BRYAN, GARNIER & CO

INDEPENDENT RESEARCH

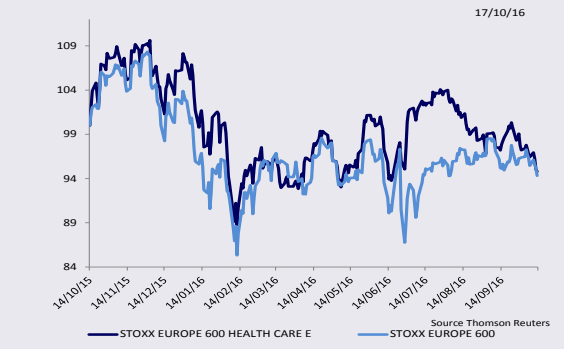
17th October 2016

Healthcare

Haemophilia: « Stemming the bleed »

Healthcare

SHIRE PLC		**BUY**	**FV 6900p**
Bloomberg	SHP LN	Reuters	SHP.L
Price	5176p	High/Low	5323/3480p
Market cap.	GBP46,738m	Enterprise Val	GBP61,711M
PE (2016e)	15.0x	EV/EBIT (2016e)	17.1x
GRIFOLS		**NEUTRAL**	**FV EUR20**
Bloomberg	GRF SM	Reuters	GRF.MC
Price	EUR18,625	High/Low	EUR22,7375/18
Market Cap.	EUR11,509m	Enterprise Val	1EUR5,083m
PE (2016e)	21.6x	EV/EBIT (2016e)	15.5x
SOBI		**SELL**	**FV SEK90**
Bloomberg	SOBI SS	Reuters	SOBIV.ST
Price	CHF101,3	High/Low	CHF139,3/95,85
Market Cap.	CHF27,391m	Enterprise Val	28,557
PE (2016e)	46.2x	EV/EBIT (2016e)	33.2x
NOVO NORDISK		**NEUTRAL**	**DKK355**
Bloomberg	NOVOB.CO	Reuters	NOVOB.CO
Price	270,5DKK	High/Low	404,2/265,7
Market Cap.	544 399 MDKK	Enterprise Val	518 987 MDKK
PE (2016e)	17,4x	EV/EBIT (2016e)	10,4x
ROCHE		**ACHAT**	**CHF293**
Bloomberg	ROG VX	Reuters	ROG.VX
Price	235,8CHF	High/Low	279,3/233,2
Market Cap.	165 664 MCHF	Enterprise Val	178 330 MCHF
PE (2016e)	14,9x	EV/EBIT (2016e)	9,1x



The haemophilia market has attracted particular investor attention in recent months. Our sector report aims notably to help investors better assess the challenges/issues in this very specific and ultimately fairly unknown market.

- We estimate that the majority of the haemophilia market, and more precisely, patients without inhibiting antibodies, will remain widely addressed by substitution therapies based on coagulation factors. On the other hand, Approaches such as ACE910 and Fitusiran are clearly set to provide an advantage. However, we believe they are primarily set to address haemophilia A patients with inhibiting antibodies, for whom the medical need is the most important.

- **Shire is still one of our top picks** as we believe that 1/ its commercial and clinical portfolio should help it continue to outperform peers (Grifols, SOBI or even CSL) in haemophilia A; and 2/ we estimate that the group should be capable of maintaining growth momentum following the arrival of Roche's ACE910 and Alnylam's Fitusiran.

- **Roche is the second name that stands out on our radar.** Admittedly, the share's performance remains above all dependent on the results of the APHINITY study. However, we estimate the group's portfolio includes a number of projects for which revenues could easily approach the USD2bn mark and ACE910 is clearly one of them in our view.

- Whereas the consensus has more than factored in the pressure caused by the arrival of ACE910 on Feiba's sales at Shire, we estimate that **forecasts are overly optimistic for NovoSeven by Novo Nordisk.**

- We are initiating coverage of **Grifols with a Neutral recommendation and a FV of EUR20,** and coverage of **SOBI with a Sell recommendation and a FV of SEK90.**

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1. Why are we writing this report?

The haemophilia market has attracted particular investor attention in recent months, not only in view of the acquisition of Baxalta by Shire but also on a fundamental level, since a number of potential breakthrough developments (including Roche's ACE910) are set to see the light soon.

Our sector report aims notably to help investors better assess the challenges/issues in this very specific and ultimately fairly unknown market. In order to do this, we obviously discuss the subject from the perspective of the companies we cover in our universe (ROG, SHP, NOVO), but in order to stand out from the crowd, we have also extended our analysis to add two mid-sized stocks to our coverage (GFS and SOBI) and include contacts with listed groups on other continents (CSL, BIIB).

As an overview, the main points we note are as follows:

- We estimate that the **majority of the haemophilia market, and more precisely, patients without inhibiting antibodies, will remain widely addressed by substitution therapies based on coagulation factors.** Long-acting therapies should also account for a rising share of this segment. However, we believe that the switch from short–acting ones (and an eventual upheaval in market shares for the various players) is likely to be far more noticeable in haemophilia B in that the incremental factor provided by these new molecules is far more obvious than for haemophilia A.

- **Approaches such as ACE910 and Fitusiran are clearly set to provide an advantage. However, we believe they are primarily set to address haemophilia A patients with inhibiting antibodies,** for whom the medical need is the most important (too many injections, disease controlled in only 80% of cases with current therapies). Patients without inhibitors are only likely to be addressed at a later stage. However, the ramp-up is unlikely to be as rapid and significant given uncertainty concerning the safety profiles of these approaches.

- On the dawn of these various scenarios, we estimate that 1/ downside potential in more traditional therapies such as NovoSeven (Novo Nordisk) and pdFVIII (Grifols), has potentially been underestimated by the market, but that 2/ the risk is exaggerated for others, and more precisely for Shire's haemophilia franchise.

1.1. Our hierarchy in this theme

- **Our Top Picks: Shire and Roche**

In our view, Shire is still one of our top picks given that 1/ its commercial and clinical portfolio should help it continue to outperform peers (Grifols, SOBI or even CSL) in haemophilia A, 2/ we estimate that the group should be capable of maintaining growth momentum following the arrival of ACE910 and Fitusiran.

