BRYAN, GARNIER & CO

INDEPENDENT RESEARCH UPDATE

17th October 2016

Shire PLC

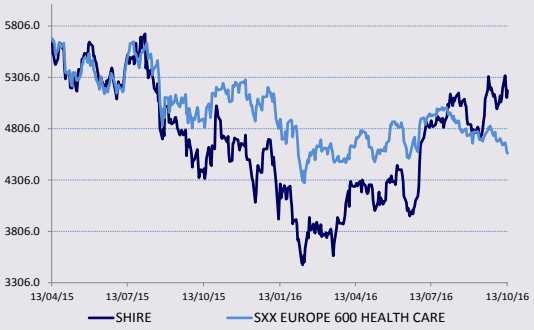
Re-rating still underway!

Healthcare

Fair Value 6900p (price 5,176p) **BUY-Top Picks**

Bloomberg	SHP LN
Reuters	SHP.L
12-month High / Low (p)	5,323 / 3,480
Market capitalisation (GBPm)	46,738
Enterprise Value (BG estimates GBPm)	61,711
Avg. 6m daily volume ('000 shares)	2,531
Free Float	87.0%
3y EPS CAGR	14.8%
Gearing (12/15)	14%
Dividend yield (12/16e)	0.32%

YE December	12/15	12/16e	12/17e	12/18e
Revenue (USDm)	6,100	11,278	15,272	16,259
EBIT (USDm)	2,785	4,408	6,287	6,919
Basic EPS (USD)	3.89	4.21	5.15	5.89
Diluted EPS (USD)	3.89	4.21	5.15	5.89
EV/Sales	9.56x	6.67x	4.67x	4.09x
EV/EBITDA	20.0x	15.6x	10.6x	8.9x
EV/EBIT	20.9x	17.1x	11.4x	9.6x
P/E	16.2x	15.0x	12.3x	10.7x
ROCE	16.3	6.4	9.1	10.4



We still consider that the market underestimates the resilience of Shire's haemophilia franchise, and consequently, its EPS growth in coming years (CAGR 2015-18 CAGR of +15%). We also reiterate our BUY recommendation as 1/ the share remains one of the cheapest in the sector in Europe (2017e P/E of 13x vs. 17x for peers) and that 2/ newsflow associated with Lifitegrast and DX2930 should reassure the market as to the group's ability to manage the decline in Feiba (Haemophilia A with inhibitors).

- **Decline in Inhibitors: a manageable risk.** We fully admit that ACE910 is likely to have a substantial impact on sales in the inhibitors franchise, and the fact that Feiba is a high-margin product has caused a considerable amount of concern for investors. However, we should not under-estimate the diversity of the group's pipeline, its positioning in niche markets and/or rare diseases and the reactive nature of its management. More precisely, we consider that 1/ forthcoming newsflow on Lifitegrast (sales ramp-up), and DX2930 (Phase III results) should reassure the market in terms of Shire's ability to manage the decline in Feiba, 2/ the company could surprise the consensus positively in terms of its ability to rapidly implement its cost-cutting plan.

- **An attractive risk-reward profile.** We reiterate our positive view on the share despite its clear outperformance since we initiated coverage (+21% vs. -2% for the STOXX 600 Euro Healthcare). Shire's valuation looks just as attractive in that 1/ it is still trading on a 20% discount to European peers, and even 40-45% relative to CSL, 2/ to justify a FV of GBP5,000, we would have to assume that the haemophilia and inhibitors franchises disappear entirely by 2018 (i.e. the first year ACE910 is on the market)… And it goes without saying that such scenario has never been observed throughout the long history of the pharma industry.

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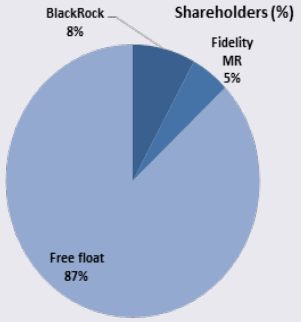

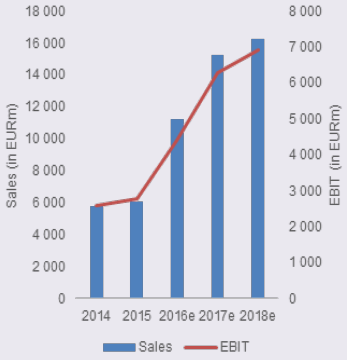

Company description

Shire is a specialty pharma with an increasing focusing on rare diseases. The recent acquisition of Baxalta reinforced this exposure, and we believe it enhanced an already-exceptional growth profile

Simplified Profit & Loss Account (USDm)	2014	2015	2016e	2017e	2018e	2019e	2020e
Revenues	5,830	6,100	11,284	15,309	16,296	16,916	17,335
Change (%)	*-%*	*4.6%*	*85.0%*	*35.7%*	*6.4%*	*3.8%*	*2.5%*
Adjusted EBITDA	2,756	2,924	4,817	6,533	7,308	7,805	8,183
EBIT	2,593	2,785	4,410	6,073	6,770	7,213	7,542
Change (%)	*-%*	*7.4%*	*58.3%*	*37.7%*	*11.5%*	*6.5%*	*4.6%*
Financial results	(39.7)	(48.9)	(414)	(594)	(489)	(339)	(189)
Pre-Tax profits	2,553	2,736	3,995	5,479	6,281	6,874	7,353
Exceptionals	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tax	468	424	715	986	1,068	1,100	1,176
Net profit	2,088	2,310	3,280	4,493	5,213	5,774	6,176
Restated net profit	2,088	2,310	3,280	4,493	5,213	5,774	6,176
Change (%)	*-%*	*10.6%*	*42.0%*	*37.0%*	*16.0%*	*10.8%*	*7.0%*
Cash Flow Statement (USDm)							
Operating cash flows	4,164	2,367	3,093	5,282	6,305	6,998	7,656
Change in working capital	(63.9)	30.6	257	226	163	175	8.4
Capex, net	77.0	115	879	1,225	1,141	1,100	1,040
Financial investments, net	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Dividends	121	134	156	197	270	313	346
Other	(3,287)	(4,935)	1,038	(3,000)	(4,000)	(6,000)	(4,000)
Net debt	(2,187)	1,360	18,251	14,616	9,885	4,475	(1,786)
Free Cash flow	4,151	2,222	1,957	3,832	5,001	5,723	6,607
Balance Sheet (USDm)							
Tangible fixed assets	838	828	865	1,360	1,731	2,035	2,254
Intangibles assets	7,409	13,321	53,853	53,123	52,354	51,558	50,737
Cash & equivalents	3,037	222	3,061	3,696	4,427	3,838	6,098
current assets	2,146	2,034	4,457	4,561	4,971	5,301	5,414
Other assets	3,239	427	(416)	220	951	361	2,622
Total assets	13,632	16,610	58,759	59,263	60,007	59,255	61,028
L & ST Debt	850	1,581	21,312	18,312	14,312	8,312	4,312
Others liabilities	4,119	5,199	7,366	7,243	7,490	7,645	7,750
Shareholders' funds	8,663	9,829	30,081	33,708	38,205	43,298	48,966
Total Liabilities	13,632	16,610	58,759	59,263	60,007	59,255	61,028
Capital employed	8,423	14,194	51,337	51,328	51,094	50,777	50,184
Ratios							
Operating margin	44.47	45.66	39.08	39.67	41.54	42.64	43.51
Tax rate	18.31	15.51	17.90	18.00	17.00	16.00	16.00
Net margin	35.82	37.87	29.07	29.35	31.99	34.13	35.63
ROE (after tax)	24.10	23.50	10.90	13.33	13.64	13.34	12.61
ROCE (after tax)	24.79	16.27	6.39	8.75	10.20	11.37	12.31
Gearing	(25.25)	13.84	60.67	43.36	25.87	10.33	(3.65)
Pay out ratio	5.80	5.82	4.75	4.38	5.17	5.42	5.61
Number of shares, diluted	591	593	778	907	907	907	907
Data per Share (USD)							
EPS	3.53	3.89	4.22	4.96	5.75	6.37	6.81
Restated EPS	3.53	3.89	4.22	4.96	5.75	6.37	6.81
% change	*-%*	*10.3%*	*8.3%*	*17.5%*	*16.0%*	*10.8%*	*7.0%*
BVPS	14.65	16.57	38.66	37.18	42.14	47.76	54.01
Operating cash flows	7.04	3.99	3.98	5.83	6.95	7.72	8.44
FCF	7.02	3.75	2.52	4.23	5.52	6.31	7.29
Net dividend	0.21	0.23	0.20	0.22	0.30	0.35	0.38

