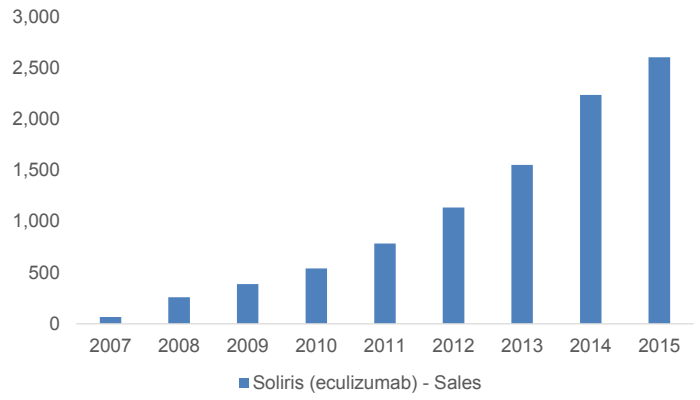
- **The time needed to develop this type of drug candidate tends to be much shorter than for non-orphan drugs** (Meekings et al). The fact of having an orphan drug designation often enables companies to fast-track commercial launches by using, for example, replacement evaluation criteria (or surrogate endpoints). Very concretely, this signifies that a marker (whether biological or not) correlated to a clinical endpoint, and

preferably more rapidly measured, may be used to conduct the trials and to obtain the marketing authorisations.

- Once the drug candidate has been approved by the different regulatory authorities, its **commercial exploitation may not only be 1/ longer** thanks to a longer exclusivity period (10 years vs 7-8 years in Europe); but also 2/ **cheaper** (number of centres to address and thus the size of the marketing teams required being much smaller (a therapy like Erwinaze, a treatment for acute lymphoblastic leukemia generating some USD200m, is now supported by only 25 reps).

- It goes without saying that the product uptake is all the more significant in that it is a first-to-market therapy meaning that there is no competition. There is no real shortage of examples but that of Soliris (eculizumab) is particularly striking in our view. Approved in 2007 for a particularly rare first indication (Paroxysmal Nocturnal Hemoglobinuria) followed by a second in 2011 (hemolytic and uremic syndrome), this product is expected to generate approaching USD3bn of sales this year !

Fig. 6: Trend in Soliris sales (eculizumab)



Source: Alexion Pharma; Bryan, Garnier & Co ests.

Fig. 7: Orphan drugs – Examples with prevalence rate and cost per patient

Drug	Indication	Company	Prevalence	Annual price per patient (USD)
Nagalzyme	Maroteaux-Lamy syndrome	Biomarin	1,100	375,000
Elaprase	Hunter Syndrome	Shire	2,000	375,000
Vimizin	Morquio A	BioMarin	3,000	380,000
Aldurazym	Hurler	Genzyme	4,000	200,000
Fabarazyme	Fabry disease	Genzyme	5,000-10,000	200,000
Replagal	Fabry disease	Shire	5,000-10,000	200,000
Myozyme	Pompe disease	Genzyme	5,000-10,000	300,000
Cerezyme	Gaucher disease	Genzyme	5,000-10,000	200,000
Vpriv	Gaucher disease	Shire	5,000-10,000	170,000

Source: Company Data; Bryan, Garnier & Co ests.

A growing number of approvals and deals involving orphan drugs

A fairly interesting trend has thus been emerging over the past twenty years: 1/ the number of orphan drugs approved by the FDA has practically doubled; 2/the types of acquisitions and in-licensing deals by big pharma tells us that this segment is the subject of growing interest (one of the most representative deals remaining to this day the acquisition of Genzyme by Sanofi in 2009). While a decade ago, these same big pharmas were not necessarily very present in this segment and were oriented more towards the development and commercialisation of products generating several billion dollars (Lipitor, etc.), the falling into the public domain of the patents protecting these blockbusters, coupled with unequivocal and manifest difficulties in replacing them, has probably been a significant catalyst for the sector's growth.

Fig. 8: List of acquisitions realised in rare diseases

Year	Acquirer	Target	Amount
2009	Sigma-Tau	Enzon Pharma	USD327m
2010	Pfizer	FoldRx	USD200m
2010	GSK	Amicus Therapeutics (20%)	USD260m
2011	Sanofi	Genzyme	USD19.5Bn
2012	Shire	Ferrokin Biosciences	USD325m
2012	Recordati	Lundbeck portfolio (10 products)	USD100m
2012	Jazz Pharma	EUSA Pharma	USD700m
2013	Jazz Pharma	Gentium	USD1.0Bn
2013	Shire	ViroPharma	USD4.2Bn
2014	Sanofi	Alnylam (12%)	USD700m
2015	Amicus Therapeutics	Scioderm	USD847m
2015	Raptor Pharma	Quinsair	USD418m
2015	Baxalta	Oncaspar	USD900m
2016	Shire	Dyax	USD5.9Bn
2016	Shire	Baxalta	USD32Bn

Source: Company Data; Bryan, Garnier & Co ests.

- **Shire's main growth driver (ex-Baxalta)**

Shire now generates more than 40% of its sales in rare diseases… and this proportion will grow to 46% in 2020

Now that we understand a little more why some pharmaceutical companies are looking to focus on rare diseases, it is time to cut to the chase. For more than ten years, Shire has been regularly making acquisitions to diversify its business and reinforce its exposure to this rapidly-growing segment (see Fig. 10)…enabling the Group to now generate more than 40% of sales in this area!

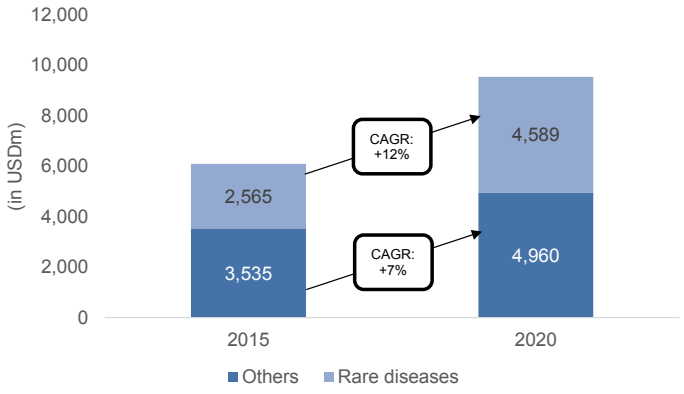
The story is, however, clearly far from over since two recent operations enabled the company to acquire two high-potential drug candidates (total peak sales > USD3.5bn) which, alongside Vyvanse, should even be the main contributors to growth in the next few years: 1/ Gattex, an GLP-2 analog since approved for the treatment of short bowel syndrome; 2/ Natpara, indicated in the treatment of hypoparathyroidism; and 3/ DX-2930, a human monoclonal antibody pKal inhibitor in Phase III which we see as the future standard bearer of the HAE franchise (currently composed of Firazyr and Cinryze). Assuming that everything pans out as we expect, **we forecast the share of rare diseases to increase to 47%e by the end of the decade,** and we shall see that this is not without incidence on the Group's profitability).

Fig. 9: Shire - Acquisitions realised since 2005

Year	Target	Key products	Amount paid
2005	Transkaryotic Therapeutics	Replagal, Elaprase, Vpriv	USD1.6Bn
2007	New River Pharmaceuticals	Vyvanse	USD2.6Bn
2008	Jerini	Firazyr	USD0.5Bn
2010	Movetis	SHP555 (resolor)	USD0.6Bn
2011	Advanced BioHealing	Dermagraft	USD0.75Bn
2012	FerroKin Biosciences	SHP602	USD0.3Bn
2012	Pervasis Therapeutics	SHP613	Undisclosed
2013	Lotus Tissue Repair	rC7	Undisclosed
2013	Premacure	SHP607 (premiplex)	Undisclosed
2013	SARCode Bioscience	Lifitegrast	USD0.2Bn
2013	ViroPharma	Cinryze, Maribavir, SHP622	USD4.2Bn
2014	Fibrotech	FT011	USD0.1Bn
2014	Lumena	LUM001, LUM002	USD0.3Bn
2015	NPS Pharma	Gattex, Natpara	USD5.2Bn
2015	Dyax	DX-2930, DX-2505, DX-4012	USD5.9Bn

Source: Shire; Bryan, Garnier & Co ests.

Fig. 10: Shire – Sales in rare diseases (risk-adjusted)



Source: Bryan, Garnier & Co ests.

3.1. DX-2930 or the renewal of the HAE franchise

■ **What is hereditary angioedema (HAE)?**

Hereditary angioedema (HAE) is a genetic disorder characterised by **temporary and recurrent episodes of localised subcutaneous and/or submucosal swelling and severe abdominal pain** (knowing that the laryngeal localisation is the most serious in terms of the vital prognosis). In the most severe cases, sufferers can have several attacks a month while the most benign cases can go several months or even years without a swelling attack. A closer look at the mechanism behind this disease shows that it is notably linked to the **poor functioning or insufficient presence of C1 esterase inhibitors (C1-INH)**, whose main function is to inhibit the classical pathway of the complement system by deactivating the enzyme complexes.

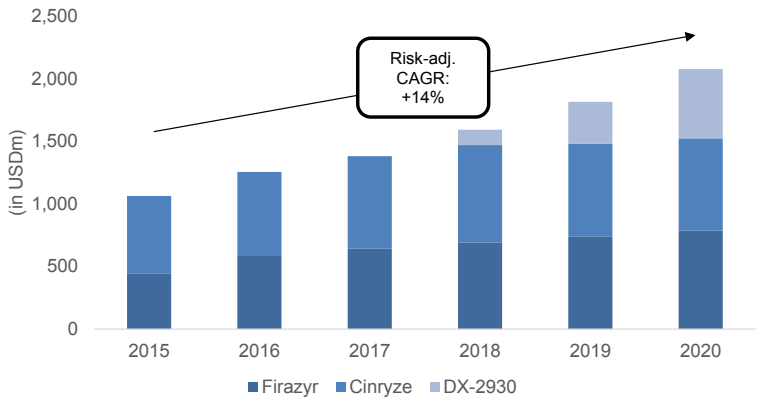
To date, three types of HAE have been identified: 1/ type I, which affects 85% of the patients suffering from the disease, results from an abnormally low level of C1-INH; 2/ type II (15% of cases), in which the level of C1-INH is normal but the existing C1-INH does not function properly; and; 3/ type III, in which the swelling or problem comes neither from the quantity nor eventual poor functioning of the C1 esterase inhibitors but rather from anomalies in the level of oestrogen production.

■ **A strong franchise for Shire**

A franchise with double-digit growth through to 2020

Shire's HAE franchise was notably built around two acquired products: 1/ Firazyr, which came from the Jerini acquisition, and 2/ Cinryze, coming from ViroPharma. With a little over USD1bn of sales realised in 2015, these two medications generate some 17% of the Group's total sales and will, in our view, remain significant growth drivers in the next few years (2015-2018e CAGR: +11.7%).

Fig. 11: HAE sales (adjusted for DX-2930 clinical risk)



Source: Bryan, Garnier & Co ests.

Increasing adoption in the US and Europe, followed by a launch on the Japanese market, will drive the growth of Firazyr and Cinryze

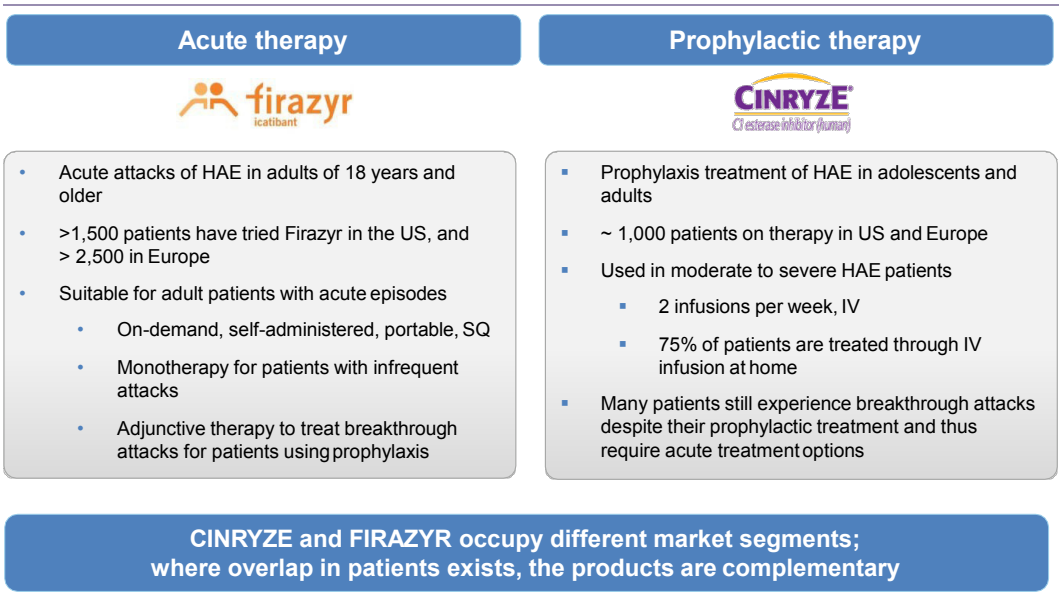
Coming from the Jerini acquisition in 2008, Firazyr is a selective β2 receptor antagonist indicated notably in the treatment of acute attacks (≠ prophylactic). If we had to explain the reasons for its success, they can be found in Firazyr's ability to be self-administered while its main competitors (CSL's Berinert, SOBI's Ruconest) need to be reconstituted before intravenous injection (which can prove fairly problematic when a patient is having to contend with severe attacks). In our view this comparative benefit will remain key for the product's growth over the next few years, knowing that

1/price rises have recently been put through in the US; 2/ with no real competitors, market share gains should continue in the countries already addressed (in any event, this proved to be the case in 2015); 3/ penetration of the Japanese market should take place in 2017e… knowing that this new market should generate an additional USD150-200m by 2023.

Remember that, in 2013, Shire acquired ViroPharma for a total consideration of USD4.2bn, the stated objective being to acquire Cinryze (a concentratration of C1 esterase functional inhibitors destined for the prophylactic treatment of HAE) given its signficant complementarity with Firazyr (Cf. Fig. 13). As with Firazyr, we expect this compound to continue to benefit from its growing adoption in the US and Europe (prophylactic treatment still being far from common practice in diagnosed patients despite its multiple benefits).

The increase we forecast for Cinryze should, however, come in particular from the extension in its geographical coverage given that 1/despite having been approved since 2011 in Europe, the sales realised in this region remain limited compared to the US; 2/ here too, Japan should be a new growth relay as of 2018 (knowing that, in time, this new market could be reflected in additional sales of USD200-250m, or at least as long as DX-2930 has yet to be marketed there); 3/ it is likely that this therapy will benefit from a label extension to a new indication (a Phase III trial currently being under way for the treatment of acute antibody-mediated rejection in patients with kidney transplants).

Fig. 12: Complementarities between Firazyr and Cinryze

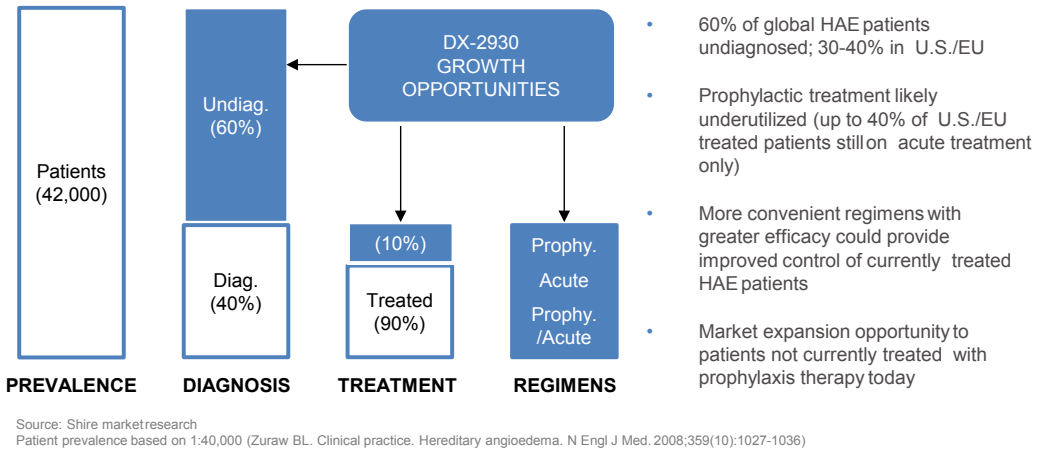


Source: Shire

- **Aiming higher with the acquisition of Dyax**

Currently in Phase III trials, DX-2930 is a monoclonal antibody inhibitor administered as a subcutaneous injection and targeting plasma kallikrein (pKal). If we had to rapidly summarise what this product represents, we would say that it is currently one of the Group's most promising assets (something which would also justify the USD5.9bn disbursed to acquire Dyax a few months ago).

Fig. 13: DX-2930 – Multiple growth vectors



Source: Shire market research
Patient prevalence based on 1:40,000 (Zuraw BL. Clinical practice. Hereditary angioedema. N Engl J Med. 2008;359(10):1027-1036)

Source: Shire

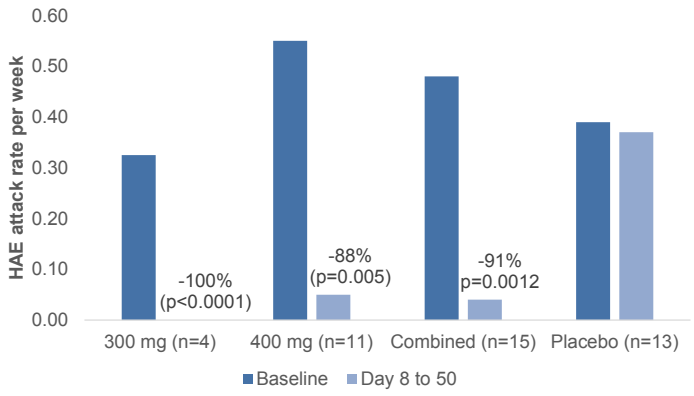
Best-in-class efficacy data, subcutaneous, once-a-month administration…. DX-2930 has everything it needs to become a blockbuster

- In addition to a highly satisfactory safety profile, a small Phase 1b trial effectively highlighted a near-91% reduction (100% in the 300mg group and 88% for the 400 mg group) in the number of attacks relative to placebo over a six-week period ($p<0.005$). Taking only the proportion of patients having suffered no attacks, the rates were respectively 100% in the 300mg and 400 mg arms (vs 27% for placebo).

- The final arbiter remains of course the publication of data from the Phase III trial initiated in 2015 (suggesting the publication of the results during H1 2017)….but these first elements look more than encouraging in our view, especially bearing in mind the fact that the therapies currently available only enable a 50% to 60% reduction in the number of attacks.

- Add to this the fact that the molecule is only administered once a month subcutaneously (vs two IV infusions a week for Cinryze) and we can easily see it becoming the new best-in-class in the HAE therapeutic landscape.

Fig. 14: DX-2930 –Phase Ib results at six weeks



Source: Dyax

Sales potential of approaching USD2bn coupled with lower production costs

In the light of these multiple elements, we expect **DX-2930 to have no difficulty in generating sales of approaching USD1.8bn** (knowing that the company guidance points to a figure of above USD2bn) 1/ starting from the principle that the Phase 1b data could be replicated with the Phase III;

and 2/ given the lack of any serious competitors (at least in our view) currently in development (see Fig. 15).

Admittedly, Cinryze is likely to be partially cannibalised by DX-2930 in view of their common positioning as a prophylactic alternative… but this negative aspect should be comfortably offset by the fact that 1/ the protection of the franchise could then be extended through to 2030 (which is by no means negligible when we know that Cinryze's patent protection will fall into the public domain as of 2020); 2/ the gross margin generated by DX-2930 should be much higher than that of its opposite number (an mAb being simpler to manufacture than an enzyme complex) and it goes without saying that the addition of this new alternative therapy is not expected to require the recruitment of additional reps.

Fig. 15: HAE (prophylaxis) – Development projects

Company	Compound	MoA	Stage	Comments
CSL Behring	Berinert SC	C1 inhibitor concentrate	Phase III	- SC version of Berinert (currently approved for acute HAE) - A prospective and retrospective study showed that the LTP administration of Berinert yielded a breakthrough attack rate per month of 0.53 (Craig et al)
BioCryst	Avoralstat	Small molecule Inhibition of pKal	Phase III	- Oral treatment given 15x a day - The OPUS-2 study did not meet its primary endpoint - OPUS-1 exhibited a statistically significant mean attack rate of 0.45 per week vs placebo (p<0.001)
BioCryst	BCX7353	Small molecule Inhibition of pKal	Phase II	- A Phase I study showed that the compound was safe and generally well-tolerated - Results from the ongoing Phase II are expected in H2 16
Pharming/Valeant	Rocunest	C1 inhibitor	Phase II	- IV with a once/twice weekly administration

Source: Companies Data; Bryan, Garnier & Co ests.

Fig. 16: DX-2930 – Non-risk-adjusted sales forecasts

	2018e	2019e	2020e	2021e	2022e	2023e	2024e	2025e	2026e
HAE - Prevalence	**24,482**	**24,727**	**24,974**	**25,224**	**25,476**	**25,731**	**25,989**	**26,248**	**26,511**
- US	12,241	12,364	12,487	12,612	12,738	12,866	12,994	13,124	13,255
% var y-o-y	1%	1%	1%	1%	1%	1%	1%	1%	1%
- Europe	12,241	12,364	12,487	12,612	12,738	12,866	12,994	13,124	13,255
% var y-o-y	1%	1%	1%	1%	1%	1%	1%	1%	1%
% Diagnosis rate	50%								
Pricing per patient - US - Prophylaxis (in USD)	400,000								
Pricing per patient - Europe - Prophylaxis (in EUR)	250,000								
Pricing per patient - RoW - Prophylaxis (in USD)	285,000								
% Market shares - US (approval: 2017)	5%	10%	15%	20%	25%	30%	35%	40%	40%
% Market shares - Europe (approval: 2017)	0%	5%	10%	15%	20%	25%	30%	35%	40%
DX-2930 - HAE - Sales (in USDm)	**122**	**335**	**553**	**774**	**1,000**	**1,230**	**1,465**	**1,705**	**1,816**
% var y-o-y		174%	65%	40%	29%	23%	19%	16%	7%

Source: Bryan, Garnier & Co ests.