Roche is the second name that stands out on our radar. Admittedly, the share's performance remains above all dependent on the results of the APHINITY study (see feedback from our first BG Oncology Day for more details). However, we estimate the group's portfolio includes a number of

projects for which revenues could easily approach the USD2bn mark and ACE910 is clearly one of them in our view.

- **Least preferred: Novo Nordisk and SOBI**

We are initiating coverage of **Grifols with a Neutral recommendation and a FV of EUR20, and coverage of SOBI with a Sell recommendation and a FV of SEK90.** Our investment summary is as follows:

- **We believe that the consensus is overly optimistic for SOBI, and especially for the haemophilia segment.** Admittedly, Eloctate and Alprolix were quite successful in the US, we have the feeling this is the reason why consensus estimates are so high for SOBI's territories (combined peak sales: USD700m-1.0Bn vs BG: USD500m)… But let's bear in mind that 1/ these two BIIB's molecules had no direct competitors for more than a year in the US; 2/ in other areas, and especially Europe, the part of plasma-derived factors is much higher than in the US… And we would say that the competitive landscape is much less favourable.

- Whereas the consensus has more than factored in the pressure caused by the arrival of ACE910 on Feiba's sales at Shire, we estimate that **forecasts are overly optimistic for NovoSeven by Novo** (whether in terms of revenues or bottom-line growth), especially since almost 40-50% of revenues from the product could be affected as of 2018e, or even end-2017e.

Fig. 1: Our hierarchy for this theme

Company	Rating	Fair Value	Upside (%)	Comments
Shire	Buy	GBp6,900	33%	- Attractive valuation (P/E 2017e: 13x) - Best-in-class growth profile (EPS CAGR 2015-2020: +15%) - Impact of Roche's ACE910 and Alnylam's Fitusiran more than integrated
Roche	Buy	CHF293	24%	- ACE910's Phase III data to be published in Q4 16 or H1 17 at the latest - First-mover advantage vs Alnylam's Fitusiran
Grifols	Neutral	EUR20	6%	- Demanding valuation (P/E 2017e: 20x) - Underestimated impact of subcutaneous IG (Hizentra, Hyqvia) in CIDP and PID - pdFVIII franchise potentially under pressure due to Eloctate/Elocta
Novo Nordisk	Neutral	DKK355	31%	- Diabetes franchise : price pressure and intensifying competition - Underestimated impact of Roche's ACE910 on the Hemophilia franchise
SOBI	Sell	SEK90	-11%	- Eloctate to be differentiated as an Immune Tolerance Induction alternative but the non-inhibitor space is increasingly crowded - Alprolix to suffer from the competition of CSL's Idelvion

Source: Bryan, Garnier & Co. ests

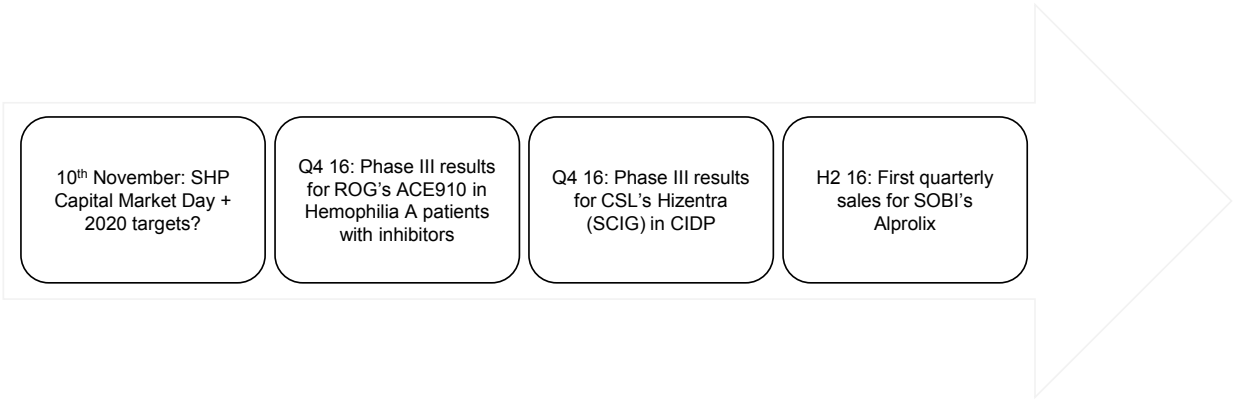
1.2. Significant catalysts over the next 12 months

Next significant catalyst: Phase III results of ROG's ACE910 (Q4 16)

We understand that **Roche is due to publish the results of a Phase III trial assessing ACE910 in patients suffering from haemophilia A and having developed inhibitor antibodies, at the end of the year** (or at the latest during H1 2017). If these were to confirm the trends noted under the framework of a small Phase I/II study, we estimate 1/ that a priority review could be obtained from the FDA and that 2/ the product could then be approved by the end of 2017.

It is also highly likely that Shire's management will set out its MT/LT vision during its Capital Market Day and this should also result in a detailed update to guidance for its earnings out to 2020. Clearly, a specific focus is likely to concern 1/ the haemophilia/inhibitors franchise and especially, how management sees the change in the therapeutic backdrop and 2/ the various levers identified in order to optimise its new cost structure.

Fig. 2: Sector newsflow over the next 12 months



Source: Bryan, Garnier & Co. ests

2. Haemophilia A: a dual-speed market

We believe the inhibitor segment will change dramatically in the coming years due to novel compounds… contrary to the non-inhibitor one

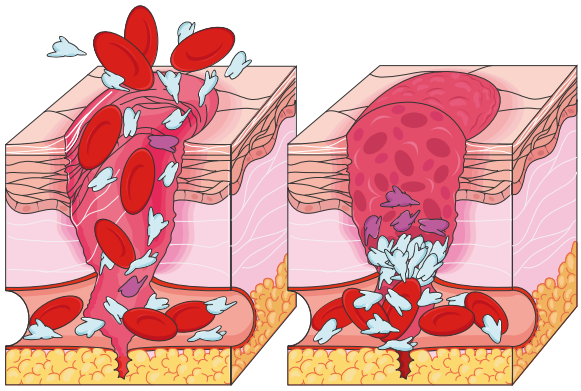
A number of observers seem to think that ACE910 by Roche or Fitusiran by Alnylam could completely change the treatment paradigm of haemophilia A (since they are more flexible but just as efficient). But we estimate that 1/ this prospective change is only likely to be very gradual in view of uncertainty concerning the safety profile, 2/ approaches with the largest breakthrough potential are still far from being a panacea.