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

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1. As hyperactive as ever!

The main cause of concern for investors clearly remains the risk of a decline in the group's haemophilia and inhibitors businesses and it is true that new treatments in development (whether ACE910 or fitusiran) could meet current medical needs in various ways (greater flexibility in administration regime, possibility of addressing haemophilia patients with or without inhibitors, and sometimes even independently of the disease sub-type (A or B).

However, as we stated in the first part of this study, we believe **the market underestimates the resilience of replacement therapies in the future therapeutic paradigm,** if only because the safety profile of the new therapies is not yet fully established (and reasons for caution are not lacking).

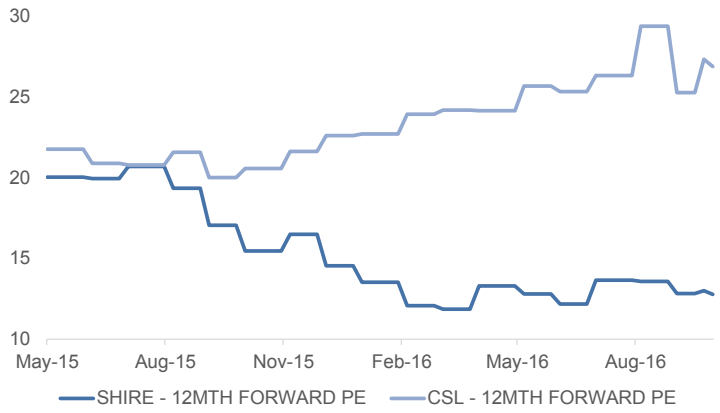
We also remain convinced that the discount relative to CSL is not only unjustified but also that it should gradually narrow in favour of SHP given that the two companies' fundamentals do not seem significantly different as a whole. From our viewpoint, three catalysts should participate especially in this re-rating: 1/ the publication of Phase I results for BAX826 in H1 2017 (which could play positively on the market's perception concerning the lasting nature of the haemophilia franchise), 2/ the read-out of the Phase III trial on DX293, also in H1 2017, which should reassure on the group's ability to absorb the loss of gross margin associated with the decline in Feiba, 3/ the first sales figures for lifitegrast and changes in the cost base under the framework of forthcoming quarterly publications.

1.1. A significant discount relative to the sector

A discount of 20% relative to European peers, and 40-45% vs. CSL

We are reiterating our positive view on the share despite its healthy performance since we initiated coverage (+21% vs. -2% for the STOXX 600 Euro Healthcare), given that its valuation still looks attractive. Shire is still trading on a 20% discount to European peers and even 40-45% relative to CSL Limited (which nevertheless shows a similar growth profile and is just as highly exposed to haemophilia A, albeit with a greater proportion of plasma products in its mix).

Fig. 1: SHP vs CSL–12m forward P/E

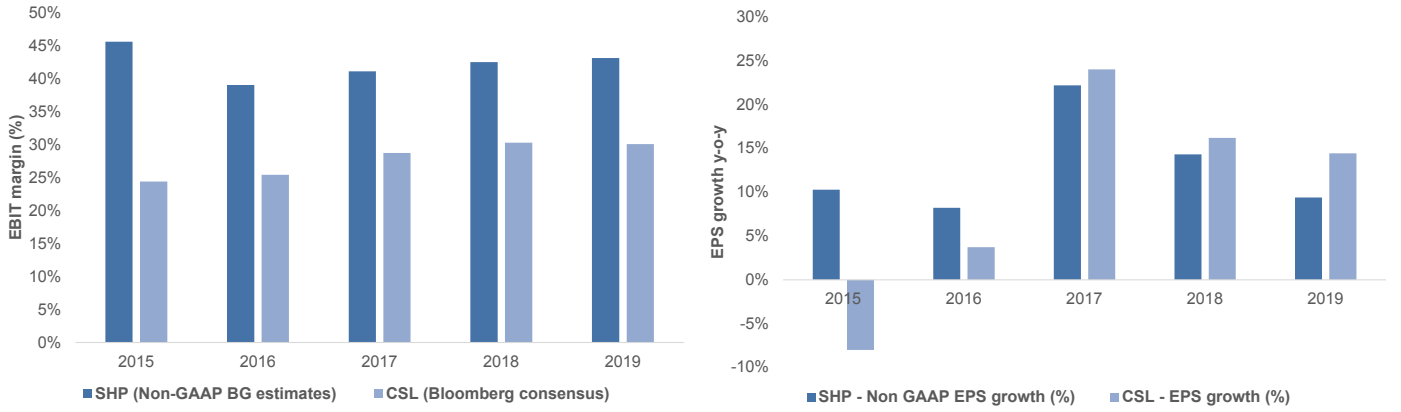


Source: Thomson Reuters; Bryan, Garnier & Co. ests.