3.2. Gattex in short bowel syndrome (SBS)

Gattex is a protease-resistant GLP-2 (glucagon-like peptide 2) analog which is currently being developed/marketed as a potential treatment for short bowel syndrome within the framework of a Phase III trial; the benefit being that this peptide is expected to stimulate the growth and regulation of intestinal tissues by inducing the generation of mediators such as IGF-1 and KGF.

What about disease itself? Short bowel syndrome (SBS) is a rare disorder which is often secondary to resection of the small bowel (e.g. following surgery to treat Crohn's disease, ischemic bowel disease and some cancers), particularly if the latter leaves in place less than 150-200cm of small bowel…in other words, the bowel is shortened by around two-thirds. However, in very rare cases, this syndrome may be present from birth. Concretely, the intestine then has more difficulty in absorbing nutrients during digestion….which is reflected in diarrhoea-like symptoms and weight loss; but also far more life-threatening complications (blood clots, liver-related complications, etc.).

Convincing long-term clinical data

The standard treatment for this pathology remains parenteral nutrition (in which, for most patients, mico and macronutrients are the subject of intravenous infusion for some 10-12 hours every day). Alternative therapies which are much more onerous (like Zorbtive and Nutrestore) from a logistical perspective enable the partial reduction in its use but, unlike the latter, **Gattex benefits from a clinical package demonstrating its efficacy and safety profile over a very long period (up to 30 months and 10 years respectively)** and, amongst other things, these diverse data establish that its use is reflected in a continuous improvement in the patients' condition (see Fig. 20).

Fig. 17: SBS – Main therapies currently on the market

Compound	Company	MoA	Comments
Gattex (teduglutide)	Shire	GLP-2 analog	- GLP-2 is a potent intestinotrophic factor (meaning it stimulates or regulates growth of intestinal tissues), and teduglutide is a protease-resistant analog of GLP-2 with thus a prolonged biological activity compared with native GLP-2 - Only drug currently approved with up to 30-month efficacy data - Reduction of more than 20% of PS after 2 years: 93% vs 55% for placebo
Zorbtive (somatropin)	Merck KGaA	Human growth hormone	- Anabolic anticatabolic agent which exerts its influence by interacting with specific receptors on a variety of cell types including adipocytes, hepatocytes, lymphocytes, etc. Some effects are mediated by IGF-1 - Change in weekly total IPN (intravenous parenteral nutrition) volume: -5.9L after 4 weeks, -7.7L if supplemented with glutamine
Nutrestore	Emmaus Medical	Glutamine powder	- Used in combination with Zorbtive to improve its efficacy

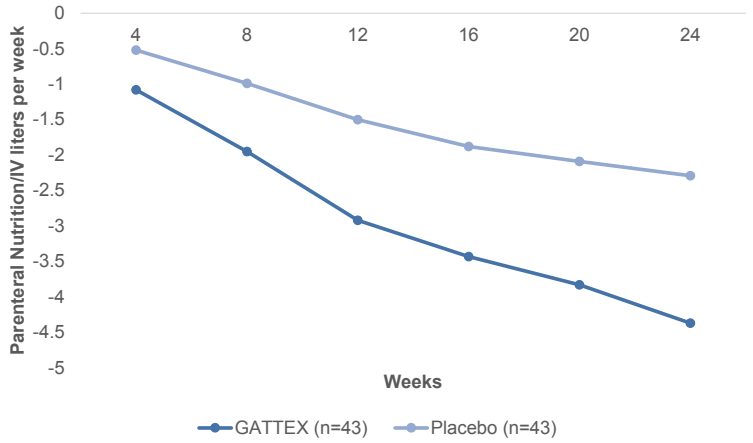
Source: Companies Data; Bryan, Garnier & Co ests.

Fig. 18: GATTEX's efficacy data over two years

Endpoint	Arm	≥ 20% reduction of Parenteral Support (PS)	Reduction in PS volume from baseline	Reduction of PS by 1 day or more per week
24-week data (STEPS)	Gattex (n=43)	63%	34%	54%
	Placebo (n=43)	30%	17%	23%
2-year data (STEPS2)	Gattex (n=30)	93%	66%	70%
	Placebo (n=29)	55%	28%	48%

Source: Company Data; Bryan, Garnier & Co ests.

Fig. 19: GATTEX – Reduction in parenteral nutrition (in L/week)



Source: Company Data; Bryan, Garnier & Co ests.

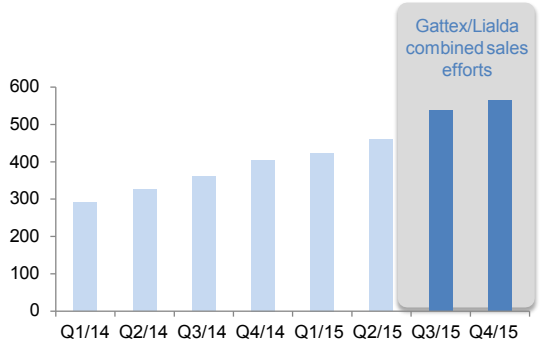
Sales to double as of this year thanks to the publication of long-term data and possible synergies with Shire's GI teams

While being fairly conservative as regards our longer-term forecasts (market share of 15-20%), in our view the product should have no difficulty in reaching the USD800m level by 2022. However, how do we see the ramp-up for this candidate? Let's start from a simple observation: Gattex already generated sales of USD142m in 2015 whereas it was approved at the very end of 2012. This is pretty encouraging in that we know that the NPS sales forces were ultimately fairly small (< 40-50 in the US in 2015).

A virtual-doubling in sales as of this year thanks to the commercial synergies with Lialda

Knowing that this medication now belongs to the Shire stable, we see sales virtually doubling as of 2016 in that 1/ the long-term data from the STEPS2 trial have only been known since 2014; 2/ marketing could be supported by the Shire teams (over 100 reps being dedicated to the United States in the gastrointestinal segment and to products like Lialda for ulcerative colitis). Admittedly, however, the commercial penetration is expected to be limited to only the most severe cases due to the risks identified over a long period (polyps, cancers, intestinal blockages). It is moreover noteworthy that risk evaluation and mitigation programs (REMS) have been put in place in the United States at the request of the FDA.

Fig. 20: GATTEX – Trend in the number of patients receiving therapy



Source: Shire; Bryan, Garnier & Co ests.

Fig. 21: BG peak sales for Gattex

	Europe	USA	Japan	TOTAL
Prevalence	6,000	6,000	2,000	14,000
Annual pricing per patient (in USD)	300,000	380,000	300,000	n/a
Market share at peak (%)	15%	20%	20%	18%
Peak sales year	2024	2022	2025	2024
Peak sakes (in USDBn)	**0.3**	**0.5**	**0.1**	**0.8**

Source: Bryan, Garnier & Co ests.

Note that Zealand Pharma is also developing a GLP-2 analog in this same indication (known as ZP1848 and for which a Phase II trial was recently launched) with a longer half-life than that of the Shire product (14-17 hours vs 2 hours respectively)… which could theoretically translate into increased efficacy in addition to offering a more practical formulation. Admittedly, the project is only in Phase II, and the results of this trial are only expected to be published next year; we nonetheless believe that this second entrant could be a very serious competitor were it to be approved (2019-2020e). As a result, our model reflects a slow-down in market share gains prior to a modest fall in sales as of 2022.

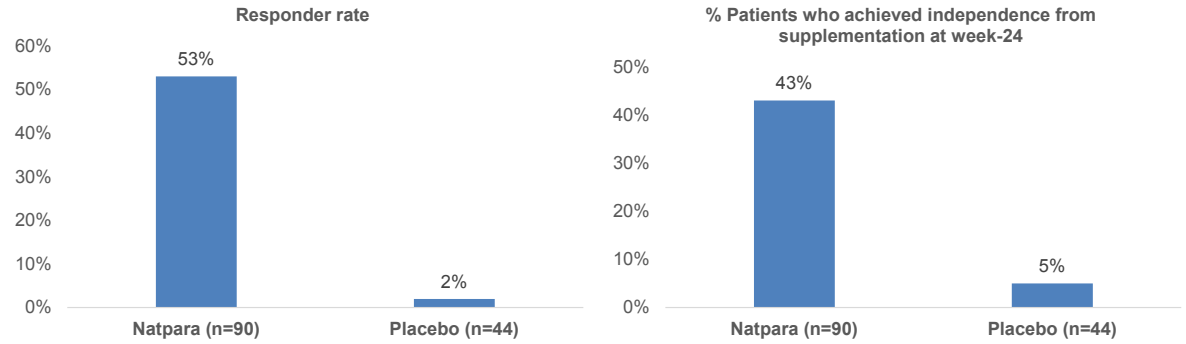
3.3. Natpara for hypoparathyroidism

Natpara is a recombinant parathyroid hormone (known for its role in regulating levels of calcium and phosphorus in the blood) which was recently approved for the treatment of hypoparathyroidism, an endocrine disorder characterised by abnormally low levels of this hormone and whose main symptoms are muscle spasms, cognitive impairment, breathing difficulties, cardiovascular or kidney disorders, etc**.** The origin of this pathology may be the autoimmune system but, in most cases, it is rather the consequence of a surgical resection of the thyroid.

Patients with the most severe forms of hypoparathyroidism as the priority target

In view of the mechanisms behind the disease (hypocalcemia), it is not really surprising that the standard therapy should be calcium and Vitamin D supplements. The situation of most patients is kept more or less under control thanks to these alternatives for which there are moreover several generics but 1/ it would seem that this is not really the case for individuals presenting with the most severe forms (around 20%), and 2/ patients under the current SOC can suffer from irreversible complications potentially affecting the heart, the brain and the kidneys should the doses of calcium and Vitamin D chronically administered be too high… hence the Shire/NPS commitment to targeting this subpopulation as a priority.

Fig. 22: Natpara – Results from the Phase III REPLACE trial



* A patient is considered as responder if he achieved 1) at least a 50% reduction from the baseline in oral calcium and vitamin D doses, and 2) an albumin-corrected total serum calcium concentration that was maintained within a range of 7.5 to 10.6 mg/dL

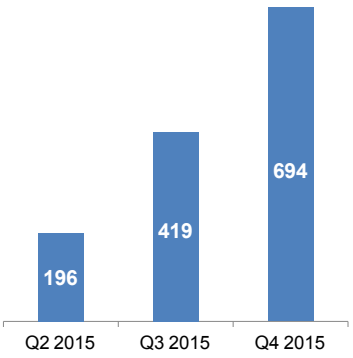
Source: NPS Pharma presentation

Virtually no competition and clinical data which is more than convincing

Given the quality of the data (see Fig. 22), the magnitude of the unmet clinical need and the low competitive intensity (only one other recombinant form of the parathyroid hormone, Lilly's teriparatide, currently being evaluated in this indication), we estimate that Shire should be able to address 30% of patients with the most severe forms of this disease (which may, at first glance, appear fairly conservative but in our view the black box warning on the risks of developing osteosarcoma is a limiting factor which should not be underestimated). Alongside this, we start from the principle that (i) the prices practiced in the United States (around USD100,000 a year per patient) are likely to remain stable over the next few years; and that (ii) the average price in Europe is likely to be closer to USD40,000.

Turning to the initial commercial data, the ramp-up looks to be more than satisfactory; while the product was only approved in January 2015, it would seem that nearly 700 patients were already receiving treatment at the end of the year!

Fig. 23: Natpara – Number of patients undergoing therapy



Shire capabilities

- 55 experienced, dedicated Rare Disease sales specialists/ managers
- Shire OnePath patient services support including field-based Patient Access Managers support every patient
- Access team; enabled coverage of >80% commercial lives in first 9 months of launch

Source: Shire; Bryan, Garnier & Co ests.

Fig. 24: BG Peak sales for Natpara

	Europe	USA	TOTAL
Hypoparathyroidism - Prevalence	100,000	80,000	180,000
Annual pricing per patient (in USD)	40,000	100,000	n/a
% Severe forms	20%	20%	20%
Market share at peak (%)	30%	30%	30%
Peak sales year	2025	2024	2025
Peak sales (in USDbn)	**0.2**	**0.5**	**0.7**

Source: Company Data; Bryan, Garnier & Co ests.

4. Vyvanse: still as hyperactive!

For many years, Shire's name has been associated in particular with attention deficit disorders with/without hyperactivity (ADHD), explained by the simple fact that the Group derived some 40% of sales from this highly specific indication at the very beginning of the decade. These days, the story is not exactly the same, this franchise now contributing only 35% of consolidated sales. However, since it remains an important pillar of cash flow generation, it is probably worth revisiting some of the fundamentals of this historic franchise, particularly with regard to Vyvanse.

Fig. 25: Shire in ADHD – Sales forecasts (2015-2020)

(in USDm)	2014	2015	2016e	2017e	2018e	2019e	2020e
Sales from ADHD	**2,159**	**2,150**	**2,487**	**2,868**	**3,100**	**3,335**	**3,564**
% var y-o-y		0%	16%	15%	8%	8%	7%
- Vyvanse (lisdexamfetamine dimesylate)	1,449	1,722	2,049	2,357	2,522	2,648	2,727
% var y-o-y		19%	19%	15%	7%	5%	3%
- Intuniv (guanfacine hydrochloride)	327	65	97	112	123	129	133
% var y-o-y		-80%	49%	15%	10%	5%	3%
- Adderall XR (extended-release amphetamine)	383	363	341	327	311	299	290
% var y-o-y		-5%	-6%	-4%	-5%	-4%	-3%
- SHP465 (Triple-bead mixed amphetamine salts)	0	0	0	72	144	259	415
% var y-o-y		n/s	n/s	n/s	n/s	80%	60%

Source: Bryan, Garnier & Co ests.

Vyvanse remains the Group's leading product

Vyvanse remains the Group's leading product with sales of USD1.7bn (i.e. 28% of total Group sales), the bulk of this figure also being generated in ADHD. A number of other indications have been explored like major depressive disorders and negative schizophrenic syndrome but all have failed…except in a bulimia-related disease known as binge eating disorder (BED).

- **ADHD: growth driven by adults in the United States and the rest of the world**

Before commenting on this last indication, it is worth highlighting a few elements concerning the first indication. **ADHD is a pathology affecting some 50 million people globally and is characterised by considerable difficulty in secreting two neurotransmitters: norepinephrine and dopamine.** This is what causes the loss of concentration, lethargy and lack of motivation. Two forms of treatment have emerged: 1/ brain stimulants like Vyvanse and, shortly, SHP465, aimed at activating the secretion of these two neurotransmitters; and 2/non-stimulants (which treat the symptoms of the disorder without increasing dopamine levels), like Intuniv.

Fig. 26: Vyvanse's main competitors in ADHD

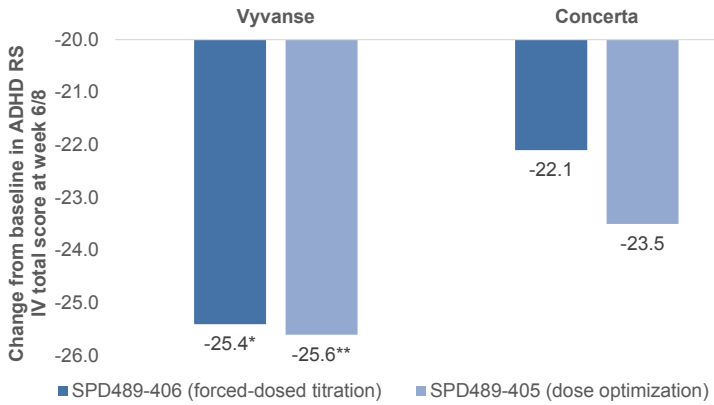
Type of medication	Drug	Generic name	Company	Duration
Short-acting amphetamine stimulants	Adderall	Mixed amphetamine salts	Shire	4-6 hours
	Dexedrine	Dextroamphetamine	GSK	4-6 hours
Short-acting methylphenidate stimulants	Focalin	Dexmethylphenidate	NVS/Celgene	4-6 hours
	Methylin	Methylphenidate	MNK	3-5 hours
	Ritalin	Methylphenidate	NVS	3-5 hours
Intermediate-acting methylphenidate stimulants	Metadate CD	Extended-release methylphenidate	Celltech	6-8 hours
	Ritalin LA	Extended-release methylphenidate	NVS	6-8 hours
Long-acting amphetamine stimulants	Adderall XR	Extended-release amphetamine	Shire	10-12 hours
	Dexedrine Spansule	Extended-release amphetamine	GSK	6-8 hours
	Vyvanse	**Lisdexamfetamine**	**Shire**	**14 hours**
Long-acting methylphenidate stimulants	Concerta	Extended-release methylphenidate	JNJ	10-12 hours
	Daytrana	Extended-release methylphenidate	Noven Pharma	10-12 hours
	Focalin XR	Extended-release dexmethylphenidate	NVS/Celgene	8-12 hours
	Quillivant XR	Extended-release methylphenidate	Pfizer	10-12 hours
Long-acting non-stimulants	Intuniv	Guanfacine	Shire	24 hours
	Kapvay	Clonidine	Shionogi	12 hours
	Strattera	Atomoxetine	Lilly	24 hours

Source: Companies Data; Bryan, Garnier & Co ests.

Vyvanse in ADHD: a focus on adults in the US

Turning now to Vyvanse, in our view the bulk of the growth should be achieved thanks to 1/ the publication of clinical data showing its superiority vs JNJ's Concerta in adolescents, or at least a positive trend (see Fig. 27), and 2/ the focus on adult patients. The last point may at first glance appear counter-intuitive, ADHD being recognised by the general public as a psychiatric disorder affecting children and adolescents (which are still responsible for 70-75% of prescriptions). Having said that, adults are the population segment for whom the number of patients under medication increased by +53% between 2008 and 2012 in the US, based on one fairly simple observation: 1/ inversely to what one might believe, a fairly substantial proportion of patients continue to suffer from the condition once they enter adulthood; 2/ trials have shown that the disorder presents a hereditary component, hence the increased diagnosis of some parents.

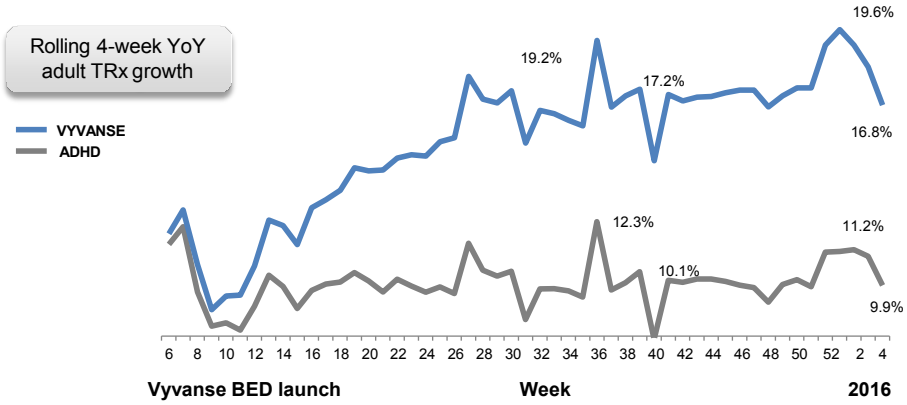
Fig. 27: Vyvanse vs Concerta – Results of the SPD489-406 and 405 trials



* p=0.0013 ; ** p=0.0717

Source: Shire

Fig. 28: Vyvanse – Market shares in ADHD



Vyvanse above-market performance driven by uptake in the adult ADHD market and in adults with Binge-Eating Disorder since launch in Q1:15

Source: Shire, FY 15 results presentation

The ex-US market should also be partly behind the compound's growth although we expect it to remain relatively minor given the less-attractive reimbursement policies (particularly in Europe where it has been approved since 2013) and (surprisingly) the higher demand for non-stimulant alternatives.

- **Binge Eating Disorder (BED): an underestimated opportunity?**

BED: an indication close to that of bulimia affecting some 3.8 million individuals in the US alone…and for which there had been no approved therapeutic option

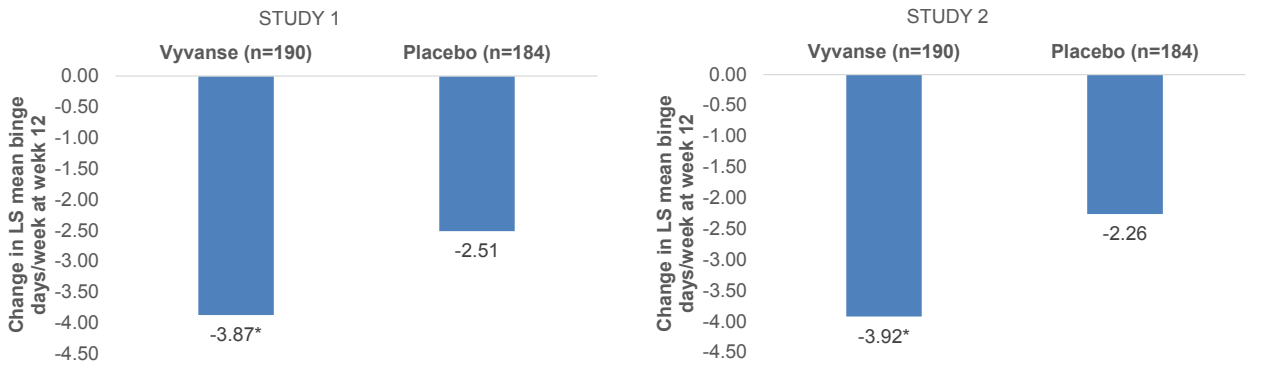
Admittedly, Vyvanse remains primarily a medication dedicated to the treatment of ADHD but we also believe that its recent approval in the treatment of binge eating disorder (BED) could be a major driver of its future growth.

- Note, firstly, that **this syndrome is a disorder relating to behaviour around food which is often linked to depression, and is related to bulimia** in that it presents as an irresistible desire to eat with no feeling of hunger, or even pleasure. It is distinguished from bulimia by the fact that it doesn't involve weight control, deliberate vomitting, the taking of laxatives and excessive sporting activity (in other words, it does not involve compensatory behaviours).