In this scenario, we believe that the standard of care remains and will remain administration of coagulation factors, while bearing in mind that new long-acting versions (x1.5 on average) are beginning to be marketed. We admit that these new therapies are unlikely to upset the market given the lack of significant additional benefits they provide. However, it was important for all the historical players to develop/market these products in order to consolidate their market shares. In our view, Shire and Bayer are the best positioned in this theme.

2.1. Patients without inhibitors: very gradual change

Before entering the heart of the subject, let's start with a few words on the disease. Haemophilia A is a fairly rare pathology (only 15,000 people affected in the US) characterised by the absence of blood clotting factors and more specifically of factor VIII.

Fig. 3: Haemophilia – clotting factor deficiency



Source: Bryan, Garnier & Co. ests.

Most Haemophilia A patients are very well-controlled with current therapies

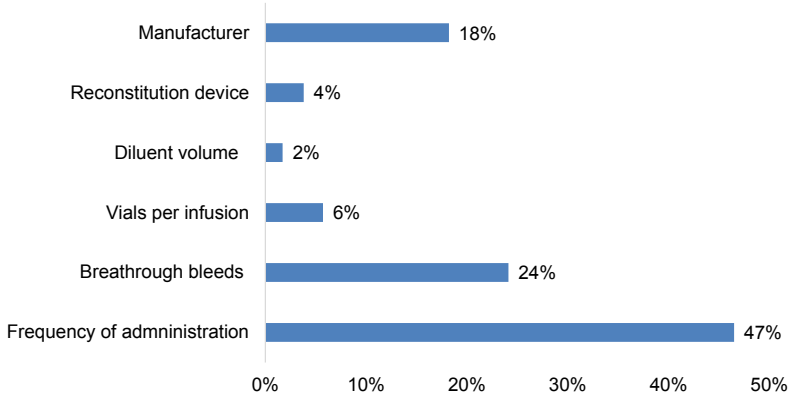
In the large majority of cases, **the disease is fairly well controlled thanks to substitutive treatments,** and more precisely, thanks to the intravenous injection of functional factors. Note however that practices and products have evolved massively since the early 1950s before giving rise to a market of almost USD6bn:

- **Heading for more prophylaxis**: An increasing share of patients diagnosed with a severe form of the disease turn to preventive/prophylactic treatments (which also help massively reduce the risks of spontaneous bleeding/hemarthrosis and irreversible lesions). The percentage remains generally fairly small with just 20-30%e of haemophilia A patients thought to be treated in this way in more mature regions, albeit with a higher rate for patients with more serious forms of the disease.

An increasing part of patients opt for recombinant FVIII and prophylactic strategies

The cost of this type of approach (around USD400-500k per patient) is probably a contributing factor to this low percentage, although we understand that frequency of administration of these products is also a subject of prime importance (see Fig.4), and is clearly the reason why the various sector players have developed long-acting products: Eloctate (Biogen/SOBI), Adynovate (Shire), Kovaltry (Bayer), and more recently Afstyla (CSL), N8-GP (Novo)…

Fig. 4: Prophylaxis - patient preferences



Source: Furlan et al (2015); Bryan, Garnier & Co. ests.

Nearly 50% of treated patients are with recombinant factors (≠ plasma-derived)

- **rFVIIIs have taken the lion's share:** while all of the factors marketed were plasma derivatives until the end of the 1980s, note that their share has fallen massively to the benefit of synthetic/recombinant approaches that 1/ by definition, present no risk of infection by viruses such as HIV or hepatitis A/B/C, and 2/ now account for 50% of FVIIIs sold in the world, bearing in mind however, that this figure is slightly higher if we limit ourselves to the most developed regions (more than 70%e in the US for example).

  Admittedly, the risk of contamination with pdFVIIIs has been slashed now that strict testing and decontamination processes have been put in place (heating, filtration, use of solvents and detergents). However, there is no zero risk, and it is very likely that this aspect played in favour of rFVIII (albeit around 20-30%e more expensive).

  In addition, one question remains hanging: can the risk of developing inhibitors be reduced depending on the factor type? Theoretically, the fact that plasma concentrates also include von Willebrand factor could indeed result in a better protection against this risk (masking of epitopes, less endocytosis by dendritic cells). However, the reality is potentially quite different with a number of large-scale studies having generated fairly contradictory results (see section on Grifols for further details). In view of this, we have the feeling that practices are unlikely to evolve drastically over coming years.

Fig. 5: Haemophilia A – Current treatments available

Company	Product	Technology	Half-life (HL)	HL vs native
Recombinant - Long-acting				
Shire/Baxalta	Adynovate	PEGylation on full length FVIII	19 hours	1.4-1.5
Bayer	Kovaltry	PEGylation on B-deleted FVIII	19 hours	1.4
Novo Nordisk	N8-GP	B-domain glycopegylated	19 hours	1.6
Biogen/SOBI	Eloctate	Fusion protein	19 hours	1.5-1.7
CSL	Afstyla	Albumin fusion protein	19 hours	1.4-1.5
Old-gen (recombinant and plasma-derived)				
Shire/Baxalta	Advate	Recombinant FVIII	n/a	n/a
Bayer	Kogenate	Recombinant FVIII	n/a	n/a
CSL	Helixate	Recombinant FVIII	n/a	n/a
Pfizer	Xyntha	Recombinant FVIII	n/a	n/a
Shire/Baxalta	Hemofil M	Plasma-derived FVIII	n/a	n/a
CSL	Monoclate	Plasma-derived FVIII	n/a	n/a
Grifols	Alphanate	Plasma-derived FVIII	n/a	n/a