The fact that CSL is more exposed to the immunoglobulins sector is perhaps a contributing factor (c.40% vs 15% pour SHP), but this would be under-estimating 1/ Hyqvia's best-in-class character and its ability to win market share from other IGs (in primary immunodeficiency and soon in CIDP),

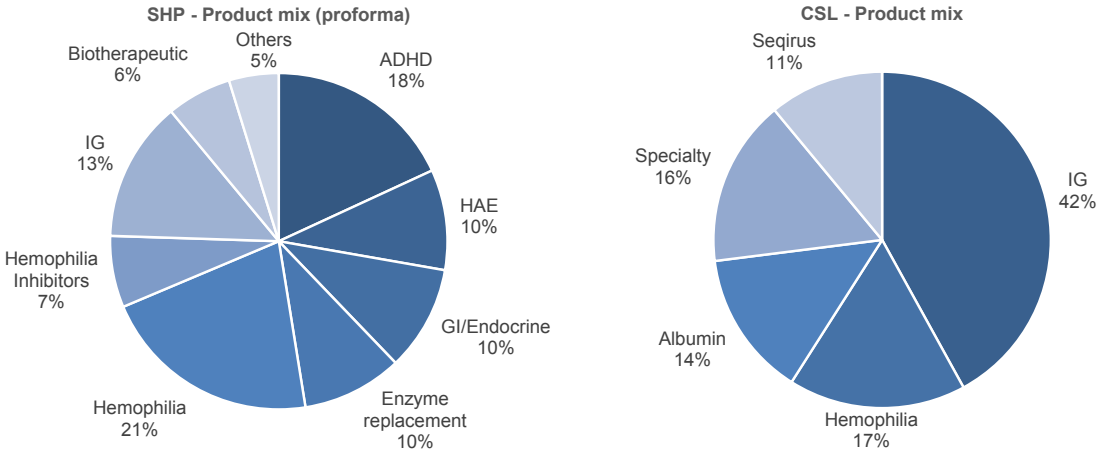
including Hizentra, and 2/ growth in historical franchises such as ADHD and HAE (see our initiation report here for further details).

Fig. 2: SHP vs CSL – Change in EBIT margins/EPS growth



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

Fig. 3: SHP vs CSL – product mix



Source: Shire; CSL; Bryan, Garnier & Co. ests

In addition, the group has been far from disappointing in recent months with: 1/ the approval of lifitegrast in the US, and for which we expect sales of c.USD1bn in 2020, 2/ Q2 2016 and guidance for the whole year both higher than expected, 3/ the hike in cost synergy targets with Baxalta (at least USD700m vs USD500m previously) etc. However, we understand that part of the market remains fairly sceptical concerning the ability to create value via the merger with Baxalta (and some even seem to anticipate significant value destruction). However, it goes without saying that we do not back this pessimistic scenario.

1.2. Buy reiterated with a FV of 6,900p

We are reiterating more than ever our Buy recommendation on the share in view of the above-mentioned factors. In addition, our DCF valuation (6,900p - implied 2017e P/E of 18x) suggests upside potential of more than 30%.

Fig. 4: SHP – DCF valuation

(in USDm)	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Revenues	**11,674**	**15,618**	**16,614**	**17,245**	**17,676**	**17,979**	**18,465**	**17,329**	**17,427**	**17,676**
% chg yoy		33.8%	6.4%	3.8%	2.5%	1.7%	2.7%	-6.2%	0.6%	1.4%
(+) Current EBIT	**4,408**	**6,287**	**6,919**	**7,290**	**7,622**	**7,509**	**7,489**	**6,792**	**6,578**	**6,812**
in % of sales	37.8%	40.3%	41.6%	42.3%	43.1%	41.8%	40.6%	39.2%	37.7%	38.5%
% chg yoy		42.6%	10.0%	5.4%	4.6%	-1.5%	-0.3%	-9.3%	-3.2%	3.6%
(-) Taxes	789	1,132	1,176	1,166	1,219	1,201	1,198	1,087	1,052	1,090
(+) D&A	307	458	537	591	640	704	777	778	833	862
= Net operating income after tax	**3,926**	**5,614**	**6,280**	**6,714**	**7,042**	**7,011**	**7,067**	**6,484**	**6,358**	**6,584**
(-) CAPEX	879	1,222	1,138	1,097	1,038	1,056	903	846	850	862
(-) Change in WCR	257	226	163	175	8	6	9	-23	2	5
= Free Cash Flows	**2,790**	**4,167**	**4,979**	**5,442**	**5,996**	**5,950**	**6,155**	**5,661**	**5,507**	**5,717**

= Enterprise Value (USDm)	**103,036**
(-) Minority interests	0
(-) Net debt	23,314
= Equity value (USDm)	**79,722**
Number of diluted shares	906.5
= Fair Value per share (USD)	88
= Fair Value per share (GBp)	**6,925**

Source: Bryan, Garnier & Co ests.

1.3. The market is pricing in an overly pessimistic scenario

1.3.1. Overly pessimistic assumptions in our inverse DCF

A FV of 5,000p would imply the disappearance of the haemophilia and inhibitors franchises in 2018!

Since the market is worrying about the lasting nature of Shire's haemophilia and inhibitors activities, we fairly naturally decided to undertake an inverse DCF calculation in order to show the various assumptions that the market is factoring in concerning changes in this franchise (all other factors remaining equal elsewhere). This exercise shows that **we would have to assume the complete disappearance of the franchise as of 2018 (i.e. the first year of marketing of ACE910) in order to justify a FV of 5,000p.** It goes without saying that a scenario such as this has never been seen in the long history of the pharma industry.

Fig. 5: SHP – Details of our inverse DCF

(in USDm)	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Revenues	**11,674**	**15,618**	**12,496**	**13,349**	**13,945**	**14,354**	**14,917**	**13,826**	**13,950**	**14,215**
% chg yoy		33.8%	-20.0%	6.8%	4.5%	2.9%	3.9%	-7.3%	0.9%	1.9%
(+) Current EBIT	**4,408**	**6,287**	**4,860**	**5,342**	**5,756**	**5,697**	**5,714**	**5,040**	**4,839**	**5,081**
in % of sales	37.8%	40.3%	38.9%	40.0%	41.3%	39.7%	38.3%	36.5%	34.7%	35.7%
% chg yoy		42.6%	-22.7%	9.9%	7.8%	-1.0%	0.3%	-11.8%	-4.0%	5.0%
(-) Taxes	789	1,132	826	855	921	911	914	806	774	813
(+) D&A	307	458	537	591	640	704	777	778	833	862
= Net operating income after tax	**3,926**	**5,614**	**4,570**	**5,078**	**5,475**	**5,489**	**5,577**	**5,012**	**4,898**	**5,130**
(-) CAPEX	879	1,222	1,138	1,097	1,038	1,056	903	846	850	862
(-) Change in WCR	257	226	42	146	16	11	14	-25	3	6
= Free Cash Flows	**2,790**	**4,167**	**3,390**	**3,835**	**4,421**	**4,422**	**4,660**	**4,191**	**4,045**	**4,262**

= Enterprise Value (USDm)	**77,874**
(-) Minority interests	0
(-) Net debt	23,314
= Equity value (USDm)	**54,560**
Number of diluted shares	906.5
= Fair Value per share (USD)	60
= Fair Value per share (GBp)	**4,739**

Source: Bryan, Garnier & Co ests.