- **Nearly 3.8 million individuals are thought to suffer from BED in United States although the diagnosis rate is likely to be only 10%** (perhaps reflecting the most severe cases?) and, even for the latter, no alternative medication is currently available to help them (the only available option at present being behavioural and cognitive therapy).

- **Two Phase III trials enabled Vyvanse's superiority to be established relative to placebo as an "appetite suppressant"** (see Fig. 28 for more details), while demonstrating a very satisfactory safety profile (not to say identical to the one noted for the treatment of ADHD).

Fig. 29: Vyvanse –Phase III results in BED



* p<0.001 vs placebo

Source: Shire

Vyvanse in BED: potential for USD500m on a conservative basis

In view of the above, we see no difficulty in Vyvanse being able to generate sales of approaching USD500m in this new indication (knowing that the company's guidance is for USD300m+ as of 2020), confining itself to the Americas. Our estimate could even prove too conservative since we currently start from the principle that the diagnosis rate for the disorder will only see a modest increase (15%e) despite the fact that we now see numerous elements which point to positive developments on this front. BED has effectively only been recognised since 2013 by the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) of the American Psychiatric Association. Concretely, this means that a valid diagnosis methodology has been introduced, now enabling patients suffering from this pathology to be covered by their health insurance.

Fig. 30: Sales estimates for Vyvanse in BED

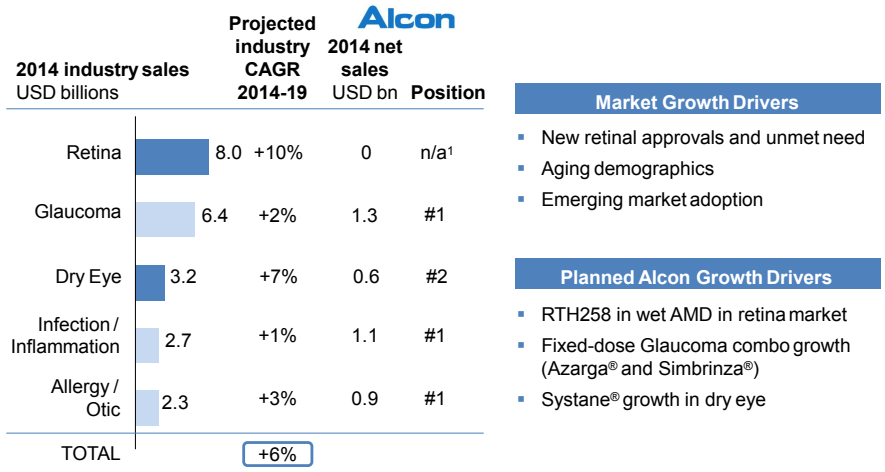
	2015	2016	2017	2018	2019	2020	2021	2022
Patients with BED - US (in millions)	**3.8**	**3.9**	**3.9**	**4.0**	**4.0**	**4.0**	**4.1**	**4.1**
% growth y-o-y		1%	1%	1%	1%	1%	1%	1%
% Diagnosed and willing to be treated	10%	11%	12%	13%	14%	15%	15%	15%
% Treated with Vyvanse	10%	15%	20%	25%	30%	35%	40%	40%
Price per month (USD)	150	153	156	159	162	166	169	172
% var y-o-y		2%	2%	2%	2%	2%	2%	2%
Vyvanse - Sales in BED (USDm)	**69**	**117**	**176**	**246**	**327**	**421**	**496**	**511**
% var y-o-y		70%	50%	40%	33%	29%	18%	3%

Source: Company Data; Bryan, Garnier & Co ests.

5. Ophthalmology: worth a look!

Rare diseases may well have been the company's main focus but note that Shire's management has made a small exception with Ophthalmology in that the main drug candidates it is developing have the potential to be first-in-class. The latter 1/ address significant yet rapidly-growing markets (see Fig. 31), and 2/ potentially respond to as yet considerable unmet medical needs.

Fig. 31: Trend in the pharmaceutical ophthalmology market



Source: Adapted from Novartis Meet the management presentation (June 2015)

A franchise which could be worth more than USD2.5bn (non-risk-adjusted) by 2024!

Beyond the fact that **this activity could generate non-adjusted sales of over USD2.5bn by 2024e**, note that two catalysts are expected in the coming few months which will be key for the construction of this future franchise and to the Group's EPS growth: 1/ the FDA response to the possible market launch of lifitegrast for the treatment of dry eye disease (PDUFA date: 22 July 2016, potential impact on our FV: +300GBp everything else being equal); and 2/ the results of the Phase II trial evaluating SHP607 as a preventive treatment in Retinopathy of Prematurity (potential impact on our FV: +150GBp). We would however recommend a degree of caution given the lack of clinical data enabling us to truly get religion on the latter.

Fig. 32: Sales forecasts for the Ophthalmology franchise

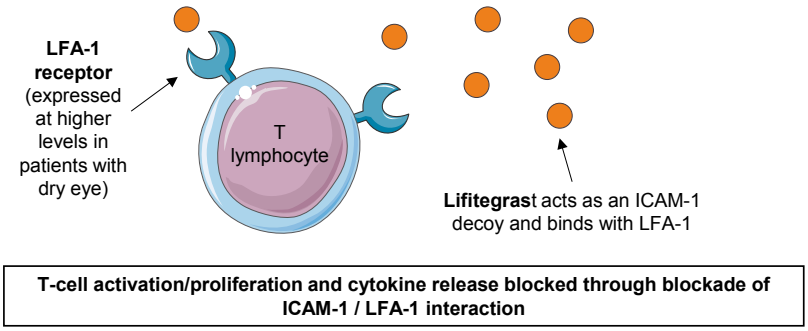
(in USDm)	Risk adj.	2016	2017	2018	2019	2020	2021	2022	2023
SHIRE - OPHTALMOLOGY		**0**	**66**	**162**	**282**	**424**	**590**	**759**	**872**
% var y-o-y			n/s	146%	74%	50%	39%	29%	15%
- Lifitegrast	50%	0	66	143	223	314	418	513	552
% var y-o-y			n/s	118%	55%	41%	33%	23%	7%
- SHP607 (premiplex)	20%	0	0	0	11	31	63	104	147
% var y-o-y			n/s	n/s	n/s	n/s	102%	66%	41%
- SHP640 (FST-100)	50%	0	0	18	48	79	110	141	173
% var y-o-y			n/s	n/s	164%	63%	40%	29%	23%

Source: Company Data; Bryan, Garnier & Co ests.

5.1. All eyes on lifitegrast

Lifitegrast is a novel small-molecule integrin inhibitor which binds to the integrin LFA-1 (lymphocyte function-associated antigen-1), a cell surface protein found on leukocytes, the aim being to block the interactin of LFA-1 with its cognate ligand ICAM-1 (intercellular adhesion molecule-1) and trigger the formation of immunological synapses resulting in T-cell activation and proliferation (in vitro trials have shown that the compound was capable of inhibiting the migration of these cells and the production of proinflammatory cytokines like IFN-γ, TNF-α and IL-2).

Fig. 33: Lifitegrast – Mechanism of action



Source: Adapted from Zhong et al, 2012; Bryan, Garnier & Co ests.

A considerable unmet medical need

The main market targeted by lifitegrast is that of dry eye disease, a disorder affecting some 35 million Americans and characterised by 1/ inflammation of the surface of the eye and at the level of the tear glands (whose function is notably to filter the blood to manufacture tears), and 2/ a chronic inability by the latter to produce tears. The eye then becomes increasingly irritated (giving the impression of trapped grains of sand) and inflamed, thereby only accentuating the symptoms characterising the disease (Jones et al, 1998).

Allergan's Restasis (a cyclosporine ophthalmic emulsion and immune suppressing agent) remains the only available pharmaceutical treatment; while it has only demonstrated a statistically significant improvement in the signs of the disease (and not the symptoms). By way of comparison, Restasis also benefits from an anti-inflammatory action although it would seem that the latter is only limited to newly-formed immune cells, whose lifespan may only be 3-4 months (and it is probably for this reason that patients rapidly become refractory on this therapy).

- **At first glance a mixed clinical package…**

It has to be admitted that the top-line Phase III results were pretty mixed since 1/ in OPUS-1, the signs of the disease were improved in a statistically significant manner ($p<0.0001$), but not the symptoms; 2/ the inverse situation was noted within the framework of the OPUS-2 trial but we need to be aware that these evaluation endpoints were not always that reliable (environmental impact, placebo effect, etc.) in addition to being non-correlated (Nichols et al, 2004).

Having completed two trials which could only demonstrate a benefit on one of the initial co-primary efficacy endpoints, it was not really surprising that Shire should have received a complete response letter (CRL) from the FDA requesting 1/ an additional clinical trial, together with 2/ more information on the quality of its product. The Group may well have been aware of this risk, hence the third Phase III trial dubbed OPUS-3 initiated in 2014 (i.e. several months prior to the OPUS-2

results). Fortunately, the primary evaluation endpoint on the improvement in the symptoms of the disease vs placebo was met (p=0.0007).

Fig. 34: Lifitegrast – Recap of the clinical data

	OPUS-1	OPUS-2	OPUS-3
Population	n=588 adults; mild-moderate dry eye	n=720 adults; moderate to severe EDS (eye dryness score≥ 40)	n=700 adults; moderate to severe EDS (eye dryness score≥ 40)
Change in signs (ICSS)	Endpoint met (p=0.0007)	Endpoint not met (p=0.6186)	No co-primary endpoint
Change in symptoms (VR-OSDI)	Endpoint not met (p=0.7894)	Endpoint met (p<0.0001)	Endpoint met (p=0.0007)
Secondary symptoms endpoints	Ocular discomfort (p=0.0273) Eye discomfort (p=0.0291)	Ocular discomfort (p=0.0005) Eye discomfort (p<0.0001)	Symptom improvement at days 14 and 42 (p<0.0001)
Safety	Subjects with ≥ 1 ocular AE: 59% vs 25% No serious ocular adverse events	TEAEs: 33.7% vs 16.4% No serious ocular adverse events	Not yet disclosed No serious ocular adverse events

Source: Company Data; Bryan, Garnier & Co ests.

- **But reasons to believe!**

A pretty favourable competitive backdrop

In our view, aside from Allergan's Tavilermide (whose rights have been acquired by Mimetogen Pharmaceuticals and for which the big pharma anticipates potential peak sales of USD500-750m), **there are relatively few candidates which look truly competitive in this indication.** In this context, we believe that the market share gains could be both rapid and significant, particularly if the FDA label were to be relatively broad (i.e. with an indication for the treatment of the symptoms and signs of the disease).

Fig. 35: Dry eye – Drug candidates in development

Company	Compound	MoA	Stage	Comments
Eleven Bio	isunakinra	Anti-IL-1	Phase 3	Missed primary endpoint of improving ocular itching vs placebo in a recent Phase III trial in allergic conjunctivitis The development in dry eye disease was abandoned
EyeGate Pharma	EGP-437	Dexamethasone phosphate	Phase 3	EGP-437 is a reformulated topically active corticosteroid delivered into the ocular tissues through a proprietary drug delivery system Topical corticosteroids are known to be used off-label to reduce signs and symptoms of dry eye), We are cautious about possible side effects (cataract, elevation of IOP)
Ocular Therapeutix	Dextenza	XR dexamethasone	Phase 2	Dextenza is a sustained-release (4 weeks) intracanalicular depot of dexamethasone Here again, we are cautious about the side effects associated with DXM

Source: Company Data; Bryan, Garnier & Co ests.

A potential green light from the FDA expected by 22 July 2016

Now that the FDA has received the whole package required to take a decision, its reponse is expected by 22 July 2016. Admittedly, the OPUS-2 trial did not meet the co-primary efficacy endpoint of an improvement in the signs of the disease but:

- We also know that the evaluation of the signs remains fairly subjective, and studies show that the results can be very variable between one physician and another. Furthermore, it

would seem that there is not necessarily any correlation between the signs and the symptoms (Nichols et al).

- From our perspective, **the improvement in symptoms is the most important co-endpoint since dry eye is a symptomatic disease.** And yet (i) the improvements observed with OPUS-2 and 3 are fairly consistent and (ii) the improvement noted with lifitegrast is the most substantial that we have seen to date amongst the different development candidates.

- **It is not impossible for the Group to be granted a label focused only on the symptoms.** Admittedly the revenue potential would perhaps not be as considerable but this would nonetheless enable the company to secure sales at least in line with those of Restasis (knowing that the latter's label is limited to an increase in tear production in patients suffering from dry eye disease).

For all these reasons, we opt for the most cautious yet positive scenario (i.e. the obtention of a label limited to an improvement in the symptoms of the disease, a launch in early 2017, peak sales of USD800m) as well as a 50% probability of success.

Fig. 36: Lifitegrast – Sales potential on the various scenarios

	BG scenario	Optimistic scenario
Number of patients with dry eye disease	25m (US), 35m (Europe)	25m (US), 35m (Europe)
% Patients with moderate-severe forms	35%	35%
% Patients seeking treatment	10%	10%
Lifitegrast - Market share at peak (%)	15%	25%
Pricing per patient - US (in USD)	2,900	2,900
Pricing per patient - Europe (in USD)	1,700	2,000
BG peak sales (in USDbn)	**0.8**	**1.2**

Source: Bryan, Garnier & Co ests.

5.2. SHP607 (premiplex) in Retinopathy of Prematurity

Retinopathy of Prematurity (ROP) is defined as abnormal/incomplete vascular development at the level of the retina in infants, and is potentially the source of poor visual acuity, or even blindness in the event of detachment of the retina. We currently estimate that at a little under 10% of premature new-born babies suffer from a severe form of this disease and thus require retinal ablative therapy.

The very first cases of ROP notably date back to the late 1940s and more specifically to the time when supplemental oxygen in incubators was introduced to increase the survival chances of premature babies (a Patz et al study in 1952 confirmed the correlation between the administration of high doses of oxygen and the incidence of the disease). We now know that it is not the only risk factor behind the development of the disease but the fact remains that we have yet to find a level of oxygenation enabling a reduction in the risk of ROP without reducing the chances of survival.

We don't plan to revisit all the details of the pathogenesis but would nonetheless like to highlight the fact that there may be a **high negative correlation between levels of IGF-1 and the incidence of ROP** (Hellström et al, 2003)

A high risk, high reward asset, hence a 20% PoS in our model

SHP607 (formerly known as premiplex) is an IV administered protein replacement therapy based on human IGF-1 and IFGBP3 (its binding protein)… which we might as well start by noting is the only alternative currently in development aimed at the preventive treatment of retinopathy in premature babies (hence a primary endpoint based on the severity of the disease vs placebo for the Phase II trial).

In our view, SHP607 is a potentially lucrative asset (first-in-class in an indication characterised by a real therapeutic vacuum) but for which we don't yet have proof of concept data. The top-line Phase II data whose publication is expected this quarter will give us a clearer vision of the potential for this drug candidate; until then, **we would urge a degree of caution (hence our 20% PoS for this development project).**

Fig. 37: SHP607 – Sales potential (non-risk-adjusted)

	USA	Europe	TOTAL
Premature births - Incidence	30,000	30,000	60,000
Annual pricing per patient (in USD)	35,000	28,500	n/a
Market share at peak (%)	45%	40%	43%
Number of patients on therapy	13,500	12,000	25,500
Peak sales year	2024	2024	2024
Peak sales (in USDbn)	**0.5**	**0.3**	**0.8**

Source: Company Data; Bryan, Garnier & Co ests.

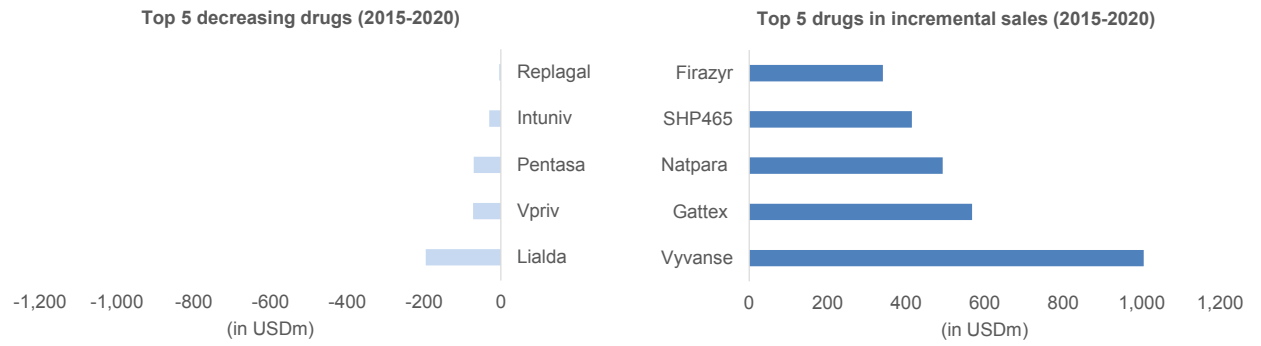
6. Towards high-single-digit growth in stand-alone EPS

- **Growth underpinned by an improvement in the product mix**

95% of the incremental sales over 2015-2020 will come from five new drugs

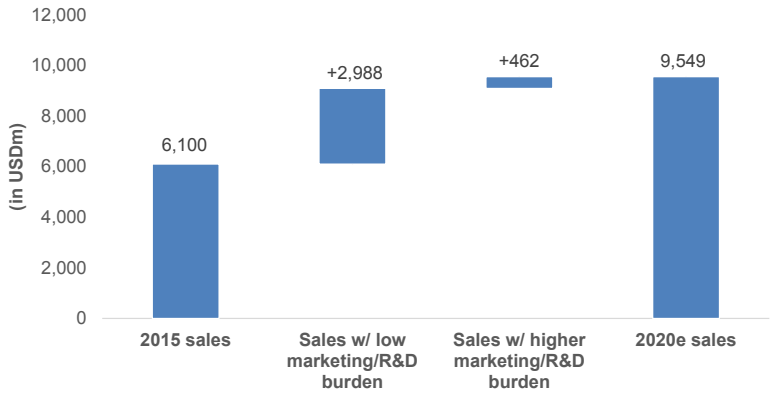
Before even mentioning the Shire-Baxalta growth prospects, it is important to stress the magnitude of the growth the company could generate on a stand-alone basis. More than 95% of the incremental sales (adjusted for clinical risk) that we are forecasting for the 2015-2020 period is expected to come from five new drugs: DX-2930, SHP465, Natpara, Gattex and Vyvanse (in ascending order). In our view, the resulting mix will be extremely positive for the Group's operating margin.

Fig. 38: Main sources of growth/negative growth over 2015-2020^{e} (risk-adjusted)



Source: Bryan, Garnier & Co. ests.

Fig. 39: Sources of sales growth as a function of the marketing burden



Note: Vyvanse (for both ADHD and BED) is included in our estimates of additional sales with low associated marketing/R&D expenses. Most of the "high burden" stems from our projections for lifitegrast (dry eye)

Source: Bryan, Garnier & Co ests.

A product mix which will favour significant margin expansion

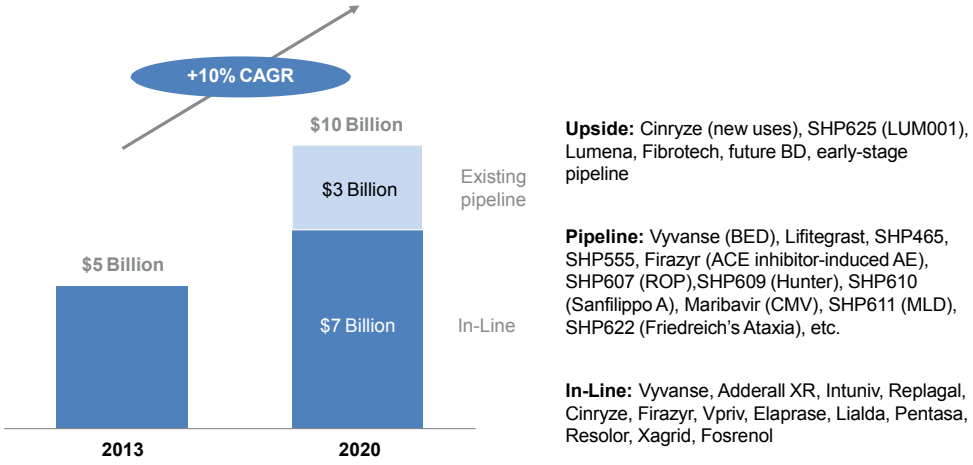
- The fact that rare diseases (in this case represented by DX-2930, Natpara and Gattex) represent an increasingly large proportion of the product mix won't only have a "non-material" incidence on the risk profile. Beyond the simple fact that they are generally more expensive, remember that these products also require a fairly small sales force given the limited size of the target population. In other words, the **percentage of products with a low marketing and R&D burden is expected to see significant growth.**

- The case of Vyvanse is a little more particular. The main target market for this amphetamine-type product is far from being a rare disease, although 1/ **Vyvanse is a mature product, generating very probably one of the highest margins by product in the portfolio,** and for which half the incremental revenues are likely to come from ADHD; 2/ the second indication addressed by this therapy is currently being reflected in rising marketing expenses although this increase should remain limited in view of the commercial synergies we foresee (diagnosis by physicians in the two cases, or simply by general practitioners).

- The only small cloud on the horizon: **in our view, the positive effects linked to these changes in mix are likely to be partially offset in the short term by the commercial launch of lifitegrast**, a high-potential drug candidate which will in all likelihood require the recruitment of several hundred sales reps just to cover the United States.
  However, we also expect this additional growth in SG&A to slow as of 2018e (once the infrastructure required for the Ophthalmological portion is effectively in place), particularly since the launch of most of the other high-potential molecules (we are thinking, notably, of DX-2930, which should further more have higher margins than Cinryze and Firazyr in the HAE franchise) will be able to proceed based on the existing teams. We thus estimate the operational leverage to be much greater between 2018 and 2020.

■ **Double-digit growth within reach**

Fig. 40: Shire – "10x20" Plan



Source: Adpated from Shire R&D Day (Dec 2014); Bryan, Garnier & Co. ests.