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

2.1.1. Long-acting FVIII: who's set to come off best?

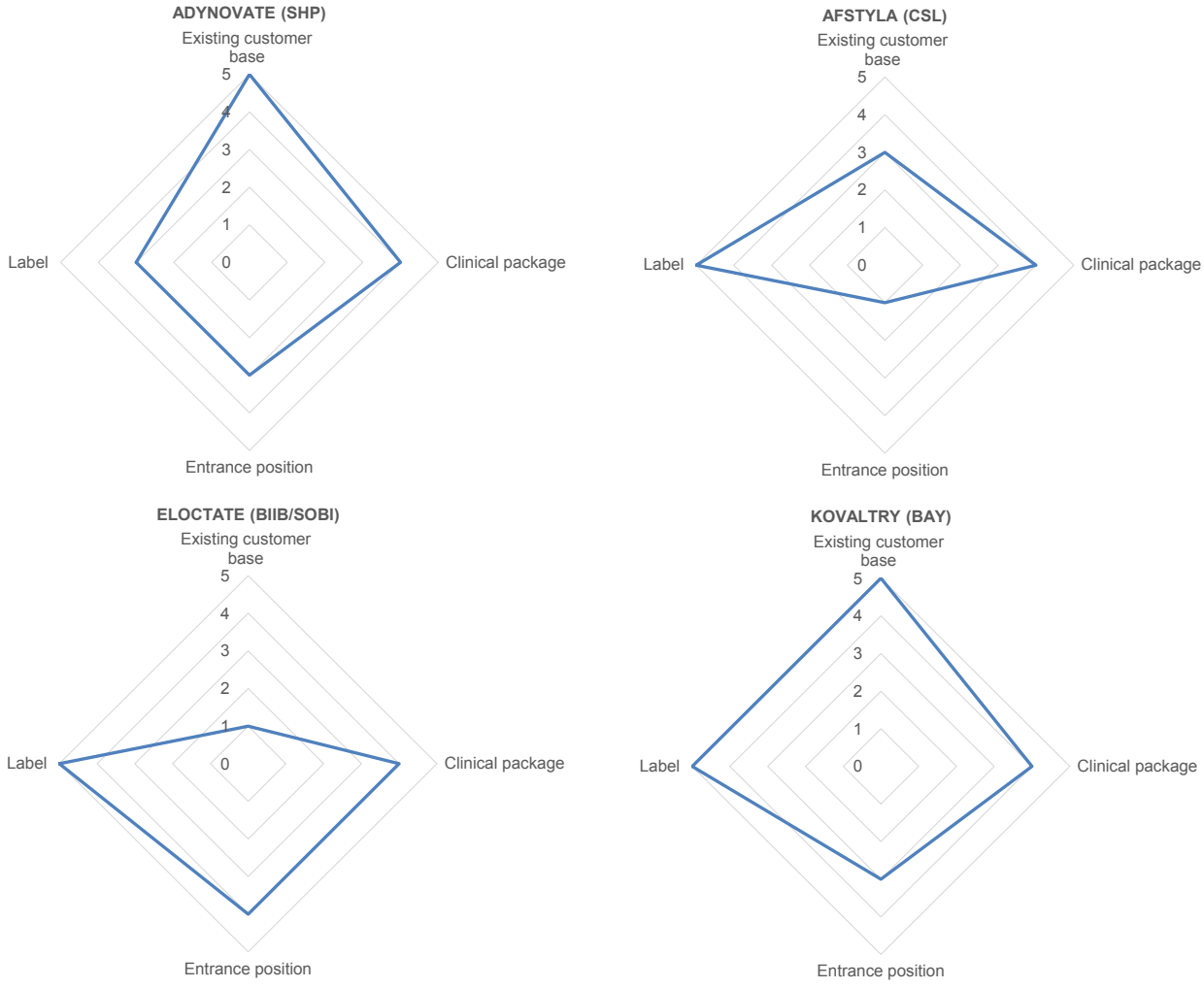
The first generation of long-acting FVIII are unlikely to change dramatically the therapeutic landscape

As discussed previously, new long-acting FVIIIs have been developed and a number of these are now already marketed, either by historical players in the segment (SHP, BAY, CSL to name just these), or also by new entrants (BIIB/SOBI). That said, the eventual benefit provided by these new approaches seems fairly minor to the extent that 1/ efficacy data is generally fairly similar to short-acting products, 2/ the number of injections required on a weekly basis remains fairly significant (around two on average vs. three) and 3/ the immunogenicity question remains hanging (even if clinical data generally seem to indicate that the risk of developing inhibitors could be reduced). As such:

- **Patients already well controlled have no real need to switch to the first long-acting products given the lack of advantage that they provide.** This is especially true since 1/ the risk of developing inhibitors is minimised after several months/years of treatment, 2/ although studies have tended to show the contrary, these same patients consider that changing their product could put them at risk again.
  Whatever the case, recent figures and declarations by players in the segment tend to favour this view since short-acting recombinant FVIIIs like Advate (SHP) remain generally on an uptrend, even in the US (the loss of patients having been more than offset by a greater adoption of prophylaxis).

- **Treatment-naive patients are the ones that most easily opt for these new molecules** and our recent contacts with BIIB, CSL and SHP tend to confirm this assumption.

Fig. 6: Long-acting FVIII – our ratings



Source: Bryan, Garnier & Co. ests.

That said, we estimate that the main winners are primarily set to be 1/ the first entrants (especially since there is no major difference in clinical results or even in pricing strategies) with fairly comprehensive labels preferably, and 2/ those marketed by companies already benefiting from a significant patient base. On this assumption, we believe that Eloctate (Biogen) is likely to keep a large share of the US market, while Kovaltry (Bayer) looks the best placed in the race in Europe.