1.3.1. Baxalta: still tax-free

We understand also that **some market players still fear the loss of Baxalta's tax-free status following its acquisition.** Admittedly, we have not factored this risk into our model contrary to some of our colleagues. However, we are fairly confident in the lasting nature of this status given that three important conditions were respected during the transaction: 1/ the deal was above all motivated by a strong business purpose, and indeed, the aim was to create a new leader in the field of rare diseases, 2/ the vast majority of Baxalta's activities have been continued (for the moment, only a few quite precise projects have been halted), 3/ the spin-off of Baxter and the takeover by Shire are not part of the same plan.

This last point is admittedly more difficult to assess as it is external to the two structures. However, we would nevertheless note that Shire and AbbVie were in discussions with a view to merging when Baxter was preparing the exit of its biopharmaceutical activities. In addition, we find it hard to believe that AbbVie was also intending to acquire Baxalta in the process given that 1/ the main reason behind the merger with Shire was probably tax-based (the deal having been abandoned following various changes in measures at the time), 2/ since then, AbbVie has made acquisitions in much larger domains, such as oncology.

Fig. 6: Baxalta – Criteria for a tax-free status

Criteria	BXLT/SHP
Device	A business purpose is considered as an evidence that the transaction was not a "device" aiming to distribute earnings (hidden dividend). In this case, the aim was to form a global leader in rare diseases.
Continuity	Baxalta's business is continuing / still expanding
Not part of an acquisition plan	When Baxter announced the spin-off, SHP was supposed to be acquired by AbbVie The main reason behind AbbVie's move was a fiscal one (SHP benefiting from a lower tax rate) rather than diversifying its business with rare diseases.

Source: Bryan, Garnier & Co ests.

1.4. Re-rating set to continue

Three catalysts should continue to drive the share's re-rating

We believe that the share should benefit from at least three significant catalysts over the next 12 months:

- **The Investor Day on 10th November** should clearly provide an opportunity to focus on the development pipeline. We above all think of the candidates recently acquired via partnership agreements (like PFE's anti-MadCAM, which is set to be developed in ulcerative colitis), but also less mature molecules such as BAX826. Optimisation of the cost structure is bound to be on the agenda and management is likely to draw a parallel with OneShire given the similarities with the new plan ("The legacy Baxalta business operated on a divisional structure akin to that which Shire used prior to 2013"). However, we will mainly focus on management's comments concerning eventual revenue synergies with BXLT.

- The publication of **Phase III data on DX2930 in H1 2017** as a prophylactic treatment for hereditary angioedema and which, we hope, should confirm its best-in-class status. Other read-outs are obviously expected in the shorter term, but their impact should be far less significant than with SHP643 (-GBp300 or +GBp200, simply by adjusting our probability of success ratio).

- **The first sales figures for lifitegrast and changes in the cost base** under the framework of forthcoming quarterly publications.

Fig. 7: SHP - Next catalysts

Date	Product	Indication	Event	BG Peak sales
H2 2016	SHP610	SanFilippo A	Phase IIb data	USD250m
H2 2016	SHP609	Hunter's syndrome	Phase IIb/IIII data	USD150m
H2 2016	Pipeline	All of them	Investor day in NYC	N/A
H2 2016	Natpara	Hypoparathyroidism	EU approval	USD700m
H2 2016	Onivyde	2L pancreatic cancer	EU approval	USD150m
H1 2017	ROG's ACE910	Haemophilia A with inhibitors	Phase III data	USD1.5Bn
H1 2017	Adynovate	Haemophilia A	EU approval	USD800m
H1 2017	BAX826	Haemophilia A	Phase I/II data	Not included
H1 2017	SHP643 / DX2930	Hereditary angioedema	Phase III data	USD1.7Bn

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

2. Decline in inhibitors: a manageable impact

We believe the decline in the inhibitors franchise should be more than offset by 1/ growth in key products such as lifitegrast and DX2930, et 2/ cost-cutting measures

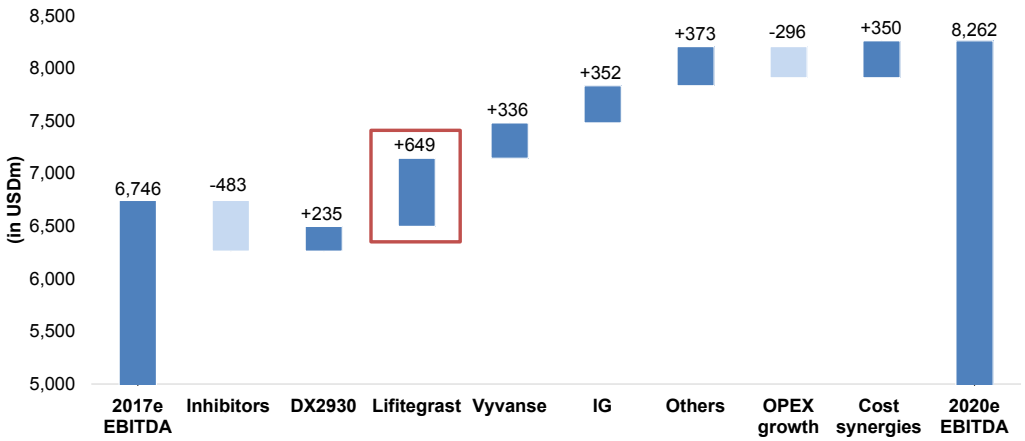
ACE910 is clearly set to have a substantial impact on sales in the inhibitors franchise and the fact that Feiba is a high-margin product (gross margin of around 90%) makes it a palpable source of concern for investors. However, we should not under-estimate the diversity in the group's pipeline, its positioning in niche markets and/or rare diseases, and the reactive nature of its management. More precisely, we estimate that 1/ newsflow associated with lifitegrast and DX2930 should reassure the market as to Shire's ability to manage the decline in Feiba, and 2/ the company could surprise positively in terms of its ability to significantly and rapidly reduce costs.

2.1. Numerous ways of cushioning the blow

As we stated in the first part of this study, we are assuming that ACE910 will above all impact sales in the inhibitors segment (2017-2020 CAGR of -23%). However, we also believe that this regression should be more than offset by 1/ growth in several other franchises/products (bearing in mind that a number of our assumptions are still adjusted for clinical risk), and 2/ cost synergies with Baxalta (bearing in mind that the last explicit target was for at least USD700m between now and 2019e).