We may be in 2016 but in our view it is important to turn to some of the elements of long-term guidance provided midway through 2014. Since at that time the company was the subject of a bid by AbbVie, the Shire management organised an investor day dedicated to the presentation of its 2020

plan ("10x20"). While sales had "only" amounted to USD5bn in 2013, the target of a doubling in Group sales by the end of the decade was clearly posted, knowing that 1/ nearly USD3bn of this incremental sales projection was expected to be linked to the drugs then in development; 2/ any acquisitions or business development operations would only represent additional upside (the best example being Dyax and DX-2930).

In our view, a sales target of USD10bn looks eminently achievable, but the product mix probably won't be as anticipated

Where do we stand currently? We may only be midway to achieving the finishing line but the company certainly seems well on the way to achieving its target. Admittedly, SHP625 has suffered clinical setbacks, wiping out some of the potential "upside". On the other hand, the Vyvanse label has been expanded to BED, the FDA green light for SHP465 is near, the growth in the HAE franchise is rather promising, etc. But it should also be admitted that the Dyax acquisition has had a significant impact on the mix behind this future growth (remember that DX-2930 is expected to cannibalise a portion of Cinryze's sales in HAE).

All this means that 1/ we see a sales target of USD10bn by the end of the decade as eminently achievable and may even be comfortably exceeded; 2/ the portion linked to the upside will very certainly be more substantial than had been anticipated in 2013 (and in our view could even offset an eventual failure with lifitegrast and SHP607). More specifically, we are **forecasting a 2015-20 CAGR of +9% for the top line CAGR for 2015-2020 and +11% for EPS on a risk-adjusted basis, giving Shire one of the most attractive growth profiles in the European pharmaceutical sector.**

Fig. 41: Recap of our forecasts (2015-2020e)

	2015	2016e	2017e	2018e	2019e	2020e
(+) Product sales	6,100	6,796	7,604	8,362	9,102	9,549
% growth y-o-y		11%	12%	10%	9%	5%
(+) Royalties	301	322	333	344	355	366
(+) Other revenues	16	0	0	0	0	0
= Total group revenues	**6,416**	**7,117**	**7,937**	**8,706**	**9,457**	**9,915**
% growth y-o-y		11%	12%	10%	9%	5%
(-) COGS	885	951	1,027	1,087	1,138	1,146
in % of product sales	14.5%	14.0%	13.5%	13.0%	12.5%	12.0%
= Gross margin	**5,532**	**6,166**	**6,910**	**7,619**	**8,319**	**8,769**
in % of product sales	90.7%	90.7%	90.9%	91.1%	91.4%	91.8%
(-) R&D	884	996	1,111	1,219	1,324	1,388
% growth y-o-y		13%	12%	10%	9%	5%
(-) SG&A	1,724	1,922	2,064	2,176	2,270	2,380
% growth y-o-y		11%	7%	5%	4%	5%
= EBITDA	**2,924**	**3,248**	**3,736**	**4,223**	**4,726**	**5,001**
in % of product sales	47.9%	47.8%	49.1%	50.5%	51.9%	52.4%
% growth y-o-y		11%	15%	13%	12%	6%
(-) D&A	139	170	205	242	282	325
= EBIT	**2,785**	**3,078**	**3,530**	**3,981**	**4,443**	**4,677**
in % of product sales	45.7%	45.3%	46.4%	47.6%	48.8%	49.0%
% growth y-o-y		11%	15%	13%	12%	5%
(-) Interest expense	42	93	117	50	11	2
(+/-) Others	-7	0	0	0	0	0
(-) Income taxes	424	478	580	668	754	795
% Corporate Taxes	15.5%	16.0%	17.0%	17.0%	17.0%	17.0%
= Net income	**2,310**	**2,508**	**2,833**	**3,263**	**3,679**	**3,880**
Basic EPS (USD)	**3.91**	**4.24**	**4.79**	**5.51**	**6.22**	**6.56**
% var y-o-y	10%	8%	13%	15%	13%	5%
Diluted EPS (USD)	**3.89**	**4.23**	**4.78**	**5.50**	**6.20**	**6.54**
% var y-o-y	10%	9%	13%	15%	13%	5%

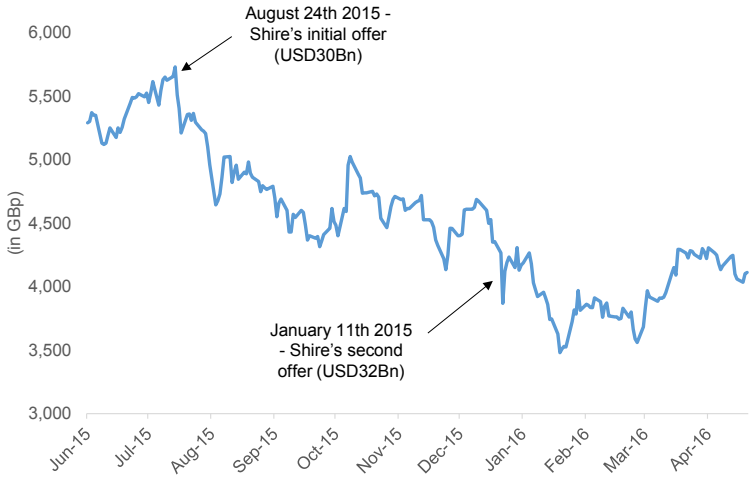
Source: Bryan, Garnier & Co ests.

7. Baxalta: a rare opportunity

■ **The merger with Baxalta: numerous uncertainties…**

It was back in early January that Shire announced the signature of its planned acquisition of Baxalta, a spin-off from the Baxter group with a particular focus on hemato-immunology (hemophilia, primary immunodeficiency, etc.), with a relatively 'simple' objective of creating a new leader in rare diseases with sales potentially exceeding USD20bn. Let's look, for a moment, at the history of this transaction since it may help us to understand why some investors should have proved dubious as to the eventual value creation (remember that the share price has fallen by 30% since the initial announcement):

Fig. 42: Shire share price over the last 12 months



Source: Bryan, Garnier & Co. ests.

Some investors are worried about 1/ the longevity of BXLT's Hemophilia business, 2/ the scale of the operational synergies and 3/ a tax liability following questions surrounding the tax-free status of the target

- Just a few weeks after its stock market listing, the Baxalta management received a first offer from Shire (amounting to USD30bn, representing a c.30% premium to the last share price), which was initially entirely in shares so as not to jeopardise the tax-free status of the spin-off. However, Ludwig Hantson's (CEO) reaction to this first offer was far from positive. ('Given our prospects and our outlook, Shire's offer is not compelling […] We don't believe, and investors have agreed, that the Shire combination is synergistic'), and it is more than likely that this currently feeds a certain mistrust on the part of the market.
  While we would agree on the fact that the commercial and production synergies will effectively be fairly limited, the common points between IG/Hemophilia and indications like ADHD and HAE being far from obvious at first glance… the guidance on the cost savings that has been given seems pretty realistic (USD500m, which is fairly comparable to our estimate of the G&A expenses at Baxalta).

- A second offer has since been submitted. For a higher amount (USD32bn, i.e. a 38% premium relative to the 3 August 2015 share price) and with the addition of a cash component (40%), it has enabled the two camps to agree on the financial terms…although it has also raised a new question: will the addition of cash jeopardise Baxalta's tax-free status (and if this were to be the case Shire could then have to pay a tax bill of approaching USD5bn)?

We currently understand that this will not be the case provided three conditions are met: 1/ the transaction is motivated by a 'strong business purpose'; 2/ during the spin-off neither Baxter nor Baxalta were expecting a takover of Baxalta; 3/ the spin-off and acquisition are not part of one and the same plan. While the first point seems pretty clear (the aim being to create the number one in rare diseases), note that the two latter points were validated by the due diligence undertaken by the firm Cravath (review of internal documents, previous discussions between the two managements, etc.). Besides, we note that AbbVie was in advanced talks with Shire when Baxter was preparing the spin-off of its BioScience business into Baxalta (in mid-2014).

- Independently of all the above points, several investors have expressed their scepticism as to the longevity of Baxalta's Hemophilia business faced with the arrival of new therapies and, in particular, Roche's emicizumab given the impressive clinical data generated within the framework of a Phase 1b trial. We have the feeling that this is the main point on which there is no consensus at present, while also being the main factor influencing the value creation behind the merger transaction. We shall, however, see that these fears are exaggerated, at least in our view.

■ **… Which have probably created an opportunity!**

In our view, these fears are exaggerated and the merger with Baxalta should create value.

How do things now stand? It should be noted that 1/ the Shire share price is still far from the levels prevailing prior to the 4 August 2015 announcement (meaning that the stock has very substantially under-performed the STOXX Europe 600 Healthcare); 2/ the 2017e ex-Baxalta P/E is currently close to 12-13x, and this level represents a significant discount relative to the company's historic rating or even relative to its peers. Evidently, the market is not really convinced of the value creation that this transaction is expected to generate…

From both a strategic and financial perspective, we see the merger with Baxalta as very positive (valued, moreover, at a total consideration of USD32bn). Firstly, because it will enable significant growth in the company's exposure to rare diseases (c.90%e of the target company's sales) and notably to markets like Hemophilia; and, unlike other houses, we see this business proving fairly resilient faced when with the arrival of new therapies (e.g. Roche's ACE910/Emicizumab which could be approved as of 2018). Secondly, the high margin activities like Oncology and Immune Globulins (IG) should comfortably underpin the Group's growth through to the end of the decade thanks to development projects like Oncaspar in acute leukemias and Hyqvia in primary immunodeficiency (PID). More specifically, **we expect Baxalta to have no difficulty in generating average annual EPS growth of +8% in 2015-2019 (vs +7% for the consensus).**

Fig. 43: Baxalta – Sales forecasts (2015-2020e)

	2015	2016e	2017e	2018e	2019e	2020e	CAGR (%)
BXLT - Group sales	**6,230**	**6,825**	**7,465**	**7,964**	**8,247**	**8,513**	**6.4%**
% growth y-o-y		9.6%	9.4%	6.7%	3.6%	3.2%	
- Hemophilia	2,840	2,824	2,915	3,013	3,085	3,090	1.7%
- Inhibitor therapies	787	944	1,086	1,119	951	856	1.7%
- Immunoglobulin	1,750	1,943	2,176	2,393	2,609	2,817	10.0%
- Biotherapeutics	766	873	961	1,047	1,120	1,188	9.2%
- Oncology	87	242	278	323	393	463	39.7%
- Biosimilars	0	0	50	70	90	100	n/a

Source: Bryan, Garnier & Co ests.

Fig. 44: Baxalta – Summary of our forecasts (2015-2020e)

	2015	2016e	2017e	2018e	2019e	2020e
(+) Product sales	**6,230**	**6,825**	**7,465**	**7,964**	**8,247**	**8,513**
% growth y-o-y		10%	9%	7%	4%	3%
(-) COGS	2,386	2,457	2,650	2,787	2,886	2,979
in % of product sales	38.3%	36.0%	35.5%	35.0%	35.0%	35.0%
= Gross margin	**3,844**	**4,368**	**4,815**	**5,177**	**5,361**	**5,533**
in % of product sales	61.7%	64.0%	64.5%	65.0%	65.0%	65.0%
(-) R&D	697	751	821	876	990	1,022
% growth y-o-y		8%	9%	7%	13%	3%
(-) SG&A	1,219	1,502	1,642	1,712	1,773	1,788
% growth y-o-y		23%	9%	4%	4%	1%
= EBITDA	**2,143**	**2,423**	**2,725**	**3,026**	**3,093**	**3,277**
in % of product sales	34.4%	35.5%	36.5%	38.0%	37.5%	38.5%
% growth y-o-y		13%	12%	11%	2%	6%
(-) D&A	207	307	373	438	495	553
= EBIT	**1,936**	**2,116**	**2,351**	**2,588**	**2,598**	**2,724**
in % of product sales	31.1%	31.0%	31.5%	32.5%	31.5%	32.0%
% growth y-o-y		9%	11%	10%	0%	5%
(-) Interest expense	139	150	120	90	40	0
(+/-) Others	26	0	0	0	0	0
(-) Income taxes	402	413	491	550	563	599
% Corporate Taxes	22.1%	21.0%	22.0%	22.0%	22.0%	22.0%
= Net income	**1,422**	**1,553**	**1,740**	**1,949**	**1,995**	**2,125**
Basic EPS (USD)	**2.10**	**2.28**	**2.56**	**2.86**	**2.93**	**3.12**
% var y-o-y	-14%	9%	12%	12%	2%	7%
Diluted EPS (USD)	**2.08**	**2.25**	**2.52**	**2.82**	**2.89**	**3.08**
% var y-o-y	-14%	8%	12%	12%	2%	7%

Source: Company Data; Bryan, Garnier & Co ests.

7.1. Hemophilia: risk of a growth slowdown overestimated

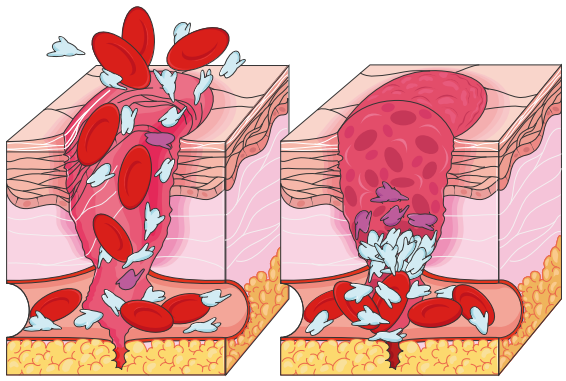
7.1.1. What about the disease and the current treatments?

Before talking about the market, let's start with a few words about this rare disease and some of the mechanisms behind it. Hemophilia is a non-evolutive hereditary disease affecting more than 420,000 people globally, characterised by the **inability of the blood to clot given the absence or virtual absence of clotting factors** (following a gene deletion or mutation). In the most severe cases, bleeding can happen unexpectedly or following minor collisions, in various parts of the patient's organism. The blood then tends to accumulate and lead to bruising which is 1/painful, and 2/ may eventually compress critical elements like nerves and blood vessels…hence the appearance of blood in the urine, the development of spontaneous and/or abnormally-prolonged bleeding, permanent damage at the level of the affected area, etc.

Hemophilia A: a disease characterised by an absence or virtual absence of the FVIII clotting factor

It is important to note that there are two main types of hemophilia in that they result in fairly distinct cases: 1/ Type A hemophilia which represents nearly 80% of the cases diagnosed (i.e. 350,000 people globally), where the disease stems from a deficit of factor FVIII clotting factor; and 2/ Type B hemophilia (a little under 20% of cases) in which patients suffer from a deficit of factor IX. In this case, however, **we are going to focus in particular on Hemophilia A in the next few pages given its preponderance in the Baxalta business mix.**

Fig. 45: Hemophilia and clotting factors



Source: Bryan, Garnier & Co. ests.

Injection of recombinant clotting factors or plasma derivatives: the Hemophilia A standard treatment

At the time of writing, **there is no real cure for Hemophilia A although the disease can be very well controlled thanks to substitute treatments** and, more specifically, injections of functional clotting factors (FVIII in this case) which may be 1/ derivatives of human blood or produced by genetic engineering and, in this latter case, we are talking about 'recombinant' factors; 2/ administered on a preventive basis (prophylaxis) or solely during a bleeding episode (on demand).

Main problem with the current therapies: the appearance of inhibitor antibodies to fight the injected FVIII

The efficacy of these therapies can, however, be affected by the emergence of an immune response/inhibitor antibodies against these proteins, which are by definition foreign and immunogenic elements (Zaiden et al, 2013; Colowick et al, 2000), in nearly 20-30%e of cases.

Fortunately, various strategies enable this problem to be circumvented although these may admittedly be fairly restrictive:

- **Induction of immune tolerance**; the aim being that the body gets used to/stops producing inhibitors to fight the injected factor following the administration of frequent doses of factor concentrates over a period of months or even years (in the majority of patients, tolerance of the factor is improved within 12 months but, in the most resistant cases, the treatment can last more than two years).

- **Factor by-passing agents**, like Feiba and NovoSeven (the first being a derivative of human plasma while the second is a synthetic product), which enable the generation of thrombin by by-passeding (hence their name) the part of the clotting process requiring Factor VIII. While these therapies are on the whole fairly effective, they have two major drawbacks: 1/ the need for frequent adminstration (every 8-12 hours for Feiba vs 2-3 hours for NovoSeven), 2/ a significant increase in the risk of blood clot formation, and 3/ a cost significantly higher than for FVIIIs and FIXs.

- **Plasma exchange** (where the inhibitors are removed from the blood using sophisticated equipment). This treatment is effective but very cumbersome and is used, in particular, when it is necessary to rapidly lower the number of inhibitors (e.g. in the case of a serious bleeding event or prior to surgical intervention).

7.1.2. A USD6bn market with mid-single-digit growth

Despite their drawbacks, Hemophilia A therapies have been able to create a significant market (c.USD6m including by-passing therapies), which is expected to see further growth of 5%-7% in the next few years. That said, we shall see that this growth is far from linear/simple in that 1/ the growth drivers vary depending on the geographical region; 2/ some highly innovative therapies are expected to emerge soon…which should at first especially benefit patients suffering from inhibitors in our view.

■ **What are the future growth drivers?**

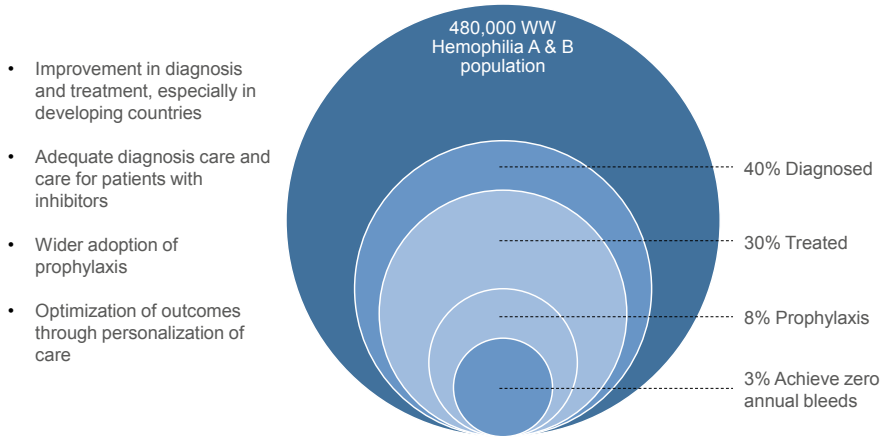
Growth in the mature countries will be underpinned in particular by the increasing adoption of prophylactic therapies

How, for example, do we see the outlook in mature countries? The majority of Hemophilia A cases in mature countries are currently treated with injections of recombinant/synthetic Factor VIII products like Baxalta's Advate or Bayer's Kogenate. Admittedly, a portion of the patients diagnosed are not necessarily treated and this aspect could serve as a driver for future growth; however we believe that the main opportunity lies in the fact that **only 25%-30%e of hemophiliac patients (40%e for the most severe cases) use the current therapies from a prophylactic perspective…although this proportion is very likely to see a gradual increase thanks to the recent arrival of therapies with a longer half-life** (e.g. Adynovate, Elocate, Kovaltry, etc.), and which are consequently less restrictive. Admittedly the related cost is far higher (10x more on average), but we need to bear in mind the fact that a significant reduction (> 90% based on the latest clinical trials) in the number of bleeding episodes enables a substantial reduction in other costs and the morbidity linked to eventual complications (brain haemorrhages, hospital admissions, arthroplasties, etc.).

Earlier-stage developments offer much more novel mechanisms of action (gene therapies, bispecific antibodies, etc.) and should also be major players in the growth of this market, especially since the initial clinical data look pretty promising in our view. We shall be going into more detail in

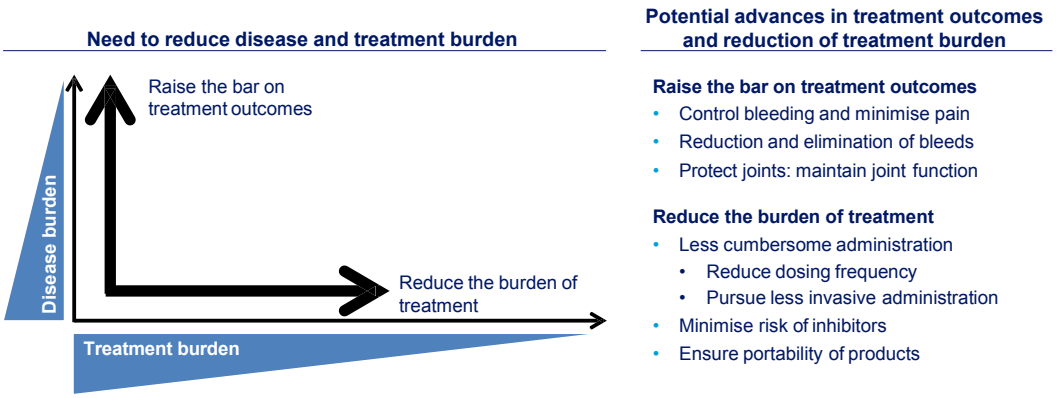
the next few pages but note that 1/ some of these new options (e.g. emicizumab) look to be viable alternatives above all for patients having developed inhibitors (remember that this subgroup represents approaching 20%-30% of patients with the most severe forms of the disease); 2/ gene therapies are those with the greatest potential since they potentially offer a cure.

Fig. 46: Hemophilia A – Patient typology



Source: Adapted from Baxalta R&D Day (2015); Bryan, Garnier & Co. ests

Fig. 47: A clinical need which remains unmet



Source: Novo Nordisk, Capital Market Day 2015

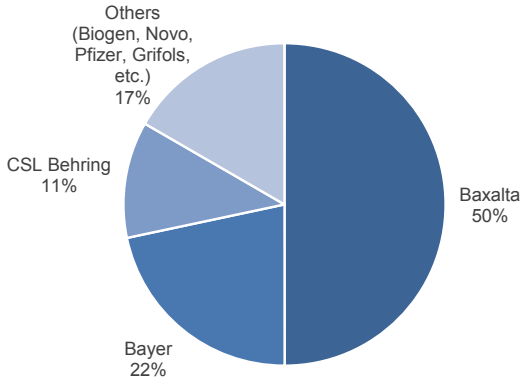
The situation is a little different in the more emerging regions where 1/ the percentage of patients diagnosed and treated remains well below the level in more developed regions and, given the cost involved in prophylactic therapies, it goes without saying that most of them are probably treated on demand; 2/ of the patients treated, most are given FVIII plasma derivatives (> 75% of cases in Brazil, China and Russia for example whereas this figure is no more than 10% in the UK). Within this context, it is more than likely that the growth generated here will primarily come from migration to more expensive but safer recombinant factors, and their wider adoption from a prophylactic perspective.