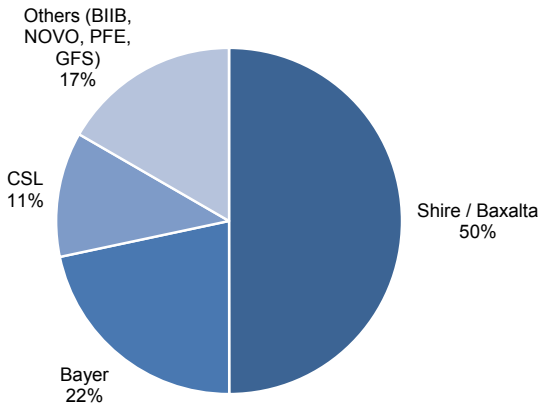
- **Bayer as the best placed in Europe**

Adynovate: 2nd entrant in the US, and potential leverage on Advate… But a currently limiting label

Adynovate should notably benefit from the fact that it is derived from a blockbuster (Advate, for which we estimate sales at almost USD2bn), and is the second entrant in the US (45% of the global market, with 60-65%e of these patients undergoing prophylaxis). However, two shadows cloud the picture and prevent us from being much more positive: 1/ the label is currently limited to adults and adolescents over 12-years of age, and this is likely to limit growth whereas the majority of rivals benefit from a fairly wide label (Eloctate, Kovaltry and Afstyla can be administered to children, whether for prophylactic use or on-demand), 2/ Europe is not yet addressed, although it is very likely that it will be as of H1 2017 (a marketing request was filed in March 2016).

On the other hand, the FDA's green light was only obtained during Q1 2016 for Kovaltry. However, we believe the drug could make up the ground lost thanks to 1/ its approval in Europe in February 2016 (i.e. a month before the FDA's green light, thereby making it the second entrant ahead of SHP and CSL) and 2/ the extent of the base of patients using Kogenate, which is the second recombinant treatment on the market, compared with SOBI, which unfortunately cannot benefit from this source of leverage.

Fig. 7: Market share in haemophilia A



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

Fig. 8: Long-acting rFVIII - Timing of approvals

Company	Product	Previous approvals (US and EU)	What's next?
Shire / Baxalta	Adynovate	- US approval in November 2015 for the treatment of adults and adolescents (> 12 years old)	- H1 2017: European approval (adults + children) - H1 2017: US approval for the treatment of paediatric patients
CSL	Afstyla	- US approval in May 2016 for the treatment of adults and children	- H1 2017: European approval (adults + children)
Biogen / SOBI	Eloctate	- US approval in June 2014 for the treatment of adults and children - European approval in November 2015 for the treatment of adults and children	
Bayer	Kovaltry	- US approval in March 2016 for the treatment of adults and children - European approval in February 2016 for the treatment of adults and children	

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

■ BIIB/SOBI: a more difficult ramp-up outside the US?

Eloctate is likely to keep a large share of the US market…

The case of Eloctate is slightly more specific. While we believe Biogen should be capable of consolidating its market share in the US, an eventual success in other regions looks more challenging in the light of recent or forthcoming moves by the competition.

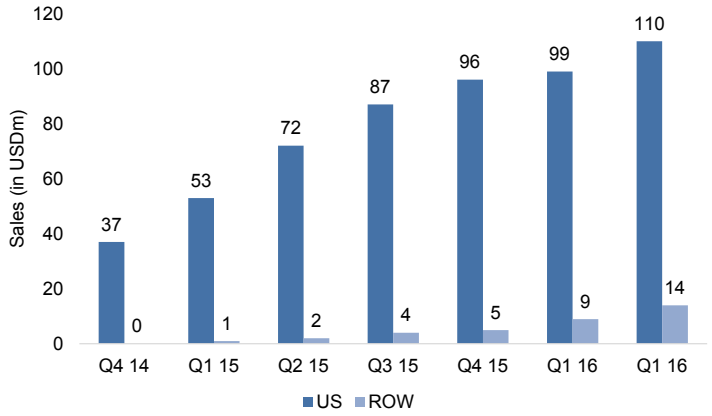
… But the competitive landscape in Europe is less favourable

The fact that it was the only alternative in its class available in the US for almost a year was a clear competitive advantage for its commercial ramp-up in the region (see Fig. 9). However, note that recent publications already revealed a slowdown in growth relative to previous quarters, and we

believe the arrival of a number of other alternatives clearly contributed to the downturn. In addition to this, the launch of Kolvatry is very likely to take a toll (especially since 70% of sales from Bayer's FVIII franchise are generated outside the US).

In all, we estimate that Eloctate's sales are unlikely to exceed USD1.0bn by 2019 (whereas the consensus is expecting more than USD1.5bn) based on the principle that 1/ market share gains in the US are set to be far more limited in coming quarters, and that 2/ the risk of disappointment for growth in Europe is far from zero, especially as of 2017e when Shire and CSL gain access to this part of the world.

Fig. 9: Biogen – Quarterly sales of Elocate



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

2.1.2. More innovative early-stage projects

Over the medium/longer terms however, we have the feeling that the landscape could be radically different in that the most early-stage recombinant FVIIIs should benefit from far longer half-lives. And for the moment, we have identified two of these: 1/ BAX826 at SHP/BXLT, which could be injected virtually once a week or every two weeks, 2/ the XTEN project by Biogen/SOBI, which is set to stand out less for its frequency (once a week) but more for its administration method (subcutaneous). However, in both cases, we have decided not to include the drugs in our forecasts pending the publication of their first clinical data.

- **BAX826: first in class in the market?**

BAX826 is the result of the marriage between the expertise boasted by Shire/Baxalta (the rFVIII part is none other than Advate) and the ability of Xenetic to produce polysialic acid polymers (PSA). **The first Phase I results should be published during H1 2017 and could result in the start of a pivotal Phase II/III trial and marketing approval in 2020.** While all this is still very theoretical, Shire could then possess the first VIII factor that we can genuinely qualify as long-acting, especially if its administration capacity of once every two weeks were to be confirmed.

In our view, the publication should nevertheless provide a substantial catalyst for Shire, first and foremost since the group would then have a therapy based on a coagulation factor (and not a mimetic), benefiting from an administration time-frame as attractive as an ACE910 and secondly, since the market does not necessarily have the project in mind, probably since it is not yet mature on the clinical front.