Among these various factors, we believe that two of them should especially contribute to the share's rerating and reassure the market as to the group's ability to absorb a shock in haemophilia A: 1/ DX2930/SHP643 in treatment of hereditary angioedema (HAE) and 2/ lifitegrast for modest/severe dry-eye syndrome.

Fig. 8: EBITDA 2017-2020 – Main drivers



Source: Bryan, Garnier & Co. ests.

Fig. 9: EBITDA 2017-2020 – BG assumptions

(in USDm)	Gross margin (%)	2017e	2018e	2019e	2020e	Var 2017-20
DX2930	80%	0	69	133	235	235
Inhibitors	90%	888	812	569	405	-483
Lifitegrast	80%	211	423	640	860	649
Vyvanse	90%	2,140	2,290	2,404	2,477	336
Hemophilia	80%	2,486	2,573	2,612	2,625	139
IG	55%	1,149	1,275	1,390	1,501	352
Others		4,566	4,698	4,831	4,799	234
Group Gross margin		**11,440**	**12,140**	**12,578**	**12,902**	**1,462**
Cost Synergies		350	525	700	700	350
OPEX (excl. Synergies)		5,045	5,209	5,398	5,340	296
% var y-o-y			3%	4%	-1%	
EBITDA		**6,746**	**7,456**	**7,881**	**8,262**	**1,516**

Source: Bryan, Garnier & Co ests.

2.1.1. Lifitegrast: an underestimated ramp-up?

Lifitegrast: a powerful blockbuster

Although the clinical history of Xiidra (lifitegrast) was admittedly fairly perturbed, it finally ended up being approved with a far wider label than that of Restasis by Allergan (which nevertheless generated sales of USD1bn). After having closely compared the labels and clinical packages of both drugs, we believe Xiidra will rapidly gain market share from its rival, especially since annual prices are very similar). A new version of Restasis in multi-dose vials with no preservatives is apparently in the approval process, but we do not see how a simple change in the administration method could radically change the landscape.

Two questions remain however: how long can it take for Xiidra to establish itself bearing in mind that it has only been available for sale since this Q3 2016? And to what extent can it extend the dry-eye market? We have assumed that 1/ the USD1bn mark will not be reached before 2020e, especially in view of its superiority and 2/ the share of patients being diagnosed and wanting to be treated should remain at around 15%e, which is fairly conservative in our view.

Fig. 10: Xiidra vs Restasis

	Xiidra (SHP)	Restasis (AGN)
MoA	Lymphocyte-function associated antigen-1 antagonist	Cyclosporine - Immunosuppressive agent
Indication	" Indicated for the treatment of the signs and symptoms of dry eye disease"	"Indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctual plugs
Adverse reactions	Most common AE (incidence 5-25%) were instillation site irritation, dysgeusia (distortion of sense of taste) and decreased visual acuity	Most common AE (incidence 17%) was ocular burning. Other events reported in 1-5% of patients included conjunctival hyperaemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging and visual disturbance

Source: FDA; Bryan, Garnier & Co ests.

Fig. 11: BG estimates –Xiidra sales (lifitegrast)

	2015e	2016e	2017e	2018e	2019e	2020e	2021e	2022e
Dry eye Prevalence (in millions)	**60**	**61**	**61**	**62**	**62**	**63**	**64**	**64**
% var y-o-y		1%	1%	1%	1%	1%	1%	1%
- US	25	25	26	26	26	26	27	27
- Europe	35	35	36	36	36	37	37	38
% Patients with moderate-to-severe forms	30%							
% Patients seeking treatment	15%							
Pricing per patient - US (in USD)	2,900							
Pricing per patient - Europe (in USD)	1,938							
% Market shares - US	0.0%	2.0%	7.0%	12.0%	17.0%	22.0%	25.0%	27.0%
% Market shares - Europe	0.0%	0.0%	1.0%	4.0%	7.0%	10.0%	12.0%	15.0%
Lifitegrast - Sales (in USDm)	**0**	**66**	**264**	**529**	**799**	**1,075**	**1,255**	**1,435**
% var y-o-y		n/s	n/s	100%	51%	34%	17%	14%

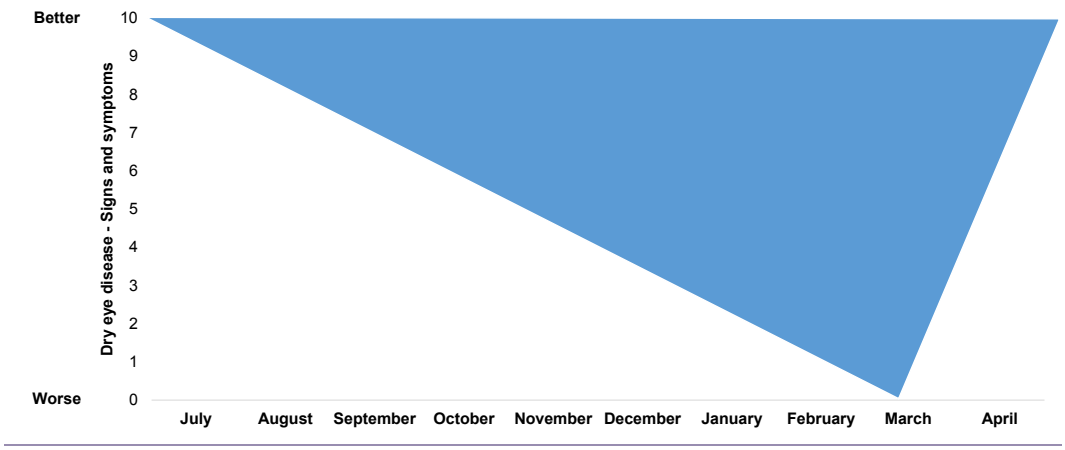
Source: Bryan, Garnier & Co ests.

Based on this, we would add two comments:

Forthcoming quarterly publications should confirm this status, and could even result in forecast upgrades

- Despite our conservative stance, our forecasts for the product are higher than those of the consensus (the average for 2018e standing at around USD400m whereas we are forecasting USD529m). However, we understand that the majority of analysts are fairly cautious relative to sales launches in the current context.
  Given this, **we will pay close attention to the first quarterly publications for the product in that they imply the winter season when symptoms of the disease tend to be exacerbated, and should therefore help confirm forecasts for 2017e, or even increase them.**

Fig. 12: Dry-eye – symptoms/signs of the disease depending on the season



Source: Review of Ophtalmology; Bryan, Garnier & Co. ests

- A number of investors could also retort that estimates are potentially at risk in a context in which the sector has suffered a number of disappointments in terms of commercial launches

(PCSK9 and Entresto being perfect examples). However, it is always important to put things back into context: 1/ there is only one direct rival option and Xiidra's pricing was aligned with this, 2/ "lifi" is not suffering from competition from generic alternatives, since patents on Restasis should remain in place until 2023. Some may have noted that patients suffering from this disease can use artificial tears, the cost of which is fairly low. However, these are above all used for the mildest cases (Bhavsar et al, 2011).