- **What are the main forces at work?**

Baxalta is by far the biggest player in the treatment of this disease with five products whose combined sales are approaching USD3bn; in our view, three of the latter will be the main drivers in this portfolio: 1/ Advate (rFVIII) in the short term, despite its advanced age, thanks to the increasing

conversion of patients in mature regions to prophylaxis; 2/ Adynovate, a new long-acting formulation of Advate on the US market for the past few months; and 3/ Feiba, a compound of FVIIa and non-activated Factors II, FIX and FX indicated for patients with inhibitors. But let's leave this biotech for a moment and concentrate on some of its main competitors:

Fig. 48: Hemophilia A – Main players on the market (c.USD6bn)



Baxalta: Advate, Adynovate, Feiba, Recombinate, Hemofil M (pdF)
Bayer: Kogenate
Novo Nordisk: NovoEight
Pfizer: Refacto AF
Biogen: Eloctate
CSL: Humate-P (pdF), Helixate
Grifols: Alphanate (pdF)

Source: Company data; Bryan, Garnier & Co. ests

- **Bayer is currently number two on the market thanks to Kogenate (2015 sales c.USD1.3bn)**, a recombinant factor VIII whose characteristics are fairly similar to those of Advate on paper (although note that some studies have shown that the risk of developing inhibitors was lower with the latter).
  However, like Baxalta, the German company has now launched a long-acting rFVIII on the market named Kovaltry (since Q1 16 to be more precise, in both Europe and the United States)…and we note that the trend seems to be much more positive now that the latter is on the market knowing, however, that the comparables for these 2016 figures were affected by the prioritisation of production capacity utilisation.

- Biogen is well known for its portfolio of multiple sclerosis drugs (Tysabri and Tecfidera to mention but a few); although note that 1/ Hemophilia is one of the therapeutic areas which have been chosen with a view to diversification; 2/ the big biotech is now marketing Eloctate, a long-acting recombinant FVIII which generated sales of USD320m during its first year of full-scale marketing.

  That said, the latest figures published for this product show that: (i) while the product may appear more attractive than Advate, Baxalta's recent reports/statements don't really show any serious loss of patients under therapy due to this new competitor…confirming the fact that there may be genuine brand loyalty; (ii) Eloctate's sequential growth in the US now looks to be slowing (see Fig. 49), something which is probably explained by the recent market launches of Adynovate and Kolvatry.

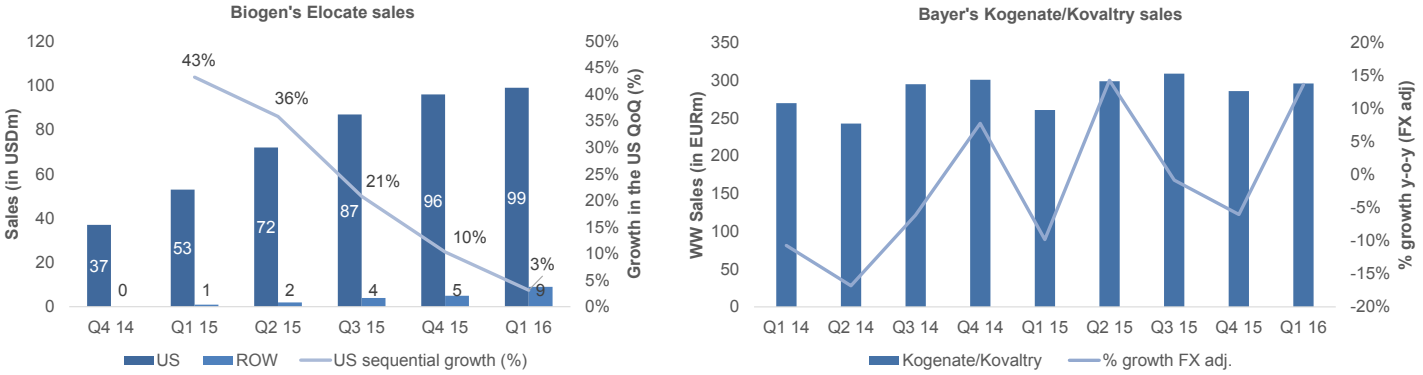
We shall see how the sales of this product evolve over the coming few quarters but it is clear that 1/ peak sales of USD1.0-1.5bn may seem very/overly optimistic given the current lack of an installed base of patients to migrate; 2/ the cards could be reshuffled were the totality of the Hemophilia business to be acquired by a player like Pfizer or CSL following the planned spin-off…

Fig. 49: Hemophilia A – Competitors on the market or in development

Company	Compound	MoA	Stage	Dosing	Launch
Baxalta	Adynovate	PEGylated rFVIII	Marketed (US, Japan), to be approved in Europe	Twice a week	2015
Baxalta	BAX 826	Long-acting rFVIII	Phase I/II	Twice or 4x a month	2020e
Baxalta	BAX 888	Factor VIII gene therapy	Preclinical	Nd	> 2020
Biogen	Eloctate	Long-acting recombinant Fc	Marketed (US, Europe, Japan)	Twice a week	2014
Novo Nordisk	N8-GP	Glyco-PEGylated rFVIII	Phase III	3-4 x a week	2019e
Bayer	Kovaltry	Long-acting rFVIII	Marketed (US, Europe), to be approved in Japan	Twice a week	2016
Roche	ACE910	Bispecific antibody	Phase III	Once or twice a month	2018e
Alnylam	ALN-AT3	RNA interferent	Phase I/II	Once a month	> 2020
Biomarin	BMN 270	Gene therapy	Phase I/II	Nd	> 2020

Source: Company Data; Bryan, Garnier & Co ests.

Fig. 50: Quarterly sales trend for Elocate and Kogenate/Kovaltry



Source: Biogen; Bayer; Bryan, Garnier & Co. ests

7.1.3. Risks/opportunities not to be underestimated

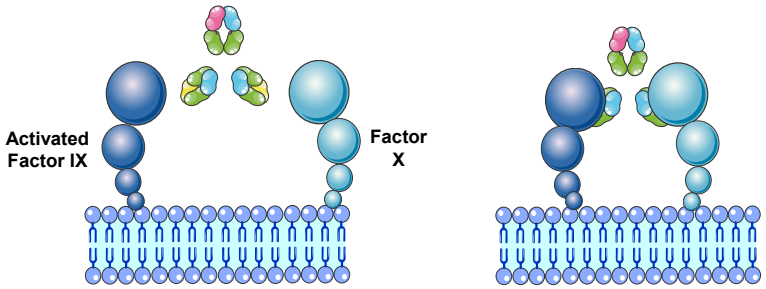
- **Roche's ACE910: primarily aimed at hemophiliacs with inhibitors**

The hemophilia market has not changed radically in recent years (the latest compounds launched on the market primarily concerned incremental innovation) but, as highlighted above, it is important to note that there are a number of therapeutic candidates with novel mechanisms of action in late-stage development. Since a part of the market appears to consider the latter to be real paradigm-changers, it is probably worth taking a closer look at their respective mechanisms of action and the initial clinical data.

Amongst them, **Roche's Emicizumab (ACE910)** in particular has appeared on our radar since the FDA granted a 'Breakthrough Therapy' designation and in that 1/ a small Phase I trial (n=18) revealed significant reductions in annualised bleeding rates in hemophilia patients with or without

FVIII inhibitors (see Fig. 52 for more details); 2/ as a bispecific antibody, it should benefit from a longer half-life and a less restrictive administration schedule (once a month).

Fig. 51: Roche's Emicizumab (ACE910) – Mechanism of action



ACE910 binding to FIXa and FX promote their interaction and **exert FVIII-mimetic activity** on the phospholipid membrane by placing FIXa and FX in spatially appropriate positions

Source: Roche; Bryan, Garnier & Co. ests

Fig. 52: Emicizumab Phase 1b – Hemophilia A patients with/without inhibitors

	Pts with inhibitors	Dose	Mean ABR 6 months prior to the study	Mean ABR Post ACE910	Mean ABR Follow-up period
C-1 cohort (n=6)	4	1 (initial) then 0.3 mg/kg	32.5	1.7	17.8 (17.4-18.5)
C-2 cohort (n=6)	4	3 (initial) then 1 mg/kg	18.3	0	12.3 (8.2-13.7)
C-3 cohort (n=6)	3	3 mg/kg	15.2	0	6.6 (5.6-7.8)

Source: Company Data; Bryan, Garnier & Co ests.

Could this molecule potentially replace therapies which are admittedly more cumbersome from a logistical perspective but whose efficacy and profile is now well established? We don't see this being the case for the following reasons:

- As we have previously suggested, in our view **it will be extremely difficult to dislodge therapies 1/ with a mechanism imitating a 'normal' physiological situation, and 2/ for which we have so much hindsight, in terms of both efficacy and safety** … and note that new recombinant FVIIIs with still longer lifespans (like BAX826 which could potentially be administered once a week) are likely to emerge.

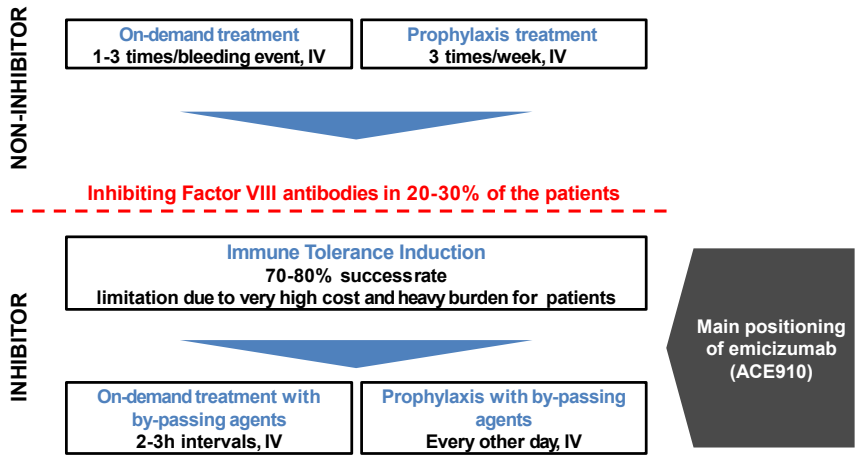
- On the face of it, the initial clinical data published by Roche are very promising although various studies seem to indicate that there are still cases of dysplasia (abnormally high proliferation in the number of normal cells composing an organ or tissue), and vascular proliferation at the level of the joints (Muto et al, Blood 2014). It is not impossible that these different elements will appear in humans; particularly within the framework of larger-scale trials (is this linked to this antibody's lower binding affinity for FIXa and FX relative to a natural or synthetic FVIII (Kitazawa et al, 2012?).

- **It is highly likely that emicizumab will initially address only those patients having developed antibodies** (particularly since the Phase III trial under way includes only this type of patient)…and notably those who only respond very badly to therapies inducing immune tolerance or by-passing therapies. On this scenario, the eventual negative impact

will be felt especially at the level of BXLT's Inhibitors business (involving products like Feiba and generating sales of USD0.8bn).

- We expect the spin-off or acquisition of Biogen's Hemophilia business (and the ensuing valuation) to be a good advance indicator of the development of the hemophilia market and the space that long-acting rFVIIIs will occupy. Were the figures circulated by the specialised press to be confirmed (USD4-6bn), the read-across would clearly be very positive for Baxalta.

Fig. 53: Positioning of Emicizumab



Source: Bryan, Garnier & Co. ests.

■ **Gene therapies: still early days**

Whether for Hemophilia A or other indications characterised by a relatively 'simple' gene anomaly, gene therapies now belong to these potentially game-changing assets in that they offer a cure. The very concept of gene therapy (involving the insertion or deletion of a gene via a most-often-viral vector of the lentivirus type) is in any case attractive in theory: if the patient has a deficient or defective F8 gene, this method enables it to be inserted or 'repaired'.

Its practical application will, however, have to contend with issues inherent in using a viral vector, which is by definition immunogenic and may potentially induce a T response against the product (Herzog et al, 2015). The addition of immunosuppressive compounds (e.g. prednisone) enabling the mitigation of these risks is one of the avenues currently being studied although this solution also raises a number of questions: should it always be administered as an adjuvant? Or should one await the appearance of resistance markers like an increase in liver enzymes? In any case, we shall be keeping a close eye on development project like Biomarin's BMN270, or even BAX888 and BAX 335 at Baxalta.

7.1.4. A franchise with low-single-digit growth

Hemophilia franchise: a 2015-2020e CAGR of +1.7%

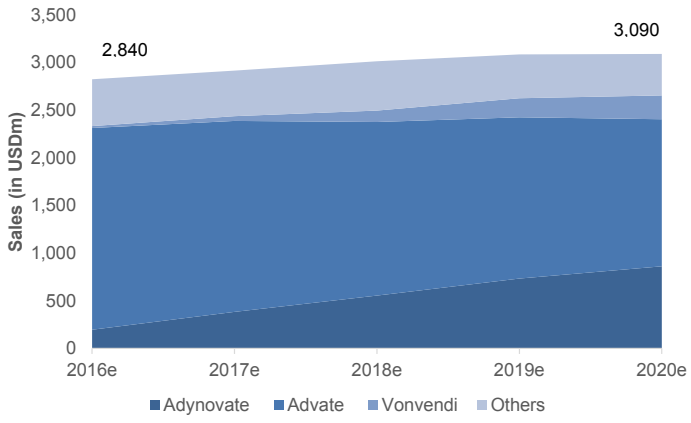
In view of our anticipation of the different dynamics, we expect BXLT's Hemophilia franchise to average growth of 1.7% over the 2015-2020e period; and, going further into the detail, we would argue that:

- Advate should again see growth this year given 1/ its ramp-up in emerging countries like Brazil and Russia, and 2/ the increased migration of US patients to prophylactic therapies, and this despite the arrival of Eloctate over the past year or so. That said, this respite won't last long, largely due to the recent market launch of Kovaltry. We nonetheless expect the bulk of the anticipated sales slowdown to come from cannibalisation by Adynovate in the developed countries.

- We expect migration from Advate to Adynovate to be easy in most patients currently on the former therapy in that the latter is 'only' a longer-acting pegylated form which is less immunogenic than its big sister (and we have enough hindsight on this technique to know that it removes none of the qualities of the basic product, quite the contrary). Hence our **sales estimate of some USD800m as of 2020e for this product,** knowing that 1/ the bulk of this figure will probably be realised in the United States (around USD600m assuming a market share of 15%-20% depending on the type of treatment); 2/ Japan is now addressed but Europe is not expected to be before 2017e; 3/ the product is currently only indicated for adults although we understand that a label extension to children is likely to be obtained next year.

- In addition to the fact that the mix is likely to be characterised by a sales slowdown for Advate to the benefit of Adynovate, we start from the premise that a new product like **Vonvendi (the very first recombinant von Willebrand factor indicated in the eponymous disease) is only likely to generate sales of USD250m in 2020** (which may seem very conservative given its emerging differentiation capability and the low competitive intensity in this sub-segment).

Fig. 54: Hemophilia franchise – Sales forecasts (2016-2020e)



Source: Bryan, Garnier & Co. ests.

Fig. 55: Baxalta – Products and therapeutic candidates in Hemophilia A

Compounds	MoA	Indication	Stage
Advate	Recombinant Factor VIII (rFVIII)	Hemophilia A	Marketed
Adynovate	PEGylated rFVIII	Hemophilia A	Marketed
Hemofil M	Anti-hemophilic factor (AHF)	Hemophilia A	Marketed
Immunate	Plasma-derived FVIII/vWF concentrate	Hemophilia A/von Willebrand disease	Marketed
Vovendi	Recombinant von Willebrand disease factor	Von Willebrand disease	Marketed (US)/Phase III (EU)
Obizur	Recombinant porcine FVIII	Acquired hemophilia A	Marketed
BAX 930	recombinant ADAMTS13	Hereditary thrombotic thrombocytopenic purpura	Phase II
BAX 826	Long-acting rFVIII targeting weekly dosing	Hemophilia A	Phase I
BAX 335	Factor IX gene therapy	Hemophilia B	Phase II
BAX 888	Factor VIII gene therapy	Hemophilia A	Preclinical

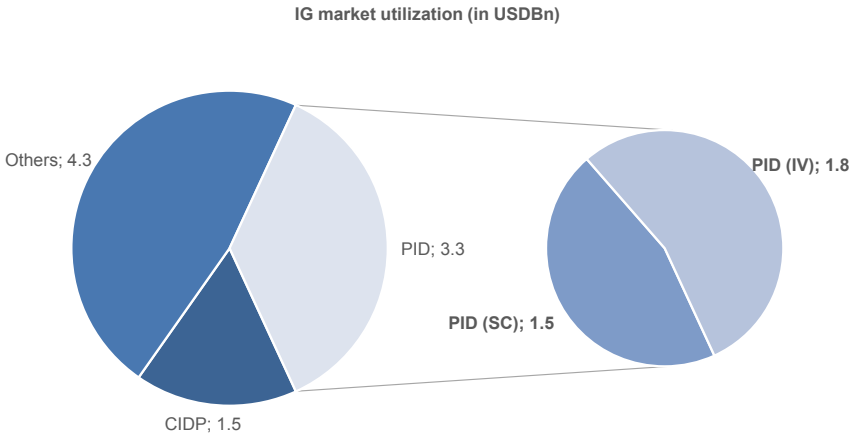
Source: Company Data; Bryan, Garnier & Co ests.

7.2. Immune globulins and Hyqvia as the main growth driver

■ A market with a very positive outlook

Although Hemophilia is expected to remain the group's most important franchise through to the end of the decade, the future source of growth is expected to lie in its second segment: Immune Globulins (also known as antibodies which play a key role in maintaining our immune defences), particularly within the framework of the treatment of primary immunodeficiency (PID).

Fig. 56: Immune globulin market by indication (in USDbn)



* PID: Primary immunodeficiency; SC: Subcutaneous; IV: Intravenous
CIDP: Chronic Inflammatory Demyelinating Neuropathy

Indication	2015-2020 CAGR	Prevalence	Diagnosis rate
Primary immunodeficiency (PID)	Around 8%	1,000,000	30%
Chronic Inflammatory Demyelinating Neuropathy (CIDP)	Around 5%	75,000	80%
Multifocal Motor Neuropathy (MMN)	Around 5%	15,000	60%

Source: Company Data; Bryan, Garnier & Co ests.

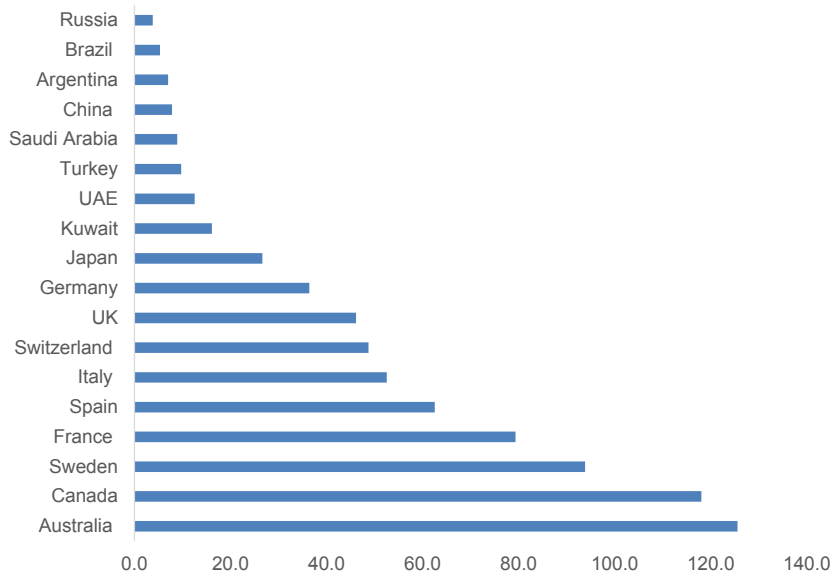
IGs in the treatment of PID: a mid-single digit growth market driven by 1/ increased penetration of SC alternatives; and 2/ the ex-US countries

Primary immunodeficiency (PID) is a relatively widespread hereditary immune deficiency (prevalence: 1 million), which is nonetheless very badly diagnosed (only 30%e of cases) for two reasons: 1/ patients with this disorder very often suffer from infections and, while they are treated, the underlying cause is not always investigated; 2/the tests currently carried out are very cumbersome and do not enable the perfect detection of the disease. **The standard treatment remains and will largely remain the administration of antibodies or IG** (and, in the most severe/complicated cases, cytokines, enzymes and even bone marrow transplants may be envisaged), and their use in this setting continues to grow for the following reasons:

- Currently, IGs continue to be administered intravenously (in some 65% of cases) but 1/ more and more patients with this type of treatment are progressively migrating to subcutaneous therapies (e.g. Subcuvia and Hyqvia at Baxalta); 2/ newly-diagnosed patients are showing a marked preference for the latter for all the reasons we already know (auto-administration, saving in time and money, etc.) **The subQ sub-segment should thus outperform the market in the next few years (+15% in volume vs +5% for IV)**.

- The main players in the sector (Grifols, Baxalta, CSL, Biotest, etc.) have historically focused on the US market where the pricing conditions tend to be much more favourable (as very often in the health sector); however, for some time the other regions have been the subject of increasing attention given their under-penetration (see Fig. 57). It is notably for this reason that they are expected be the main growth driver for the market through to the end of the decade (+6%-7%e for Europe and more than +10%e for the rest of the world).

Fig. 57: IG market – Units per capita



Source: Baxalta

- **Hyqvia: towards sales of USD850bn in 2020!**

Hyqvia: SC channel, injection once a month, convincing data…the compound has everything going for it

Baxalta has significantly benefited from the afore-mentioned trends in recent years thanks to the exhaustiveness of its product portfolio and growing commercial coverage. …And we are convinced that a novel therapy like Hyqvia should enable the group to capture more market share.