- **rFVIII-XTEN: what about production costs?**

Like BAX826, rFVIII-XTEN by Biogen and SOBI could potentially be administered once weekly. However, its comparative advantage lies more in its possible subcutaneous administration that we understand would be possible thanks to the fact that it can bind to a von Willebrand factor. The technology behind the extension in the half-life is more complex than with Shire's candidate: in addition to being a factor VIII attached to wWF, it would seem that the complex is not only 1/ joined to an Fc fusion protein (which would reduce intra-hepatocyte clearance, as with Eloctate), but also 2/ covered with an XTEN polymer, certain properties of which are very similar to those of PEG (low immunogenicity, improvement in half-life etc.), while improving others (biodegradable, greater homogeneity etc.).

While this construction looks very promising on paper, we ask ourselves whether it could be far more expensive than its peers. Admittedly, we understand that the addition of an XTEN-type polymer should not cause significant excess costs. But what about the vWF and the Fc fusion protein?

2.2. Patients with inhibitors: where the cards are really set to be redealt

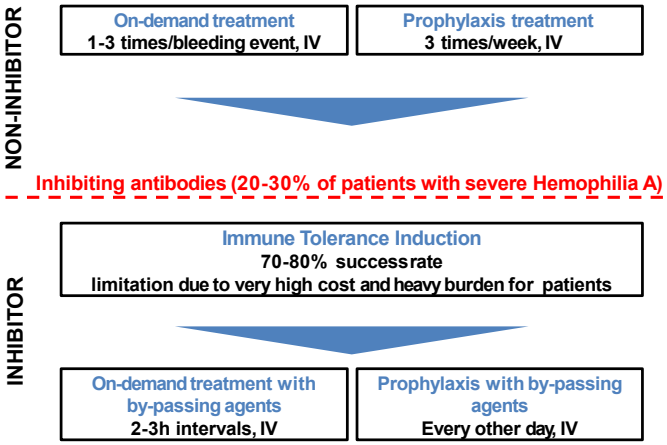
2.2.1. The current SOC: heavy, not particularly efficient and expensive

Between 5% and 20% of all patients can develop inhibitors during the very first weeks of treatment

As we have seen previously, the very large majority of haemophilia A sufferers are pretty well controlled thanks to injections of recombinant factor VIIIs or more simply, human plasma derivatives. However, during the very first weeks of treatment, between 5% and 20% of patients can develop inhibiting antibodies directed against these concentrates, with occurrence far higher in sufferers presenting the most serious form of the disease.

In very concrete terms, a patient with this type of complication does not necessarily suffer from bleeding (indeed, they even tend to bleed less by being far more cautious in their daily lives). However, the risk of death is multiplied by 10 in the absence of an appropriate treatment.

Fig. 10: Haemophilia A - Current SOC depending on inhibitor status



Source: Bryan, Garnier & Co. ests.

The question is whether there is a standard profile of patients that develop these antibodies. A number of factors have been investigated with more or less conclusive results (for example, it is still difficult to draw a conclusion on the risk caused by the origin of the factor used). However, if we limit ourselves to factors for which we are virtually certain, we would say that three of these stand out in particular, beyond the severity of the disease:

- Anomalies affecting the FVIII gene and encouraging the condition, and especially those that are particularly harmful/prevent all synthesis of the protein, and especially concerning: i) extensive deletions affecting several exons (68% risks), and ii) nonsense mutations (50%). It also goes without saying that the existence of a family history is also a fairly important factor.

- Non-Caucasian subjects, and especially those with African origins, are empirically twice as likely to develop inhibiting antibodies.

Fig. 11: Haemophilia A – Inhibitors - Risk factors

Clear evidence of increased risk	
F8 mutation type	Gross genetic abnormalities
	Mutations resulting in a null allele
	Specific missense mutations: R2150H, R2209Q, W2229C
Ethnicity	Afro-Caribbean
Age at first treatment	Treatment before six months age
Treatment during co-existent inflammation	
Weaker or uncertain evidence of increased risk	
HLA type	
F8 polymorphism	
Factor concentrate type	Recombinant products

Source: Gomez, et al (2014); Bryan, Garnier & Co ests.

Two therapeutic strategies are available: the induction of immune tolerance (first-line), and bypassing therapies

What therapeutic alternatives are currently available for this type of patient? In general, we understand that two therapeutic approaches are applied depending on the specific characteristics of each patient (we have deliberately left out Obizur, an rFVIII of porcine origins, due to its label limited to on-demand treatment):

- **Immune tolerance induction (ITI)**

Immune tolerance induction or ITI should be seen as a sort of first-line treatment, fairly well adapted to patients, or with few inhibiting antibodies. The strategy here is fairly simple, namely to regularly inject FVIII in more or less high doses, with the aim being to get the immune system used to the presence of the said factor, and over the long term, to eliminate the inhibitors.

If we go slightly further into the practice, we note that 1/ this approach is apparently the best suited to patients with low inhibitor titers (BU < 5 ideally), 2/ given the excess costs it causes, doctors apparently favour plasma factors rather than their recombinant equivalents for cost reasons, especially since success rates are fairly similar and the duration of the treatment can be spread over several years.

- **Bypassing agents**

Another strategy can be envisaged if ITI fails, or more simply if the number of inhibitors is too high (and consequently, the concentrates are neutralised too rapidly). The therapies implied do not include human FVIII and aim to bypass this need by using 1/ pro-thrombotic complex concentrates (e.g. Feiba at Shire), 2/ animal-based FVIIIs and especially porcine (Obizur), or 3/ activated VIIa factors (NovoSeven).

While these alternatives are fairly efficient in general, note nevertheless that 1/ the risk of thrombosis is far higher than for other treatments (which is potentially problematic if the patient is fairly old), 2/ the administration schedule is not particularly patient-friendly (every eight/12 hours), 3/ the cost is far higher than other options (up to USD1m according to Roche and Shire).

Fig. 12: Bypassing agents currently on the market

	Recombinant FVIIa	Activated prothrombin complex concentrates (aPCC)
Drug names	NovoSeven	Feiba
Contents	Activated FVII	FII, FIX, FX, FVIIa and Fxa
Mechanism of action	Activate FX on platelet surface	Action of FXa and FII
Half-life	2-3 hours	8-12 hours
Bleeding treatment		
Dose/frequency	90-120 µg/kg every 2-3 hours	50-100 U/kg every 8-12 hours
Efficacy	c.80%	c.80%
Prophylaxis		
Dose/frequency	90-270 µg/kg a day	85 U/kg 3 times a week
Efficacy	45-59% reduction in bleeding frequency	62% reduction in bleeding frequency

Source: Kempton et al; Bryan, Garnier & Co ests.