2.1.2. DX2930/SHP643: a try to convert

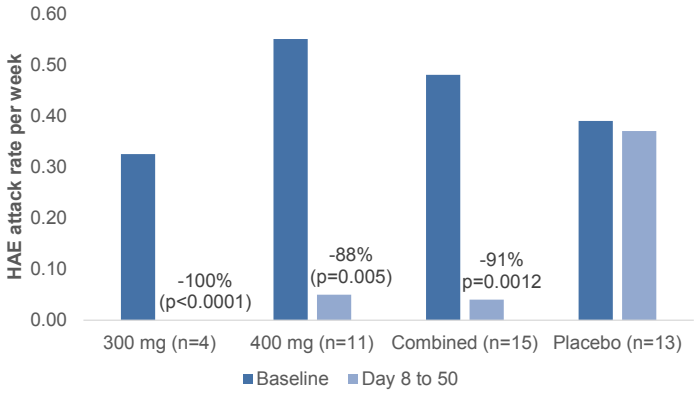
- **A potential new best-in-class in HAE**

DX2930 in HAE: a potential game-changer for which results of Phase III trials are expected in H1 2017

DX2930 has everything it takes to become the future standard treatment in HAE. The fact that it can be administered subcutaneously once a month is a first argument whereas Cinryze needs to be injected twice a week intravenously. However, its efficacy and safety profile also make it a potential game-changer since the number of attacks was reduced by 90% relative to the placebo ($p<0.005$) over a six-week period under the framework of a Phase I/II trial, whereas this rate is closer to 50-60% for current options (Cocchio et al, 2009).

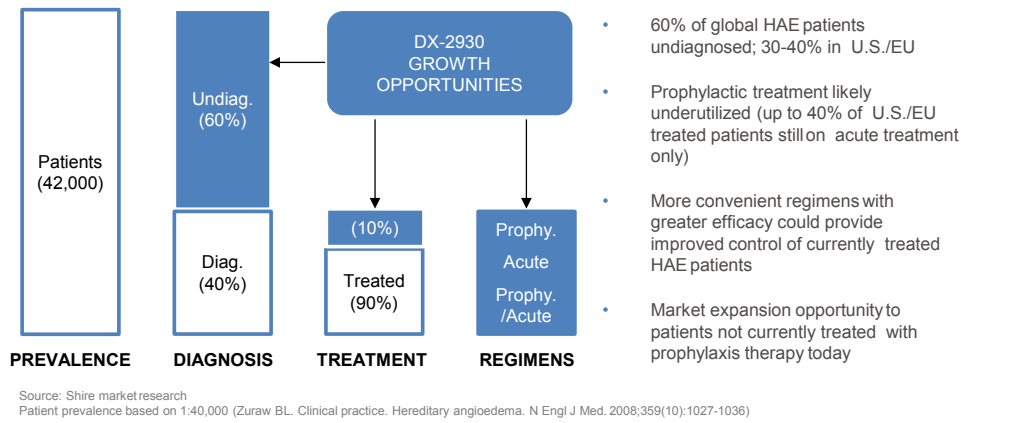
Given this, we estimate that a large portion of patients treated with Cinryze could rapidly be switched to this new approach (which would be positive for margins, since a monoclonal antibody is far less complex and expensive to produce than a plasma derivative). More efficient and more convenient, it is also possible that the drug could massively contribute to a wider-scale adoption of prophylactic treatment since almost 40% of patients treated in Europe and the US are still treated on demand.

Fig. 13: DX2930 – Results of Phase Ib at six weeks



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

Fig. 14: DX2930 – Growth potential



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

■ **A significant cushion for margins set to be confirmed in H1 2017**

Sales and margin potential for DX2930 is such that it could fully offset losses caused by Feiba

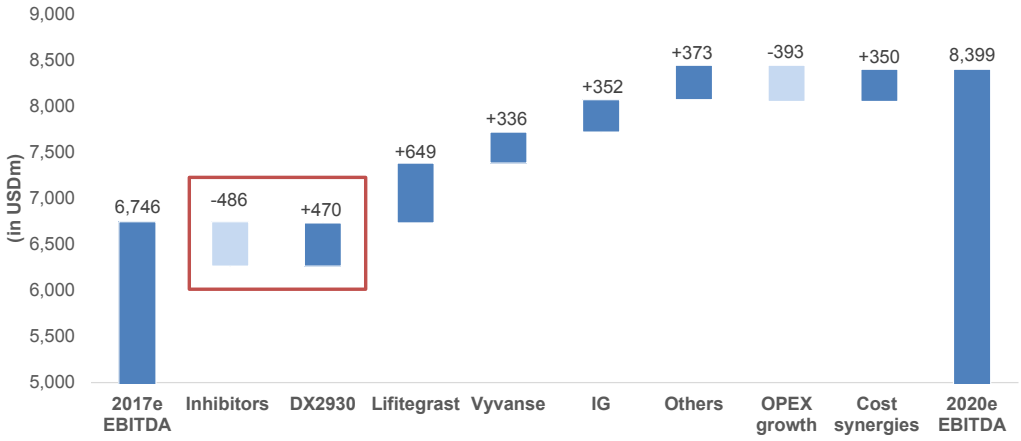
An important point to note: our sales assumptions for this project are currently adjusted for clinical risk, and more precisely, we only take into account 50% of its potential pending its approval (BG: 2018e). If it is approved, we estimate that its commercial launch should enable the group to fully absorb the margin loss associated with the decline in the inhibitors franchise (especially since DX2930 should generate a (conservative) gross margin of close to 80%e given the price-positioning that we expect, and the COGS generally associated with the manufacturing of an mAB).

Fig. 15: DX2930 - Sales forecasts unadjusted for risk

	2018e	2019e	2020e	2021e	2022e	2023e	2024e	2025e
HAE – Prevalence	**24,482**	**24,727**	**24,974**	**25,224**	**25,476**	**25,731**	**25,989**	**26,248**
% yoy change								
- US	12,241	12,364	12,487	12,612	12,738	12,866	12,994	13,124
% yoy change	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
% yoy change	1%	1%	1%	1%	1%	1%	1%	1%
% Diagnosis rate	50%							
Pricing per patient - US - Prophylaxis (in USD)	400,000							
Pricing per patient - ROW - Prophylaxis (in USD)	280,000							
% Market shares – US	7%	12%	20%	25%	30%	35%	40%	40%
% Market shares – Europe	0%	2%	5%	10%	15%	20%	25%	30%
DX-2930 - HAE - Sales (in USDm)	**171**	**331**	**587**	**807**	**1,032**	**1,261**	**1,494**	**1,601**
% yoy change	n/s	93%	77%	38%	28%	22%	19%	7%

Source: Bryan, Garnier & Co ests.