Fig. 58: Baxalta – Immune globulin-type products and drug candidates

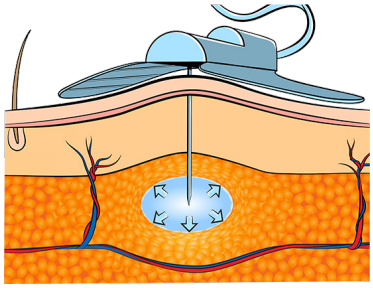
Compound	MoA	Indications	Est. 2015 sales
Gammagard Liquid	IV immune globulin (IG)	- Primary immunodeficiency (PID)	USD1.6Bn
Hyqvia	SC human IG and recombinant hyaluronidase	- Adults with PID syndromes	USD100m
		- Myeloma or CLL with severe hypoglobulinemia and recurrent infections	
Gammagard S/D	IV immune globulin (IG)	- Children and adults with PID (> 2 years old)	< USD100m
		- Prevention of bacterial infections in hypogammaglobulinemia	
		- Recurrent bacterial infection associated with B-cell CLL	
		- Adults with idiopathic thrombocytopenic purpura	
		- Prevention of coronary artery aneurysm associated with Kawasaki Syndrome	
Subcuvia	SC human IG	- Children and adults with PID	< USD100m
		- Myeloma and CLL with severe hypogammaglobulinemia and recurrent infection	

Source: Company Data; Bryan, Garnier & Co ests.

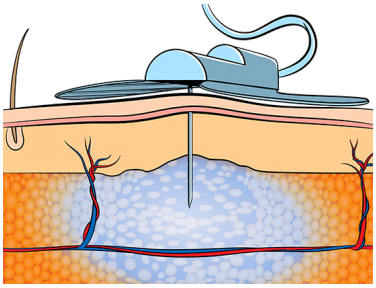
Hyqvia is effectively **an exotic combination of human immune globulin and human hyaluronidase enabling a single subcutaneous injection per month, making it the SCIG with 1/ the longest-lasting action ever seen to date** (CSL's Hizentra 20%, for example, being administered twice a month and all the others once a week); 2/ the lowest annual cost (the price per mg is said to be higher, but fewer injections are needed over a year).

The originality and the practical aspect are both clearly key arguments for the marketing of a development project but they would not be required had the clinical package not been up to the task. Fortunately the latter is unrivaled since 1/ the efficacy profile compares very favourably with the other IGs (see Fig. 61), and 2/ the safety profile is more than satisfactory (the main secondary effect by far being a reaction at the infusion site, and no SAEs having been noted during the clinical trials).

Fig. 59: Hyqvia – Advantages / Mechanism of action



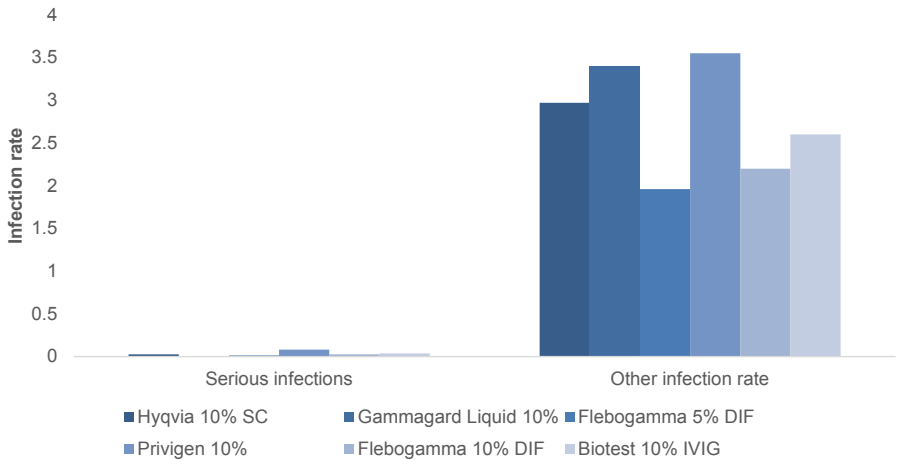
The subQ tissue is filled with a substance called **hyaluronan**, which limits the flow of fluids through subQ at local infusion sites
Because of this, conventional subQ IG treatments may require more frequent injections



As part of the Hyqvia infusion, **recombinant human hyaluronidase** locally increases the amount of hyaluronan that is turned over (thus temporarily opening up the subQ tissue).
Note that the effect is reversible (24-48 hours after the infusion)

Source: Baxalta; Bryan, Garnier & Co ests.

Fig. 60: Comparison of the efficacy of the different IGs on the market



Source: Companies Data; Bryan, Garnier & Co ests.

We are forecasting sales of USD850m in 2020 for this product (versus c.USD100m in 2015)

Given the advantages offered by the compound and the dynamic which is currently underpinning the market growth, we expect 1/ **Hyqvia to generate sales of approaching USD850m by 2020**, even assuming the absence of a probable extension to a market like chronic inflammatory demyelinating polyneuropathy (CIDP) in 2019e; and 2/ the IG franchise to deliver average annual growth of 10% through to 2020e driven by Hyqvia's momentum (whereas the management's guidance is nearer to +8%).

A major driver to EBITDA margin growth

- We understand the annual run rate of Hyqvia currently stands at USD200m; but we expect this figure to grow on a sequential basis as 1/ the geographical coverage has recently been expanded, or will be, to high-IG consuming countries like Canada and Australia; 2/ the European label will probably be enlarged to children and adolescents in the next few months (knowing that this population accounts for nearly 50% of all diagnosed patients).

- Currently it would seem that 1/ 50% of the gains in market share involve the migration of patients treated with competitor alternatives; 2/ around 25% of new patients are likely to be newly diagnosed; 3/ the remaining 25% is likely to correspond to cannibalisation of GammaGard Liquid. We don't expect this latter point to last long, as we believe patients receiving the latter will naturally be attracted to a cheaper/less cumbersome but equally effective therapy… And because it will be in Shire/Baxalta's interests from an economic standpoint to push migration to Hyqvia (especially if production capacity in the IG segment remains relatively limited).

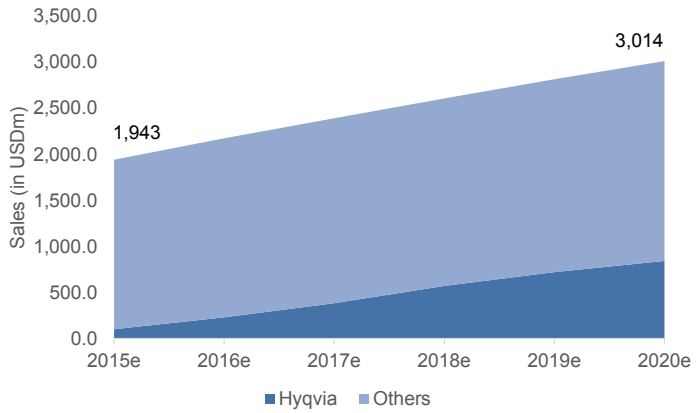
- Admittedly, the growth in the other products in the portfolio is likely to be partially cannibalised by this new entrant but we also expect the change in mix it induces to be very positive for the bottom line (the management now ranking it alongside the products with the highest margin potential). As 1/ our top line estimates are superior to the latest company's guidance, particularly thanks to Hyqvia, and 2/ the IG unit is set to become a major growth driver, our EBITDA margin forecast in 2020 is a also higher than the guidance given by the company during its R&D Day in 2015 (38% vs 35%-36% respectively).

- In our view, the caution shown by the lower end of the consensus is partly linked to the lack of transparency in Baxalta's financial disclosure; for the moment, we have only a vague idea

of the mix within each business segment although it is very likely that this will change once these different products have been integrated in Shire's portfolio (the latter being, on the other hand, very well known for disclosing details on the sales progression of its different development projects).

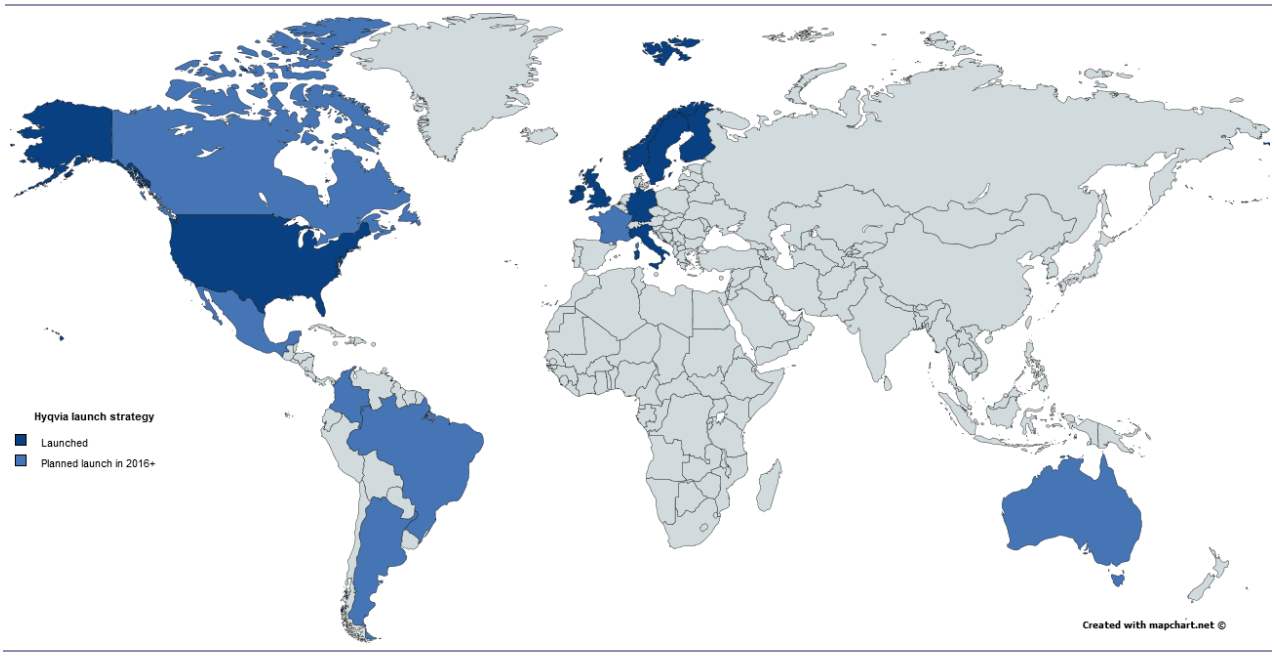
The release of the Q2 16 sales figures based on this new classification could be a catalyst not be underestimated…

Fig. 61: IG franchise – Sales forecasts (2016-2020e)



Source: Bryan, Garnier & Co. ests.

Fig. 62: Hyqvia – Launch strategy



Source: Baxalta; Bryan, Garnier & Co. ests.

7.3. Oncology: a growth pillar not to be underestimated

Fig. 63: Sales forecasts for the Oncology franchise (2016-2023)

(in USDm)	Risk adj.	2016	2017	2018	2019	2020	2021	2022	2023
BAXALTA - ONCOLOGY		**257**	**308**	**374**	**478**	**579**	**655**	**698**	**727**
% var y-o-y			20%	21%	28%	21%	13%	7%	4%
Oncaspar franchise	**100%**	**222**	**238**	**255**	**274**	**297**	**320**	**321**	**328**
% var y-o-y			7%	7%	8%	8%	8%	0%	2%
- o/w ALL	100%	222	238	255	274	297	320	321	328
- o/w AML	0%	0	0	0	0	0	0	0	0
Onivyde (nal-IRI)		**35**	**70**	**119**	**204**	**282**	**335**	**377**	**400**
% var y-o-y			100%	70%	71%	39%	19%	13%	6%
- o/w 1L mPancreatic cancer	50%	0	0	0	25	50	80	112	134
- o/w 2L mPancreatic cancer	100%	35	70	119	179	232	255	265	265
Pacritinib (JAKi)		**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
% var y-o-y			n/s	n/s	n/s	n/s	n/s	n/s	n/s
- o/w Myeolofibrosis	0%	0	0	0	0	0	0	0	0
- o/w Others	0%	0	0	0	0	0	0	0	0

Source: Bryan, Garnier & Co ests.

7.3.1. Oncaspar: strong growth through to 2020

Oncaspar (PEGaspargase) is a pegylated form of asparaginase, a therapeutic enzyme which depletes the amino acides that are key to the growth and survival of some tumours, and much less so that of healthy cells (making it a relatively well-targeted therapy). Having been approved for the past ten years, this chemotherapy is now a major part of the standard first-line treatment for acute lymphoblastic leukemia (Phi-ALL), alongside other chemotherapies like cytarabine and cyclophosphamide.

- **More promising opportunities in ALL**

Europe, Japan and the adult segment: the main growth factors for Oncaspar in ALL

We expect Oncaspar's growth to remain strong (2016-2020 CAGR: +8%) thanks to 1/no real competition in the first line of treatment through to the end of the decade, and 2/ a major extension in its addressable market to Europe and Japan.

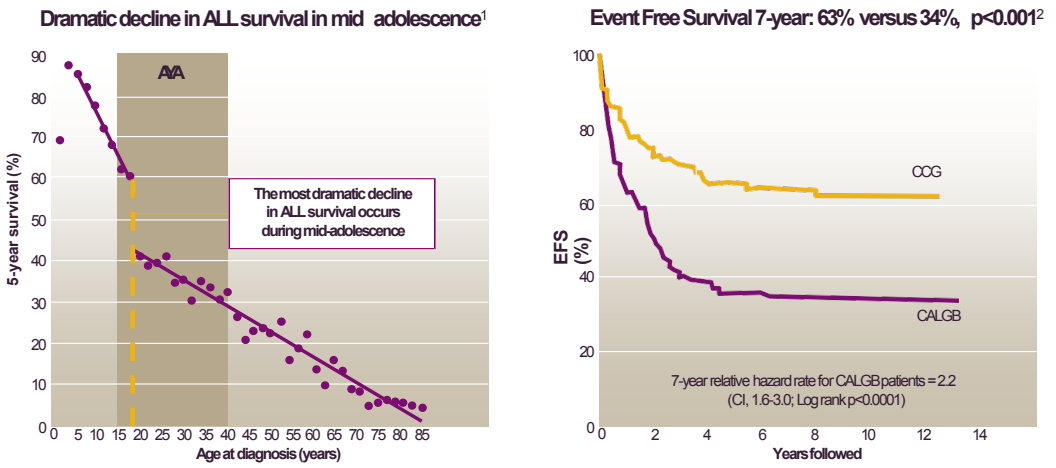
- GRASPA/ERY-ASP is potentially a more novel form, offering a better safety profile (see our last research note for more details). However, in that the Erytech therapeutic candidate is not expected to reach the first line of treatment before 2019 or even 2020, the risk of market share losses looks relatively low over the short term in our view especially since 1/a freeze-dried form (easier to store) of the product should be available as of 2017 in the US, and in 2018 for Europe; and 2/ a new generation of pegylated asparaginase enabling fewer injections (it remains to be seen whether its immunogenic profile has also been improved) could also be launched on the market before the end of the decade.

- In addition, we expect **all the forms of this enzyme to benefit from the accumulation of clinical data demonstrating the superiority of asparginase-based regimens in adults** (Cf. Fig. 65) since 1/ their use is mainly restricted to the least fragile patients, children in this case, given its toxicity; and 2/ we currently estimate that adults under 55 years of age are likely to account for approaching 30% of the patients newly diagnosed with this disease (vs 50%-60% for children).

- At the beginning of the year, **the European Commission gave its green light for the marketing of this product in the first line treatment of pediatric patients and adults suffering from ALL**. In that 1/ the marketing authorisations had only been granted in some countries (notably Germany and Poland); 2/ hitherto the main asparaginase used in this setting had been the free form, it is more than likely that this approval will be the main driver in this product's growth.

- The administration of CAR-T cells is admittedly being reflected in impressive tumour regressions but 1/ the safety profile is far from benign, and 2/ the fact that the first versions developed should also be autologous implies logistical and cost issues which are also likely to hold back their adoption. We consequently only expect these immunotherapies to be last line alternatives in ALL and other cancers of the blood (where Oncaspar is not used).

Fig. 64: Superiority of the asparaginase-based treatment protocols in adults and adolescents suffering from ALL



[1] Stock W et al. *Leuk Lymphoma* 2011;52:2237-2253.
[2] Stock W et al. *Blood* 2008; 112:1646-1654.
[3] Stock W et al. ASH2014, Oral presentation, abstract 796, Tuesday, December 9, 2014.
AYA = Adolescents and Young Adults, CCG = Children's Cancer Group, CALGB = Cancer and Leukemia Group B, EFS = Event Free Survival

Source: Jazz Pharmaceuticals

A possible expansion in indications with AML?

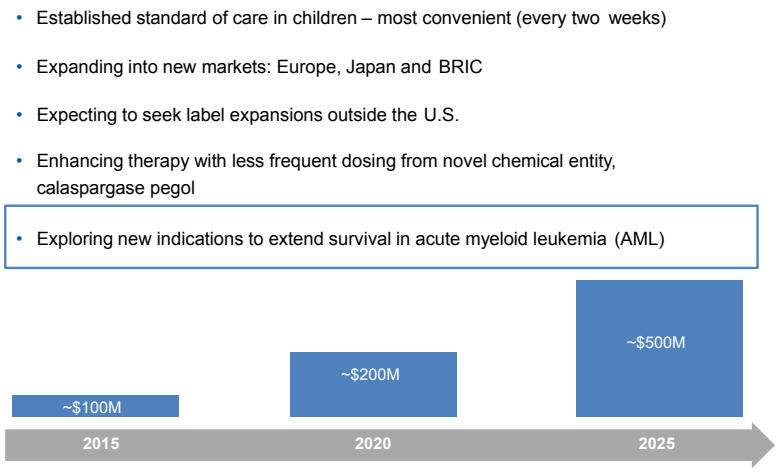
A real development rational in AML…

All the points previously highlighted concern only ALL but note that the range of possibilities could be expanded to other indications and notably to acute myeloid leukemia (AML). Currently, the cytarabine and anthracyline-based regimens remain the therapies the most commonly used in this indication; whereas they have been on the market for over four decades. This does not, however, mean that they are a panacea. While they are relatively effective, it should be remembered that their

safety profile is far from satisfactory (high mortality rate, contraindicated in a large number of patients, etc.). Hence the need to develop new alternatives offering a better therapeutic window.

The possibility of including asparaginase in therapeutic cocktails for this indication has been explored several times in the past, notably given its ability to rapidly and significantly reduce the levels of asparagine but also glutamine in the blood. You could argue that the efficacy surplus it enables is potentially far from insignificant. A trial conducted in 1988 and including 195 refractory or relapsing patients had moreover shown that its combination with a high dose of cytarabine was reflected in a higher percentage of full remission than cytarabine on a stand-alone basis (40% vs 24%, p=0.02). **That said, it is not so much efficacy but the safety of use which is the real issue for this indication**. The toxicity intrinsic to the compound is obviously regrettable but we also need to take into account the type of patients: most are over 65 years old at diagnosis, and cannot withstand therapies which are too toxic.

Fig. 65: Oncaspar (PEG-asparaginase) development plan



Source: Baxalta, May 2015 Presentation

… but the competitive landscape requires a degree of caution

Leaving aside the difficulties inherent to this type of development, we also note that the competitive landscape has become significantly more crowded in recent years. Venetoclax (a small BCL2 inhibitor molecule developed by Roche), for example, is on our radar due to the response rates it has obtained in combination with hypomethylating agents (ORR: 70%-75% in newly-diagnosed patients who are not eligible for standard chemotherapy), and its recent obtention of a Breakthrough Therapy designation. A second name would definitely be sorafenib (a multi-tyrosine kinase inhibitor) given its efficacy in combo with 5-aza in pre-treated patients with FLT3+ (ORR: 46%).

Last but not least, remember that GRASPA is also being developed in this indication. While Oncaspar is unlikely to suffer from much competition from this asparaginase reformulation in ALL in the short term, in our view the situation is very different in AML, a Phase II trial involving the Erytech development project expected to be finalised by H1 17.

In this setting, we have decided not to include a possible extension to AML in our sales forecasts for Oncaspar.

- **Sales potential of USD320m by 2020**

We are currently forecasting sales of USD320m by the end of the decade based on the asumption that 1/ growth in the US will be driven, in particular, by the increase in prescribing to adult patients; 2/ adoption in Europe should be fairly rapid (40% market share by 2021), knowing that the prices practiced are likely to be 40% below those achieved in the US.

Fig. 66: Sales forecasts for Oncaspar (2016-2020e)

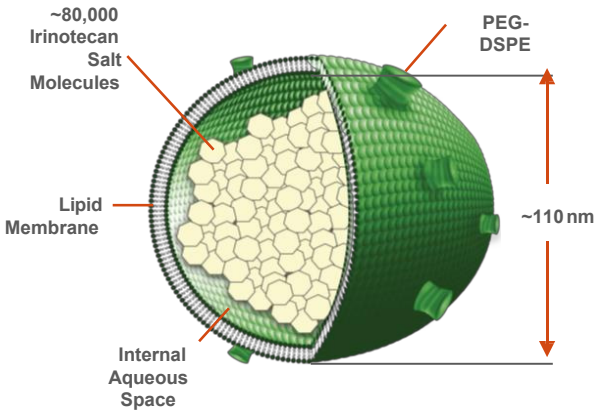
	2015e	2016e	2017e	2018e	2019e	2020e	2021e	2022e
Incidence								
US	7,000	7,070	7,141	7,212	7,284	7,357	7,431	7,505
Europe	8,000	8,080	8,161	8,242	8,325	8,408	8,492	8,577
Japan	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000
% Children with ALL (%)	60%							
% Phi- ALL children (%)	95%							
% Adults with ALL (%)	30%							
% Phi- ALL adults (%)	80%							
Pricing in the US (in USD)	55,000	55,550	56,106	56,667	57,233	57,806	58,384	58,967
% var y-o-y		1.0%	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%
Pricing in Europe (in EUR)	30,000	30,300	30,603	30,909	31,218	31,530	31,846	32,164
% var y-o-y		1.0%	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%
Pricing in Japan (in USD)	34,800	34,542	34,887	35,236	35,589	35,945	36,304	36,667
% var y-o-y		-1%	1%	1%	1%	1%	1%	1%
Children								
Market shares - US - Children	80%	80%	80%	80%	80%	80%	80%	80%
Market shares - Europe - Children	8%	15%	20%	25%	30%	35%	40%	40%
Market shares - Japan - Children	0%	0%	0%	0%	5%	15%	25%	20%
Adults								
Market shares - US - Adults	10%	13%	16%	19%	21%	23%	25%	25%
Market shares - Europe - Adults	0%	5%	7%	9%	11%	13%	15%	15%
Market shares - Japan - Adults	0%	0%	0%	0%	2%	5%	7%	10%
Net sales	**197**	**222**	**238**	**255**	**274**	**297**	**320**	**321**
% var y-o-y		12%	7%	7%	8%	8%	8%	0%

Source: Company Data; Bryan, Garnier & Co ests.