2.2.2. ACE910 by Roche: the first game-changer

ROG's ACE910: a novel mechanism of action, potentially best-in-class for the treatment of patients with inhibitors

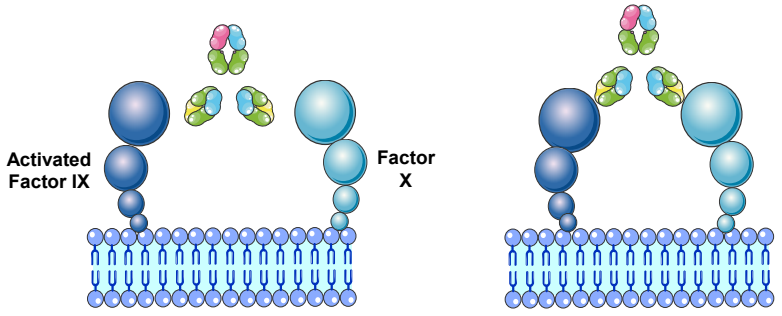
Although we consider that the majority of the haemophilia A market is unlikely to change in coming years, we nevertheless believe that the segment concerning patients with inhibiting antibodies could be overturned with the arrival of new molecules, especially Roche's bispecific antibody ACE910. We have fairly little anteriority on the clinical profile of this candidate, but the results of a small Phase Ib trial were fairly promising:

- By definition, the construction of this candidate cannot be neutralised by anti-FVIII antibodies, and this aspect was confirmed by pharmacokinetic analyses.

- Whatever the patient's inhibitor status, the annualised bleeding rate was zero 1/ in patients having benefited from the highest doses (1 - 3 mg/kg), and 2/ over the entire duration of the study. While this rate is nothing exceptional compared with rFVIII in patients without inhibitors, the differential is nevertheless far more obvious relative to Feiba (whose ABR is closer to eight in a fairly similar setting).

- So far, ACE910 has above all been administered once a week and subcutaneously. However, trials underway also test the possibility of administration every two weeks, which would obviously make it all the more attractive.

Fig. 13: ACE910 – Action mechanism



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: Bryan, Garnier & Co. ests

Fig. 14: ACE910 –Phase I/II data

Treatment Arm	Bleeding events	Median ABR Baseline	Median ABR 12 week follow-up	Median ABR LT follow-up
0.3 mg/kg emicizumab (n=6)	All bleeds	32.5	4.4	1.4
	Joint bleeds	27.4	4.3	1.1
1 mg/kg emicizumab (n=6)	All bleeds	18.3	0	0.2
	Joint bleeds	15.2	0	0.2
3 mg/kg emicizumab (n=6)	All bleeds	15.2	0	0
	Joint bleeds	9.1	0	0

Source: Roche; Bryan, Garnier & Co ests.

- **Peak sales of more than USD1.5bn in the inhibitors segment**

Phase III data should be published at the end of the year, or at the latest during H1 2017. If these confirm what we have seen previously, we believe the project should have no trouble imposing itself as the future standard for those suffering from haemophilia A with inhibitors. Indeed, we estimate that it could generate sales of USD1.5bn in this segment alone, based on the following assumptions:

Fig. 15: BG estimates – ACE910 – haemophilia A inhibitors

	2016e	2017e	2018e	2019e	2020e	2021e	2022e	2023e
Congenital Hemophilia A - Prevalence	**37,000**	**37,370**	**37,744**	**38,121**	**38,502**	**38,887**	**39,276**	**39,669**
- US	15,000	15,150	15,302	15,455	15,609	15,765	15,923	16,082
- Europe	22,000	22,220	22,442	22,667	22,893	23,122	23,353	23,587
- RoW (Japan, Canada)	11,000	11,110	11,221	11,333	11,447	11,561	11,677	11,793
% Severe hemophilia A (FVIII levels < 1%)	70%	70%	70%	70%	70%	70%	70%	70%
% Diagnosed & treated	65%	65%	65%	65%	65%	65%	65%	65%
% Incidence of inhibitors	30%	30%	30%	30%	30%	30%	30%	30%
% High-titer (> 5BU)	70%	70%	70%	70%	70%	70%	70%	70%
% Market penetration - US	0%	0%	20%	40%	55%	65%	60%	45%
% Market penetration - Europe	0%	0%	5%	20%	40%	60%	65%	50%
% Market penetration - RoW	0%	0%	1%	15%	35%	50%	65%	50%
Pricing per patient - US (in USD)	600,000							
Pricing per patient - Europe (in USD)	480,000							
ACE910 - Non-risk adjusted sales (in USDm)	**0**	**0**	**232**	**640**	**1,096**	**1,489**	**1,592**	**1,226**
% var y-o-y		n/s	n/s	176%	71%	36%	7%	-23%
- US	0	0	175	354	492	587	548	415
- Europe	0	0	51	208	420	636	696	541
- ROW	0	0	5	78	184	265	348	270

Source: Bryan, Garnier & Co ests.

- **We also assume that the annual cost from a prophylactic stance could be close to USD600,000** given that this level would show 1/ a slight premium relative to prices for patients without inhibitors (the aim being to not overly reduce the chances of penetrating this other segment), 2/ a significant discount relative to the high-end of the range for a product such as Feiba in terms of inhibitors, which would automatically maximise its penetration potential in this lucrative niche market.

- **In this case, we estimate that almost 65% of patients treated with Feiba or NovoSeven would switch to ACE910 within a very short period** (just three years). However, this rate should then narrow gradually as new alternatives come on the market (such as Fitusiran, and even other FX-FIXa bispecifics).

- As for a large number of other candidate drugs, we assume that the US will be the only region addressed as of H1 2018 if a priority review is obtained, whereas Europe and the rest of the world is unlikely to be targeted before H2 2018, or even H1 2019.