Fig. 16: 2017-2020 EBITDA if DX2930 is approved



Source: Bryan, Garnier & Co. ests.

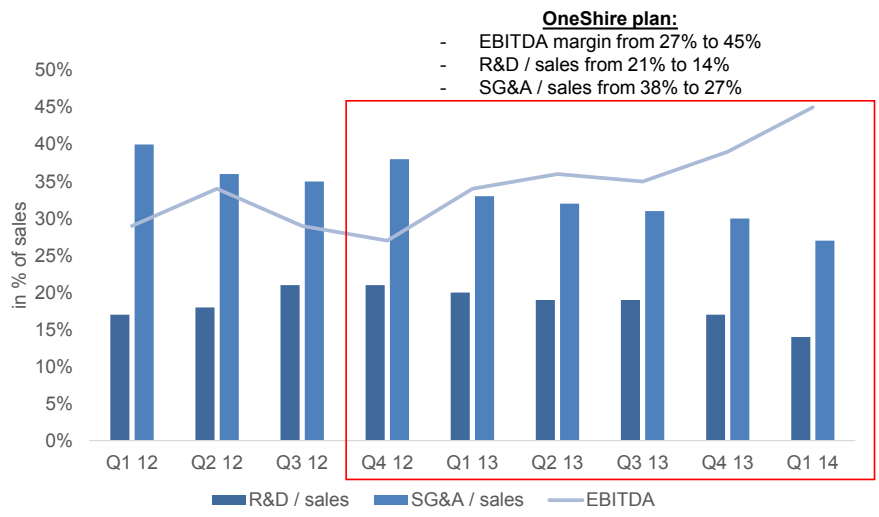
2.2. Remember OneShire…

Cost-cutting: an outstanding track-record

We believe that management could positively surprise the market in terms of its ability to optimise its cost base. A look in the rear-view mirror is also useful for assessing this likelihood and more specifically the arrival of Flemming Ornskov and the roll-out of the OneShire plan, especially since the structure of Baxalta is apparently fairly similar to that of Shire before this initiative ("the legacy Baxalta business operated on a divisional structure akin to that which Shire used prior to 2013").

At the time, this initiative resulted in a near 700bp improvement in EBITDA margin within the space of a year! Clearly, the current situation is very different since we are now talking about the integration of a far larger company than Shire was at the beginning of the decade (and the geographical mixes were far from similar), but at least this leaves an attractive benchmark in our minds.

Fig. 17: OneShire plan - change in the cost structure



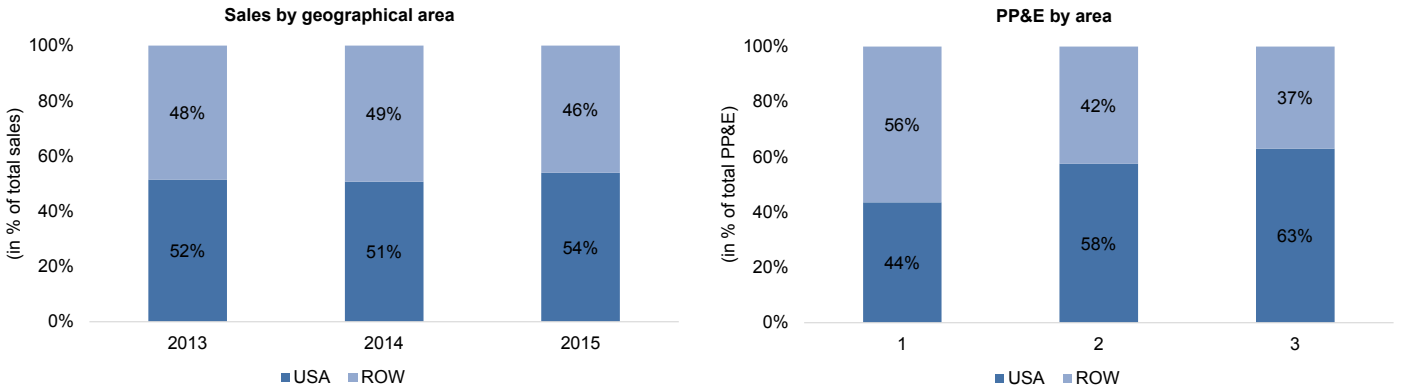
Source: Shire; Bryan, Garnier & Co. ests

Potential for welcome news that should not be under-estimated

In addition to this, a number of factors make us fairly confident in forthcoming events:

- From our viewpoint, **the dominance of the US in Baxalta's cost base is a key factor for assessing the speed at which its optimisation could go ahead** (we are deliberately leaving out emerging markets in this reflection given Shire's low historical exposure to these areas and hence, low synergy potential). And in this case, around 50-60% could be derived from the region.
  If we then assume that half of G&A costs (which we estimate at around USD500m) are located in the US, this would mean that almost USD250m in savings could theoretically be rapidly extracted, thereby representing around 80%e of the amount expected by the company in 2017.

Fig. 18: Geographical breakdown of sales + PP&E de BXLT



Source: Baxalta; Bryan, Garnier & Co. ests

- **A first review of R&D projects has already been undertaken and resulted in the halt to early/mid-stage projects, and we believe that several other developments could be halted soon.**
  Recently, the company announced the discontinuation of its bio-similars business (BAX2200/etanercept and BAX2923/adalimumab) given its complete opposition with Shire's aim to extend its footprint in rare diseases. Admittedly, exceptions have been made in the past and the construction of an ophthalmology franchise is a perfect example. However, the risk-reward profile associated with these projects does not seem as attractive given that 1/ BXLT was far from being the only company to have embarked on this type of development, 2/ whether in rheumatoid arthritis or plaque psoriasis, a number of new action mechanisms have emerged and proved to be more efficient than anti-α: anti-IL17, anti-IL23p19, JAK inhibitors etc.

- The question of sales and marketing spend is always slightly trickier given its potential impact on the group's growth prospects. Note nevertheless that the group's CFO recently discussed the subject during a healthcare conference ("There are a couple of areas where there's a disproportionate number of BXLT employees. Manufacturing being one given the size of the manufacturing network, and then certainly from a commercial standpoint in the Haemophilia, Immunology and Oncology businesses").