7.3.2. Onivyde: a promising alternative in pancreatic cancer

Onivyde (naI-IRI) is a form of irinotecan encapsulated in a liposome vehicle 1/ whose rights were acquired from Merrimack in 2014 (potential milestone payments: USD870m in addition to royalties) and 2/ recently approved for the second line treatment of metastatic pancreatic cancer in the United States.

Fig. 67: Onivyde (nal-IRI)



Source: Merrimack Pharmaceuticals

An irinotecan reformulation as the new second line standard of care in pancreatic cancer

The rational behind a reformulation of this old chemotherapy was relatively robust. In the past, a number of trials have effectively shown that these free forms of irinotecan had tended to improve the response rates in combination with gemcitabine in this type of patient thanks to diverse synergies between the two compounds (Rocha Lima et al, 2001). However, the problem was especially the toxicity level of the combination, explaining why reformulations have been envisaged.

In the case of Onivyde, we understand that 1/the half life may be greatly improved relative to a free form thanks to its encapsulation in a pegylated lipid vehicle; and that 2/ thanks to this prolonged circulation in the blood, these very small elements (nanometre sized) can accumulate more easily in tumour tissues via an enhanced permeability and tissue retention effect (EPR). In other words, **the medication interacts more with the tumour cells and over a longer period than is the case for its free form.**

What do we see in practice? A Phase III trial notably established the superiority of Onivyde relative to the current post-gemcitabine (5-FU, leucovorin) second line standard therapy in terms of overall survival (6.1 vs 4.2 months for the control arm, HR: 0.57, p=0.0009). However, we also deem the toxicity profile for the combination to be unrivaled given the fact that the incidence of the most severe cases of neutropenia (abnormally low level of neutrophils in the blood) or neuropathy seem to us to be much less significant than with cocktails used in first line like Abraxane/Gemcitabine or Folfirinox/Gemcitabine.

Fig. 68: Onivyde (nal-IRI) – Phase III – Main results

NAPOLI-1 summary	Onivyde + 5-FU/LV vs 5-FU/LV
Setting	Post-gemcitabine metastatic pancreatic cancer
Efficacy data	
OS stratified Hazard Ratio (HR)	0.57 (0.41-0.80), p=0.001
Median Overall Survival (OS)	6.1 months vs 4.2 months
Change vs control	+1.9 months
Adverse events ≥ Grade III	
Neutropenia	20%
Febrile neutropenia	3%
Fatigue	21%
Vomiting	11%
Diarrhea	13%
Neutopathy	NA

Source: Company Data; Bryan, Garnier & Co ests.

- **USD350m of sales based only on pancreatic cancer**

We are currently forecasting peak sales of USD350m for this product (i) in Europe and (ii) in the treatment of pancreatic cancer based on the following assumptions:

Fig. 69: Sales forecasts for Onivyde in Europe

	Second line	First-line	TOTAL
Annual incidence - Europe	100,000	100,000	
% Exocrine tumours	90%	90%	
% Metastatic patients	70%	70%	
% Second line treatment (post-gemcitabine)	50%	na	
Monthly cost per patient - in USD	4,000	4,000	
% Market share	30%	13%	
Average Progression Free Survival (in months)	4.0	6.0	
Average cost per patient (in USD)	16,000	24,000	
Onivyde - Non-risk adjusted peak sales (in USDm)	**151**	**197**	**348**

Source: Company Data; Bryan, Garnier & Co ests.

- We model a monthly cost per patient of USD4,000 (a 50% discount to the prices practiced in the United States). Starting from here, we then model the assumption that 1/ an average patient is likely to be treated until an eventual progression in the tumour, i.e. four months for the second line based on the PFS data obtained in Phase III; and 2/ that this duration of treatment could be six months in first line based on the premise that the Onivyde efficacy results will be at least similar to those of Abraxane (at least on the HR front).

- Our assumption of a 30% market share for the second line of treatment is relatively cautious in our view (especially bearing in mind the fact that the product is now included in the

ESMO guidelines); but we prefer to be cautious in the face of earlier-stage drug developments, and in particular Abraxane in combination with atezolizumab (a paclitaxel present in some chemotherapies offering synergies with the therapies modulating the immune system). In addition, we model a peak market share of 15% ahead of the results involving the first line of treatment (expected in H1 17).

7.3.3. Pacritinib in myelofibrosis: caution required…

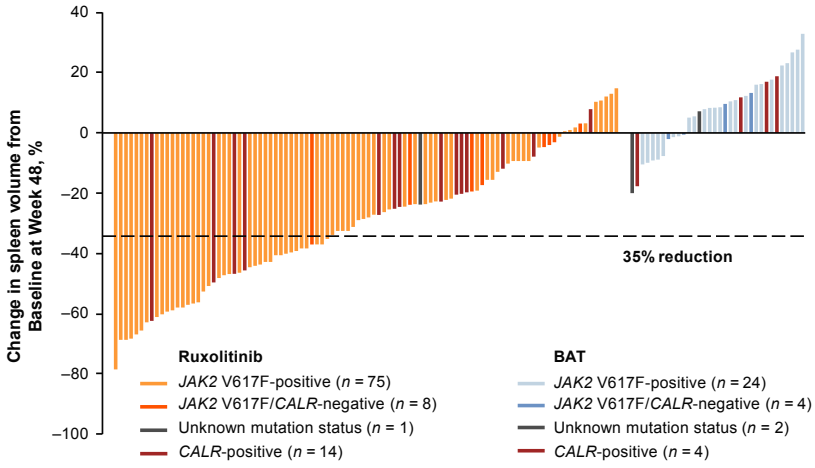
Pacritinib is a small molecule inhibtor of JAK2 and other kinases (FLT3, IRAK1, CSF1R) for which Baxalta acquired the rights from CTI BioPharma in 2013 (upfront: USD30m, potential milestone payments: USD112m, profit-sharing in the US and royalties ex-US) to develop it in myelofibrosis.

Incyte's ruxolitinib: effective and safe in myelofibrosis, but a failure in solid tumours

The failure of Incyte's JAK1 (ruxolitinib) in a solid tumour like metastatic pancreatic cancer might prompt a degree of caution; bear nonetheless in mind the fact that 1/ the indication concerned is intrinsically challenging given its extreme genetic complexity; 2/ Incyte has decided to pursue the trials evaluating INCB39110 (an inhibitor with a higher affinity for JAK1) in solid tumours in combination with immunotherapies like pembrolizumab (anti-PD-1) and epacadostat (IDOi). Moreover, the story is probably very different for hematological tumours, and notably those of myelogenous origin in that JAK2 overactivity has largely been noted in pathologies like myelofibrosis, polycythemia vera and myeloproliferative neoplasms (Chen et al, 2012). In this case, we are going to focus in particular on the first.

Generally assimilated with a cancer of the blood, myelofibrosis is a rare diease with debilitating symptoms (severe fatigue, fever, weight loss, splenomegaly) often combined with other pathologies. The entire mechanism behind its development remains unknown but note that 1/ it is characterised by scarring of the bone marrow following a pathological increase in collagen, and that 2/ this fibrosis alters the environment of the bone marrow cells, some of which will migrate and colonize the spleen to find an environment more favourable to their development (hence the swelling in this organ).

Fig. 70: Ruxolitinib - Phase III COMFORT – Spleen volume reduction



Source: Guglielmelli et al, 2015

Pacritinib: a worrying safety profile

The data on ruxolitinib in any case enable us to validate at least one important point: the JAK1/2 inhibitors seem to be fairly effective in this indication… otherwise the Incyte product would never have been approved. However, a number of elements have prevented us from including any prospective sales of pacritinib in our model:

- The primary endpoint of the Phase III PERSIST-1 clinical trial had effectively been reached (spleen volume reduction at 24 weeks≥ 35% vs best available therapy: 25.1% vs 5.9%, p=0.0001); but note that ruxolitinib's efficacy data were not really superior to those of pacritinib in this setting (even though we have to admit that the characteristics of the patients at baseline were far from the same).

- Whereas Baxalta and CTI had largely initiated the procedures required to obtain marketing approval, **the FDA requested the total suspension of the Phase III PERSIST-2 clinical trial** (evaluating pacritinib in myelofibrosis with thrombocytopenia vs best standard of care, knowing that the latter could include ruxolitinib) **having noted that several patients in the active arm had died following cardiac arrests or intracranial bleeding.** It goes without saying that CTI withdrew its AMM request following this event.

7.3.4. Increasing investment in immuno-oncology

Two cooperation agreements show that the company is looking to reinforce its footprint in the immuno-oncology segment; one with Symphogen to develop checkpoint inhibitors and the other with Precision Biosciences for allogeneic CAR-T cells (total potential milestones: USD3.2bn). Other deals will doubtless be signed in the near or relatively near future to complete the company's development portfolio and effectively address the complexity of the interaction between the immune system and tumour cells. Prior to engaging in speculation on the future of this franchise, let's focus on the platforms already acquired.

Some may appreciate the fact that the company should be investing in such a promising segment, particularly since the therapeutic classes implied are more than attractive…but all this remains highly theoretical/nebulous, in our view, something which prevents us from factoring these development projects into our valuation.

That being said, in view of the rapid developments in this sector, they are worth a quick review (particularly since we deem them to be fairly differentiating factors).

- **Checkpoint inhibitors with Symphogen…**

We have already addressed the subject of checkpoint inhibitors in our initition of coverage research on Innate Pharma but a quick recap seems worthwhile. A checkpoint inhibitor is very often a monoclonal antibody blocking an axis/interaction between two proteins involved in helping the tumor to evade the immune response; in other words, the aim is to remove a screen behind which the cancerous cells are hiding to escape attack by the soldiers of our immune system.

The six therapeutic targets retained within the framework of this deal have yet to be disclosed; but in all likelihood 1/ PD-1/PD-L1 seems to us to be a prerequisite given its key role in the downregulation of the T response (Carter et al, 2002); 2/the other activatory or inhibatory targets should be fairly similar to those seen in the pipelines of other large pharmaceutical companies: OX40, LAG3, 4-1BB, GITR, etc.

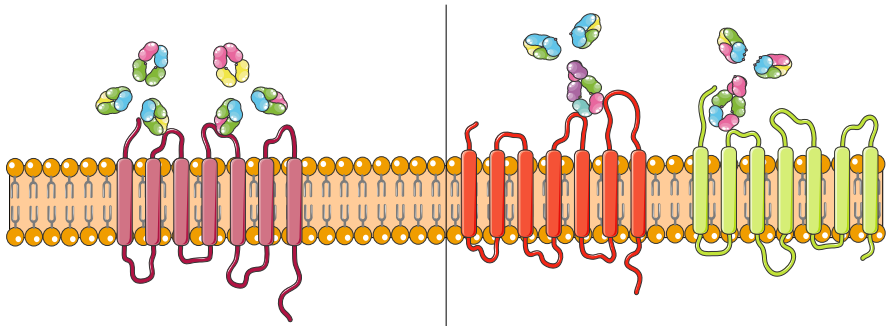
Fig. 71: Terms of the Baxalta-Symphogen agreement

Terms	Comments
Number of therapeutic targets	Six (with PD-1/PD-L1 likely to be one of them)
Upfront payment	USD175m
Potential milestones payments	USD1.6Bn
Royalties on sales	Undisclosed (BG estimate: <10%)
Clinical funding	Symphogen is responsible for performing R&D through Phase I trials at its own expense
	Baxalta have exclusive option rights to complete late-stage development and WW commercialization

Source: Company Data; Bryan, Garnier & Co ests

Where is the Symphogen added value? We understand that this small company is developing antibody mixtures enabling the targeting of several receptors or different parts of the same receptor in a single injection. The approach looks pretty promising on paper, its advantages being fairly close to those of multi-species antibodies from a pharmacoeconomic and mechanistic perspective (but it is probably too early to pronounce on the eventual superiority of one approach relative to another); and the initial data obtained with Sym004 (a mixture of two mAbs which bind to two separate non-overlapping epitopes on EGFR) looked pretty promising in our view (ORR: 48% of 27 patients suffering from metastatic colorectal cancer, who had moreover been pre-treated with anti-EGFRs).

Fig. 72: Symphogen – Principle of antibody mixtures



One receptor - Multiple binding sites
More 1) efficient internalization of the receptors (and subsequent receptor elimination) and 2) sustained tumor suppression

Multiple targets
Greater efficacy and prevention of tumor resistance associated with tumor heterogeneity and adaptability

Source: Symphogen; Bryan, Garnier & Co ests.

Fig. 73: Symphogen/Baxalta – Potential targets

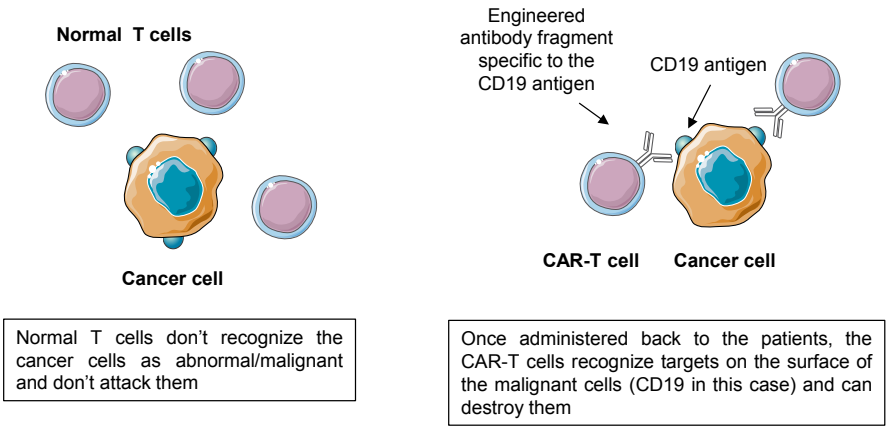
Targets	Competitors	Comments
IDO	BMS, Merck, Roche, AZN	IDO is an enzyme that creates a suppressive milieu in tumour by promoting Treg formation and activation (thus allowing tumours to escape immune surveillance) Merck/Incyte's epacadostat with pembrolizumab induced a 53% ORR in R/R patients with advanced solid tumours
OX40	Roche, AZN	OX40 is an activating receptor located on the surface of T cells It is said to 1/ augment the clonal expansion of effector and memory populations, 2/ suppress the differentiation and activity of T-regulatory cells, 3/ regulate cytokine production from T cells, DCs, NK cells, etc.
CD137 / 4-1BB	BMS, Pfizer	CD137 is found on various immune cells including T cells, NK cells and DCs. Engagement of CD137 by an agonist mAb is said 1/ to enhance T cell proliferation, 2/ to provide protection to CD8+ T cells from activation-induced cell death, and 3/ to activate DCs, NK cells and macrophages. Note that some bispecific antibodies also retained CD137 as a target
GITR / CD357	Merck, Roche	Similar to OX40 and 4-1BB ligation promotes co-stimulatory signals that enhance T-cell proliferation and effector function, and protect them from activation-induced cell death. Several studies also showed it may lead to a loss of Treg lineage stability and abrogation of intratumor Treg suppressive function
CSF1R	BMS, Novartis	Blockade of CSF1R is said to reprogram macrophage responses that enhance antigen presentation and productive anti-tumour T cell responses by alleviating immune suppression. Investigations also revealed that this strategy also upregulates T cell checkpoint molecules, including PD-L1 and CTLA-4

Source: Companies Data; Bryan, Garnier & Co ests.

… and CAR-Ts with Precision Biosciences

This subject has also been addressed in one of our recent research notes and, more specifically, the research on Cellectis (see Super Mario CAR-T!), but here is a summary of some of the contextual elements. **CAR-T cells are T lymphocytes onto which high-affinity synthetic receptors have been 'grafted' by genetic engineering.** Most of the therapies currently under development are so-called autologous, which underlines the fact that these immune cells must be harvested in the patient prior to their ex vivo modification then re-injection.

Fig. 74: CAR-T cells mechanism of action



Source: Bryan, Garnier & Co ests.

One thing is certain: the efficacy of these new therapies, at least those targeting the CD19 protein, is unparalleled in hematological tumours like acute lymphoblastic leukemia and non-Hodgkin's lymphomas. It should however be admitted that 1/ the resulting toxicity profile is still far from satisfactory, a non-neglible proportion of patients suffering from CRS or tumor lysis syndromes; 2/ the manufacturing process is complex, costly and applicable to a limited number of patients (more than 50%e of young children suffering from LAL do not have enough lymphocytes to benefit from this therapy).

Precision Biosciences is pursuing the same strategy as Cellectis: develop allogeneic CAR-Ts which are more standardised, less costly and available to the highest number of patients. We don't have many details on the editing strategy which has been adopted to reach this objective…but we would be not be surprised were the process to involve notably the deletion of the gene coding one of the TCR components in that 1/ the appearance of the graft reaction against the host (GvHD) is notably mediated by this receptor, and 2/ this working hypothesis has been adopted by several companies, including Cellectis and Celyad.

Fig. 75: Allogeneic vs autologous CAR-T - Advantages and inconveniences

	Autologous	Allogeneic
Cost of manufacturing	High (hence the very high treatment price)	USD5,000-15,000 per vial (estimate for Cellectis)
Availability	Few days due to the manufacturing	Immediate
	Cell supply potentially limited (lymphopenia)	High supply, due to the number of donors
Editing	Limited by cell supply and inefficiencies	Much less limited, the only hinder being the risks of mis-translocation
GVHD risk	No	Yes (but TCR editing should reduce it)

Source: Company Data; Bryan, Garnier & Co ests.

8. Valuation

8.1. BUY with a FV of 5,900p

The earnings momentum in our forecasts is more than positive and we shall see that the operation with Baxalta will only bolster this exceptional growth profile. However, it should be noted that 1/ the share price has fallen by 25% over twelve months (vs –13% for the STOXX Europe 600 Healthcare); 2/ on our numbers, the multiples make a pretty compelling case compared with the rest of the sector, the 2017e P/E trading, for example, at a 30% discount relative to a sample of diversified and specialist pharma companies. Is it just that the market has fallen out of love with a company which doesn't necessarily lack positive qualities? Is it because the consensus and BG itself are much too optimistic on the growth prospects for these two companies? It is in any case probable that this mismatch is also explained by the pressure on the share price from technical arbitrage transactions.

In our view the share price is completely decorrelated from the fundamentals, something which currently represents a very rare opportunity. **For all these reasons, we are initiating coverage on the stock with a BUY recommendation and a FV of 5,900p per share**, knowing that 1/ this figure is based on our Shire ex-Baxalta forecasts; and that 2/ we are likely to increase this once the deal is written in stone (particularly since our initial estimates suggest that it will be earnings accretive for Non-GAAP EPS as of 2017e).

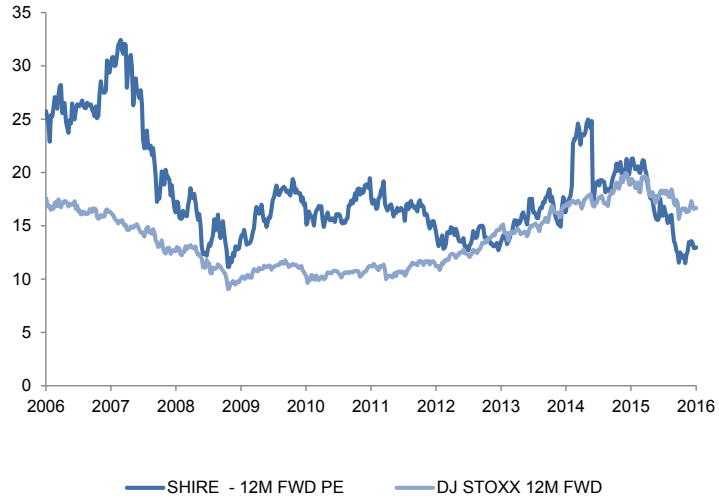
Fig. 76: Shire ex-Baxalta – BG valuation

(in USDm)	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
(+) Current EBIT	**3,078**	**3,538**	**3,989**	**4,452**	**4,677**	**4,675**	**4,862**	**3,887**	**3,740**	**3,677**
in % of sales	43.2%	44.6%	45.8%	47.1%	47.2%	47.2%	47.2%	43.4%	43.0%	42.0%
% chg yoy		14.9%	12.8%	11.6%	5.0%	0.0%	4.0%	-20.1%	-3.8%	-1.7%
(-) Taxes	492	601	678	757	795	795	827	661	636	625
% Tax rate	16.0%	17.0%	17.0%	17.0%	17.0%	17.0%	17.0%	17.0%	17.0%	17.0%
(+) D&A	170	198	234	273	325	324	337	291	282	283
= Net operating income after tax	**2,755**	**3,134**	**3,545**	**3,969**	**4,206**	**4,205**	**4,373**	**3,517**	**3,386**	**3,335**
(-) CAPEX	306	319	334	355	363	353	357	299	282	283
(-) Change in WCR	78	-16	-15	-15	-9	0	-8	27	5	-1
= Free Cash Flows	**2,371**	**2,831**	**3,226**	**3,628**	**3,852**	**3,852**	**4,023**	**3,190**	**3,099**	**3,052**

(+) ∑ Discounted FCF (USDm)	24,562
(+) Discounted terminal value (USDm)	30,206
= Enterprise Value (USDm)	**54,768**
(-) Provisions & tax liability	3,005
(-) Minority interests	0
(-) Net debt	1,360
= Equity value (USDm)	**50,403**
Number of diluted shares	593.3
= Fair Value per share (USD)	**85**
= Fair Value per share (GBp)	**5,927**

Source: Bryan, Garnier & Co ests.

Fig. 77: Shire vs peers – P/E 12m forward



Source: Thomson Reuters, Bryan, Garnier & Co. ests

In terms of the detail, we would highlight in particular the following elements:

- **Our discount rate or WACC comes out at 7.1%** based on a risk-free rate of 1.6%, an equity risk premium of 7.0, a beta of 0.80 (i.e. similar to the one we would use for diversified big pharmas like Sanofi) and a net cost of debt at 3.3%.

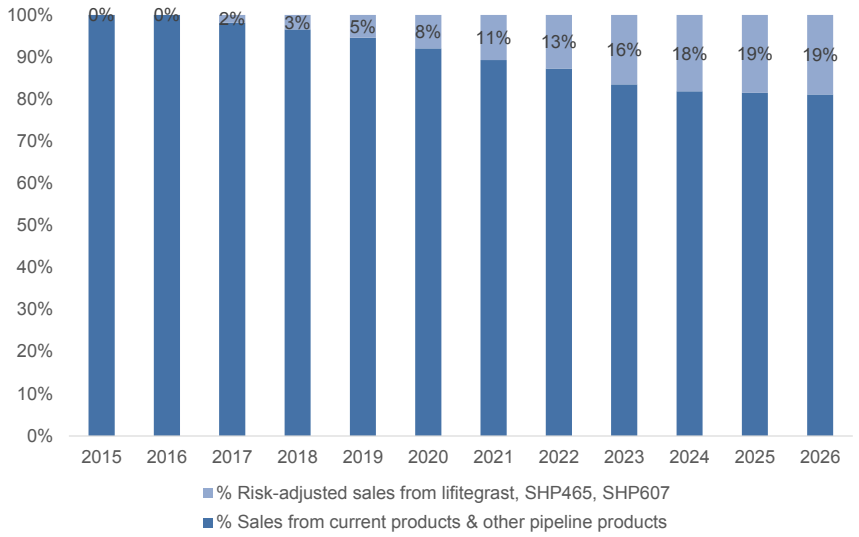
- **We assume that the long-term EBIT margin will stabilise at around 44% by 2025** (having peaked at 50%-51%) given the fact that Vyvanse will very probably come off patent. At first glance, this assumption may seem very pessimistic in that the product portfolio should be significantly expanded but it is probably preferable to remain conservative at this stage. Further down the income statement, we apply a normative tax rate of 17% (in line with the company's long-term guidance).

- Lastly, **we use a growth rate to perpetuity of +1.5%** for our terminal value calculation.

8.2. How high can our FV go? Where are the risks?

Since the Shire story is primarily one of EPS growth, it is important to see where the major risks (or opportunities) lie with respect to the latter. Leaving aside potential positive/negative surprises associated with quarterly reporting, we would point to three potential risks on the clinical side in the next twelve months:

Fig. 78: Shire – Proportion of sales from the pipeline



Source: Bryan, Garnier & Co. ests

- **Lifitegrast in dry eye disease (impact: +300 GBp or -300 GBp)**

As mentioned above, lifitegrast is currently being evaluated by the FDA in the treatment of dry eye disease. The probability of a red light on the part of the regulator looks relatively low, in our view, given the quality of the clinical package. Note, however, that if necessary our FV would then be reduced by around 300 GBp (everything else being equal).

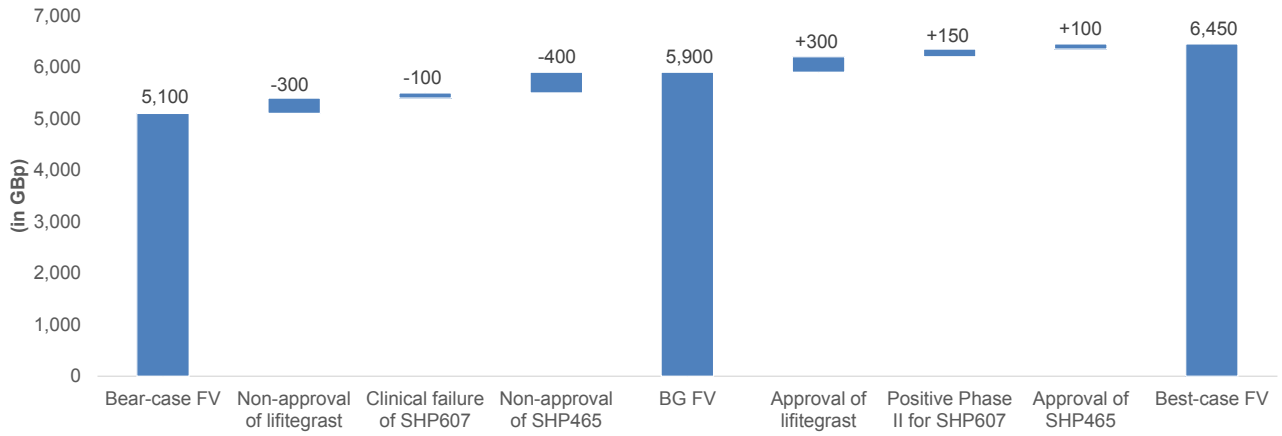
- **Clinical success or failure for SHP607 (impact: +150 GBp or -100 GBp)**

In that we deem SHP607 to be a high-risk/high-reward asset, we have deliberately factored in a low probability of success (20%) for this development project. Any news concerning this therapeutic candidate, whether good or bad, should thus have a fairly limited impact on our valuation calculation (and the consensus looks to be cautious on the subject).

- **Approval or rejection of SHP465 by the FDA (impact: +100 GBp or -400 GBp)**

The probability of regulatory approval being turned down for SHP465 seems to us to be very low in view of the quality of the clinical data and within a setting where cocktails of amphetamines (like Adderall XR) have been used for years in the treatment of ADHD. However, note that our FV could be reduced by 400 GBp in the event of a negative response, while it would be increased by +100 GBp were it to get the green light.

Fig. 79: Shire – Potential change in our FV over 12 months



Source: Bryan, Garnier & Co. ests

8.1. Shire/Baxalta: an operation which will be earnings accretive as of 2017e

In that the transaction has yet to close, we have notably based our valuation calculation on Shire ex-Baxalta but we shall certainly revisit this once the integration materialises (and the proforma accounts are available). Note nonetheless that our initial estimates point to this deal being very certainly earnings accretive as early as 2017e (in other words, as of the first year of full consolidation).

Fig. 80: Merger with Baxalta – Strategic and financial rational

Growth profile	• Double-digit top-line growth
Earnings accretion	• Expected accretion to Non-GAAP diluted EPS in 2017 and beyond
Operating cash flow	• Expect combined annual operating cash flow of approximately $6B beginning in 2018
ROIC	• Attractive ROIC; projected to exceed Shire cost of capital in 2020
Cash consideration	• $18 per Baxalta share • Will not jeopardize the tax-free status of the Baxalta spinoff from Baxter
Financing	• $18B fully funded bank facility; • Shire plans to de-lever rapidly post-close • Structured to maintain an investment grade credit rating for combined entity

Strategic Fit: Global Leader In Rare Diseases

$1B+	Multiple $1B+ durable, best-in-class franchises
65%	Revenue from rare diseases
>50	Rare disease pipeline programs

Compelling Financial Profile and Value Creation

>$500M	Operating cost synergies alone
+	Additional revenue synergies
16-17%	Attractive non-GAAP effective tax rate

Proven Track Record of Integration

8 Companies successfully integrated in past 3 years

Highly experienced management team

Extensive diligence performed on tax liability

Source: Shire, JPM Healthcare Conference (Jan 2016)

Beyond our P&L estimates for Shire and Baxalta on a stand-alone basis, what are the main elements to bear in mind?

- For each Baxalta share, Shire will offer 0.1482 ADS (i.e. the equivalent of 0.45 per Shire share, knowing that one ADS was then valued at USD199.03) and USD18.0 in cash; 2/ the cash portion will notably be financed by the issuance of debt (around USD12bn).

Cost synergies amounting to at least USD500m (BG: USD500m)

- At the time of the merger announcement, **the Shire management promised synergies amounting to USD500m** (knowing that these savings are not expected to fully come through before 2019)…more than reasonable in our view given that this figure represents only 6% of the new entity's OPEX.
  In fact, we see the guidance as deliberately conservative, a sentiment backed up by the statements from Flemming Ornskov during a Bloomberg TV interview ('I like to be a manager that under-promises and over-delivers, so I think we can say it's a fairly conservative number, but this is not about cost synergies […] There will be revenue synergies and there will also be tax synergies, but that did not drive the deal'). Whatever happens, we use a low-case assumption of USD500m for the calculation of the post-transaction earnings accretion/dilution calculation.

- Amongst other important elements, we would like to underline the fact that we have used/ a **17% tax rate** (in line with the company's guidance of 16%-17%); and 2/ **an interest rate on the future bond debt of 4-5%e**.

Fig. 81: Calculation of the post-transaction EPS accretion/dilution

(in USDm)	2016			2017			2018			2019		
	SHP	BXLT	NewCo	SHP	BXLT	NewCo	SHP	BXLT	NewCo	SHP	BXLT	NewCo
(+) Net sales	**7,117**	**6,825**	**13,943**	**7,937**	**7,465**	**15,402**	**8,706**	**7,964**	**16,670**	**9,457**	**8,247**	**17,704**
% growth y-o-y				12%	9%	10%	10%	7%	8%	9%	4%	6%
(-) COGS	951	2,457	3,409	1,027	2,650	3,677	1,087	2,787	3,874	1,138	2,886	4,024
= Gross margin	**6,166**	**4,368**	**10,534**	**6,910**	**4,815**	**11,725**	**7,619**	**5,177**	**12,795**	**8,319**	**5,361**	**13,680**
in % of sales	87%	64%	76%	87%	65%	76%	88%	65%	77%	88%	65%	77%
(-) R&D	996	751	1,747	1,111	821	1,932	1,219	876	2,095	1,324	990	2,314
(-) SG&A	1,922	1,194	3,116	2,064	1,400	3,464	2,176	1,504	3,681	2,270	1,463	3,732
(-) D&A	170	307	477	198	373	571	234	438	672	273	495	768
(+) Synergies	0	0	0	0	0	250	0	0	375	0	0	500
= EBIT	**3,078**	**2,116**	**5,194**	**3,538**	**2,221**	**6,008**	**3,989**	**2,358**	**6,723**	**4,452**	**2,413**	**7,366**
in % of sales	43%	31%	37%	45%	30%	39%	46%	30%	40%	47%	29%	42%
(-) Net financial expenses	93	150	720	117	120	750	50	90	525	11	40	275
= PBT	**2,985**	**1,966**	**4,474**	**3,421**	**2,101**	**5,258**	**3,939**	**2,268**	**6,198**	**4,441**	**2,373**	**7,091**
(-) Taxes	478	413	761	582	491	894	670	550	1,054	755	563	1,205
% Tax rate	16%	21%	17%	17%	23%	17%	17%	24%	17%	17%	24%	17%
= Net income	**2,508**	**1,553**	**3,713**	**2,839**	**1,610**	**4,365**	**3,270**	**1,719**	**5,144**	**3,686**	**1,811**	**5,885**
EPS (in USD)	**4.2**	**2.3**	**4.2**	**4.8**	**2.4**	**4.9**	**5.5**	**2.5**	**5.8**	**6.2**	**2.7**	**6.6**
Number of shares	592	681	894	592	681	894	592	681	894	592	681	894
Dilution/Accretion			**-2%**			**2%**			**4%**			**6%**

Source: Bryan, Garnier & Co ests.

Where is the potential upside? **Intriguingly, Baxalta's gross margin is well below those of other listed biotechs or specialty pharmas** (around 60%-65%e vs 80%-90% for pharmas like Celgene or Amgen). Why such a big difference? In our view, this almost certainly comes from the preponderance of non-recombinant and plasma-derivative products, particularly within the IG activity, given the complexity/heavy manufacturing relating to this type of product (something which may partially explain why, similarly, the Grifols gross margin only approaches 50%).

For the moment, we assume that the gross margin could increase by between 0 and+100 bps every year through to 2019, given the on-going improvement in the product mix (growing proportion of oncology, progressive migration of patients suffering from primary immunodeficiency to Hyqvia, etc.). **However, we could well be way too cautious on the ramp-up of these new products and their impact on the bottom line.**

- **The same for our FV post the close on the transaction?**

The stock is currently trading in line with our worst-case valuation

As we have already seen, a part of the market is more than dubious as to the transaction's potential value creation. On our base scenario, we estimate that our valuation could be increased by +0-10% in an initial approach and depending on the different assumptions.

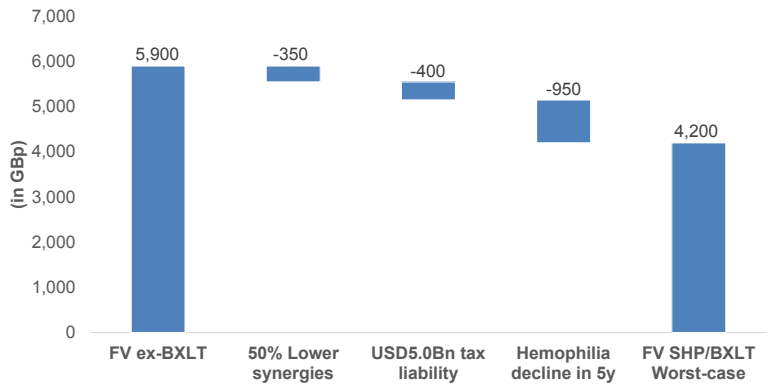
Were we to be mistaken, what might be the potential margin of error? To answer this question, **we have notably calculated a worst case valuation with exaggeratedly-pessimistic assumptions,** namely 1/ a total decline in the Hemophilia and Inhibitors businesses (-100% over five years, coupled with a reduction in gross margin despite the ramp-up of a high-margin blockbuster like Hyqvia); 2/ operational synergies potentially reaching only half the level communicated by Shire (i.e. USD250m); 3/ the payment of USD5.0bn – see Fig. 83 for the detailed calculation – linked to the loss of Baxalta's tax-free status… And the resulting FV would be in line with current levels.

Fig. 82: Worst-case - Estimation of the tax liability

(in USDm)	
(-) Net asset value before IPO	4,080
(+) Current Baxalta's Market capitalization	28,558
= Capital gains at current share price (as of 13th of May 2016)	24,478
Applied tax rate on capital gains (%)	20%
= Tax liability estimate	**4,896**

Source: Bryan, Garnier & Co ests.

Fig. 83: SHP/BXLT – FV dans un *worst-case*



Source: Bryan, Garnier & Co. ests

Fig. 84: BXLT – P&L on a worst case

(USDm)	2015	2016e	2017e	2018e	2019e	2020e	2021e	2022e
(+) Product sales	**6,230**	**6,825**	**7,465**	**6,833**	**5,712**	**4,867**	**5,050**	**5,169**
% growth y-o-y		10%	9%	-8%	-16%	-15%	4%	2%
= EBITDA	**2,143**	**2,355**	**2,650**	**2,016**	**1,713**	**1,339**	**1,313**	**1,370**
in % of product sales	34.4%	34.5%	35.5%	29.5%	30.0%	27.5%	26.0%	26.5%
% growth y-o-y		10%	13%	-24%	-15%	-22%	-2%	4%
= Net income	**1,422**	**1,480**	**1,682**	**1,221**	**1,042**	**792**	**748**	**766**
Basic EPS (USD)	**2.10**	**2.19**	**2.48**	**1.80**	**1.54**	**1.17**	**1.11**	**1.13**
% var y-o-y		4%	14%	-27%	-15%	-24%	-5%	2%
Diluted EPS (USD)	**2.08**	**2.17**	**2.46**	**1.79**	**1.53**	**1.16**	**1.10**	**1.12**
% var y-o-y		4%	14%	-27%	-15%	-24%	-5%	2%

Source: Bryan, Garnier & Co ests.

9. Appendices

Fig. 85: Shire – Sales forecasts (2015-2021e)

(in USDm)	Main indication	PoS (%)	2015	2016	2017	2018	2019	2020
TOTAL SALES			**6,100**	**6,796**	**7,604**	**8,362**	**9,102**	**9,549**
% var y-o-y				11.4%	11.9%	10.0%	8.9%	4.9%
Vyvanse	ADHD	100%	1,722	2,049	2,357	2,522	2,648	2,727
Intuniv	ADHD	100%	65	38	35	35	35	35
Adderrall XR	ADHD	100%	363	370	366	363	359	355
SHP465	ADHD	80%	0	0	72	144	259	415
Lifitegrast	Dry eye	50%	0	0	66	143	223	314
SHP640 (FST-100)	Bacterial conjunctivitis	50%	0	0	0	18	48	79
Premiplex	Retinopathy of prematurity	20%	0	0	0	0	11	31
Firazyr	HAE	100%	445	583	641	693	741	785
Cinryze	HAE	100%	618	673	741	778	739	739
DX2930	HAE	50%	0	0	0	61	168	276
Kalbitor	HAE	100%	0	60	66	73	76	79
Lialda	Ulcerative colitis	100%	684	760	790	806	814	488
Pentasa	Ulcerative colitis	100%	306	245	242	240	237	235
Gattex	Short bowel syndrome	100%	142	240	384	538	645	710
Natpara	Hypoparathyroidism	100%	24	96	192	306	414	517
SHP621	EoE	50%	0	0	0	0	25	69
SHP555	Chronic constipation	50%	0	0	8	17	28	39
Vpriv	Gaucher Disease	100%	342	312	296	284	276	270
Elaprase	Hunter syndrome	100%	553	553	558	564	569	569
SHP609	Hunter syndrome	50%	0	0	9	25	42	59
SHP610	Sanfilippo A	30%	0	0	0	0	16	47
Replagal	Frabry disease	100%	441	437	437	437	437	437
Others	Others	100%	395	381	346	317	292	273

Source: Company Data; Bryan, Garnier & Co ests.

Fig. 86: Shire – Clinical pipeline prior to the Baxalta transaction

Compounds	Mechanism	Indication	Clinical stage
Natpar (parathyroid hormone)	Parathyroid hormone receptor agonist	Hypoparathyroidism	Registration
Lifitegrast	Anti-LFA-1	Dry eye disease	Registration
Intuniv (guanfacine)	Alpha-2A-Adrenoceptor agonist	Attention Deficit Hyperactivity Disorder (ADHD) - Japan	Registration
Firazyr	Bradykinin B2 Receptor Antagonist	HAE (Hereditary Angiogedema)	Phase III
Cinryze	C1-esterase inhibitor	HAE prophylaxis	Phase III
Cinryze SC	C1-esterase inhibitor	HAE prophylaxis - Japan	Phase III
Cinryze	C1-esterase inhibitor	Acute antibody mediated rejection	Phase III
SHP621 (oral budesonide suspension)	Corticosteroid	Eosinophilic esophagitis	Phase III
DX2930	Anti-pKal mAbs	HAE prophylaxis	Phase III
Gattex (teduglutide)	GLP-2 receptor antagonist	Short Bowel Syndrome - Japan	Phase III
SHP465	Triple-bead mixed amphetamine salts	Attention Deficit Hyperactivity Disorder (ADHD)	Phase III
SHP555	Serotonin (5-HT4) receptor agonist	Chronic constipation - US	Phase III
SHP609	Iduronate-2-sulfatase enzyme	Hunter IT	Phase II/III
Cynrize	C1-esterase inhibitor	Acute Neuromyelitis Optica	Phase II/III
Vyvanse	Isdexamfetamine Dimesylate	ADHD - Japan	Phase II/III
SHP607 (premiplex)	IGF-1 agonist	Pevention of ROP	Phase II
SHP610	Recombinant human SGSH	Sanfilipo A	Phase II
SHP620 (maribavir)	Oral anticytomegalovirus (CMV) agent	CMV in transplant patients	Phase II
SHP625	Inhibitor of SLC10A2	Primary biliary cirrhosis	Phase II
SHP625	Inhibitor of SLC10A2	Progressive familial intrahepatic cholestasis	Phase II
SHP625	Inhibitor of SLC10A2	Alagille syndrome (ALGS)	Phase II
SHP625	Inhibitor of SLC10A2	Primary sclerosing cholangitis	Phase II
SHP640	Dexamethasone + povidone iodine	Infectious conjunctivitis	Phase II
SHP611	Recombinant human arylsulfatase A	Metachromatic leukodystroph (MLD)	Phase I
SHP622	Antioxidant disrupting amyloid plaques	Freidrich's Ataxia	Phase I
SHP623	C1-esterase inhibitor	HAE prophylaxis	Phase I
SHP627	Antifibrotic agent	Focal segmental glomerulosclerosis	Phase I
SHP631		Hunter syndrome	Phase I
SHP626	Inhibitor of SLC10A2	Non-alcoholic steatohepatitis	Phase I

Source: Shire, FY15 results presentation

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Bryan Garnier stock rating system

For the purposes of this Report, the Bryan Garnier stock rating system is defined as follows:

Stock rating

BUY — Positive opinion for a stock where we expect a favourable performance in absolute terms over a period of 6 months from the publication of a recommendation. This opinion is based not only on the FV (the potential upside based on valuation), but also takes into account a number of elements that could include a SWOT analysis, momentum, technical aspects or the sector backdrop. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

NEUTRAL — Opinion recommending not to trade in a stock short-term, neither as a BUYER or a SELLER, due to a specific set of factors. This view is intended to be temporary. It may reflect different situations, but in particular those where a fair value shows no significant potential or where an upcoming binary event constitutes a high-risk that is difficult to quantify. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

SELL — Negative opinion for a stock where we expect an unfavourable performance in absolute terms over a period of 6 months from the publication of a recommendation. This opinion is based not only on the FV (the potential downside based on valuation), but also takes into account a number of elements that could include a SWOT analysis, momentum, technical aspects or the sector backdrop. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

Distribution of stock ratings

BUY ratings 56.3% NEUTRAL ratings 34.5% SELL ratings 9.2%

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