Fig. 19: Baxalta's development pipeline before acquisition by Shire

Program	MoA	Indication(s)	Area	Clinical stage
HAEMOPHILIA				
Adynovate	Long-acting recombinant FVIII	Haemophilia A (adults)	Europe	Phase III
Adynovate	Long-acting recombinant FVIII	Haemophilia A (pediatric)	US	Phase III
Vonvendi	Recombinant von Willebrand Factor	Von Willebrand disease	Europe	Phase III
BAX930	Recombinant ADAMTS13	hTTP	WW	Phase II
BAX335	FIX gene therapy	Haemophilia B	WW	Phase II
BAX826	PSA rFVIII	Haemophilia A	WW	Phase I
IMMUNOLOGY				
Hyqvia	Subcutaneous 10% IG	CIDP	WW	Phase III
Glassia	Alpha-1 Antitrypsin	Acute graft-versus-host disease	WW	Phase III
SM101	Recombinant FcγRIIb	Systemic lupus erythematosus		Phase II
ONCOLOGY				
Imalumab	Anti-oxMIF mAb	3L metastatic colorectal cancer	WW	Phase II
Onivyde	Nanoliposomal irinotecan	2L metastatic pancreatic cancer	Europe	Phase III
Onivyde	Nanoliposomal irinotecan	1L metastatic pancreatic cancer	Europe	Phase III
Calaspargase pegol	New-gen PEG-asparaginase	Acute lymphoblastic leukaemia	WW	Phase II/III
BIOSIMILARS				
BAX2200	Etanercept (anti-TNF-α)	Rheumatoid arthritis	Europe	Phase III
BAX2200	Etanercept (anti-TNF-α)	Plaque psoriasis	Europe	Phase III
BAX2923	Adalimumab (anti-TNF-α)	Plaque psoriasis	WW	Phase III

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

3. Appendices

Fig. 20: SHP – P&L estimates (2015-2020e)

(in USDm)	2015	2016e	2017e	2018e	2019e	2020e
(+) Product sales	**6,100**	**11,278**	**15,272**	**16,259**	**16,879**	**17,300**
% growth y-o-y		85%	35%	6%	4%	2%
(-) COGS	885	2,548	3,832	4,118	4,301	4,397
in % of product sales	14.5%	22.6%	25.1%	25.3%	25.5%	25.4%
= Gross margin	**5,215**	**8,731**	**11,440**	**12,140**	**12,578**	**12,902**
in % of product sales	85.5%	77.4%	74.9%	74.7%	74.5%	74.6%
(+) Royalties & Others	317	395	345	356	366	376
(-) R&D	884	1,443	1,680	1,788	1,688	1,730
% growth y-o-y		63%	16%	6%	-6%	2%
(-) SG&A	1,724	2,868	3,360	3,252	3,376	3,287
% growth y-o-y		66%	17%	-3%	4%	-3%
= EBITDA	**2,924**	**4,815**	**6,746**	**7,456**	**7,881**	**8,262**
in % of product sales	47.9%	42.7%	44.2%	45.9%	46.7%	47.8%
(-) D&A	139	307	458	537	591	640
= EBIT	**2,785**	**4,408**	**6,287**	**6,919**	**7,290**	**7,622**
in % of product sales	45.7%	39.1%	41.2%	42.6%	43.2%	44.1%
% growth y-o-y		58%	43%	10%	5%	5%
(-) Interest expense	42	413	594	489	339	189
(+/-) Others	-7	-2	0	0	0	0
(-) Income taxes	424	715	1,025	1,093	1,112	1,189
% Corporate Taxes	15.5%	17.9%	18.0%	17.0%	16.0%	16.0%
= Net income	**2,310**	**3,279**	**4,668**	**5,337**	**5,839**	**6,243**
Basic EPS (USD)	**3.91**	**4.21**	**5.15**	**5.89**	**6.44**	**6.89**
% var y-o-y	10%	8%	22%	14%	9%	7%
Diluted EPS (USD)	**3.89**	**4.21**	**5.15**	**5.89**	**6.44**	**6.89**
% var y-o-y	10%	8%	22%	14%	9%	7%

Source: Bryan, Garnier & Co ests.

Fig. 21: SHP ex-BXLT – Sales forecasts (2015-2020e)

(in USDm)	Main indication	PoS (%)	2015	2016	2017	2018	2019	2020
SHP - Sales			6,100	7,005	7,886	8,518	9,033	9,295
% var y-o-y								
Vyvanse	ADHD & BED	100%	1,722	2,069	2,378	2,544	2,672	2,752
Intuniv	ADHD	100%	65	69	62	62	62	62
Adderrall XR	ADHD	100%	363	376	372	368	364	361
SHP465	ADHD	80%	0	0	56	112	202	323
Lifitegrast	Dry eye	100%	0	32	264	529	799	1,075
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	570	638	574	488	391
Cinryze	HAE	100%	618	702	772	695	486	340
DX2930	HAE	50%	0	0	0	86	166	293
Kalbitor	HAE	100%	0	68	72	75	78	81
Lialda	Ulcerative colitis	100%	684	798	829	846	854	512
Pentasa	Ulcerative colitis	100%	306	306	300	294	288	282
Gattex	Short bowel syndrome	100%	142	213	298	403	504	579
Natpara	Hypoparathyroidism	100%	24	84	168	269	363	454
SHP621	EoE	50%	0	0	0	0	25	69
SHP555	Chronic constipation	50%	0	0	8	17	28	39
Vpriv	Gaucher Disease	100%	342	338	321	305	290	275
Elaprase	Hunter syndrome	100%	553	557	562	556	540	523
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	441	432	423	415	394
Others	**Others**	**100%**	**395**	**381**	**346**	**317**	**292**	**273**

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

Fig. 22: BXLT activities – sales forecasts (2015-2020e)

	2015	2016e	2017e	2018e	2019e	2020e
BXLT - Group sales	6,230	6,876	7,387	7,741	7,846	8,005
% growth y-o-y		10.4%	7.4%	4.8%	1.4%	2.0%
- Hemophilia	2,840	2,938	3,108	3,216	3,265	3,281
% growth y-o-y		3%	6%	3%	2%	1%
- Inhibitor therapies	787	957	987	902	632	450
% growth y-o-y		22%	3%	-9%	-30%	-29%
- Immunoglobulin	1,750	1,874	2,089	2,319	2,528	2,730
% growth y-o-y		7%	11%	11%	9%	8%
- Biotherapeutics	766	866	925	980	1,029	1,081
% growth y-o-y		13%	7%	6%	5%	5%
- Oncology	87	242	278	323	393	463
% growth y-o-y		178%	15%	16%	22%	18%
- Biosimilars	0	0	0	0	0	0

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

Price Chart and Rating History

Shire PLC

Ratings		
Date	**Ratings**	**Price**
23/05/2016	BUY	42,81p

Target Price	
Date	**Target price**
03/08/2016	6900p
12/07/2016	6750p
03/06/2016	6500p
23/05/2016	5900p

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