■ **Patients without inhibitors: a more challenging segment**

Whereas we are fairly confident in the ability of ACE910 to take market share from Feiba and NovoSeven, we are more circumspect concerning the segment of patients without inhibitors (bearing in mind that a Phase III trial implying this population is due to be launched). We estimate that it will be difficult to unseat the current standard of care which is simply an injection of the lacking proteins (with a few improvements eventually) and on which we have a degree of perspective whether in terms of efficacy or safety.

Fig. 16: BG estimates – ACE910 – Haemophilia A without inhibitors

	2019e	2020e	2021e	2022e	2023e	2024e	2025e	2026e
Congenital haemophilia A - prevalence	**38,121**	**38,502**	**38,887**	**39,276**	**39,669**	**40,066**	**40,466**	**40,871**
- US	15,455	15,609	15,765	15,923	16,082	16,243	16,405	16,569
- Europe	22,667	22,893	23,122	23,353	23,587	23,823	24,061	24,302
- RoW (Japan, Canada)	11,333	11,447	11,561	11,677	11,793	11,911	12,031	12,151
% Severe haemophilia A (FVIII levels < 1%)	70%	70%	70%	70%	70%	70%	70%	70%
% Diagnosed & treated	65%	65%	65%	65%	65%	65%	65%	65%
% Market penetration - US	2%	3%	4%	5%	5%	5%	5%	5%
% Market penetration - Europe	0%	1%	2%	3%	4%	5%	5%	5%
% Market penetration - RoW	0%	1%	2%	3%	4%	5%	5%	5%
Pricing per patient - US (in USD)	600,000							
Pricing per patient - Europe (in USD)	480,000							
ACE910 - Non-risk adjusted sales (in USDm)	**84**	**203**	**324**	**447**	**529**	**612**	**618**	**624**
% yoy change	n/s	n/s	n/s	38%	18%	16%	1%	1%

Source: Bryan, Garnier & Co ests.

Indeed, it would seem that ACE910 suffers from a lower affinity for FIXs and FX relative to a natural or recombinant FVIII (Kitazawa *et al*, 2012), and that it only has 10% of the latter's catalytic power. We wonder whether this could explain why 1/ cases of dysplasia and vascular proliferation in joints in primate models (Muto *et al*, 2014) and 2/ side effects such as severe mesenteric bruising, were noted in clinical trials (whereas this was never the case with FVIIIs). In addition, it would appear that antibodies directed against ACE910 developed in three patients, but have so far proven to be non-neutralising (no impact on PK or PD).

In all, we assume that the product generates sales of just USD500-600m in this segment.

2.2.3. What impact on Shire and Novo?

For all of the reasons mentioned above, we estimate that sales of Feiba and NovoSeven are likely to take a nosedive once ACE910 comes on the market. However, this impact should be fairly diffuse given the geographical diversity underlying sales performances. Based on this assumption, two factors stand out:

- **Impact well priced in for Shire...**

The impact on Feiba's sales is more than fully priced in…

The market seems to have fully priced in the fact that sales in Shire's inhibitors segment are set to decline as of 2018e. However, we would also note that our forecast is potentially too bearish in that 1/ Feiba and other products addressing this segment "only" generate around 35% of their revenues in the US (and in our assumption for a 9% decline in 2018 overall, this implies a 30% fall in sales in the country as of the first full year of marketing of ACE910), 2/ the impact on the rest of the world, and especially in Europe, should be far slower/diffuse as of 2018e.

Fig. 17: Shire – Haemophilia and inhibitors - sales estimates (2015-2020^{e})

(USDm)	2015	2016e	2017e	2018e	2019e	2020e
Inhibitors (Feiba, Obizur, etc.)	**787**	**957**	**987**	**903**	**632**	**450**
% yoy growth	6%	22%	3%	-9%	-30%	-29%
% change CER	16%	22%	3%	-9%	-30%	-29%
- US	**295**	**326**	**326**	**228**	**160**	**120**
in % of inhibitors	37%	34%	33%	25%	25%	27%
- ROW	**492**	**631**	**661**	**675**	**472**	**331**
in % of inhibitors	63%	66%	67%	75%	75%	73%
Haemophilia (Advate, Adynovate, Vonvendi, etc.)	**2,840**	**2,937**	**3,108**	**3,217**	**3,202**	**3,108**
% growth yoy	-5%	3%	6%	3%	0%	-3%
% chg CER	4%	4%	6%	3%	0%	-3%
- US	**1,339**	**1,410**	**1,523**	**1,584**	**1,536**	**1,459**
in % of Haemophilia	47%	48%	49%	49%	48%	47%
- ROW	**1,501**	**1,527**	**1,585**	**1,633**	**1,665**	**1,649**
in % of Haemophilia	53%	52%	51%	51%	52%	53%

Source: Bryan, Garnier & Co ests.

■ **… But potentially underestimated for Novo**

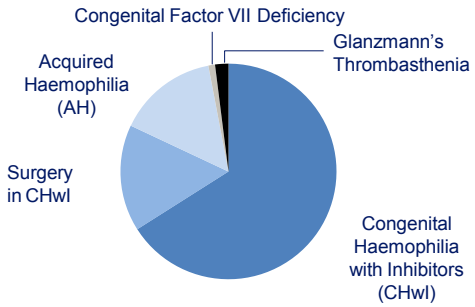
… Which is less the case for NovoSeven

On the other hand, the consensus on NovoSeven looks far more optimistic predicting falls of just 3% and 5% in 2018 and 2019, whereas the product's positioning is similar to that of Feiba and almost 40-50% of its sales stem from the US.

Maybe this is because the market is above all obsessed with issues that the group is encountering in diabetes (and we can understand this really since the segment is the main generator of sales). However, we believe that things should change once Novo's management has provided guidance including this new entrant (potentially when 2016 earnings are reported, especially if Phase III results for ACE910 are published before this communication).

Fig. 18: NovoSeven positioning

NovoSeven® RT US sales across indications[1]



US indications and key dynamics

NovoSeven® RT US indications

- Congenital Haemophilia with Inhibitors (CHwI)
- Surgery in CHwI
- Acquired Haemophilia (AH)
- Congenital Factor VII Deficiency
- Glanzmann's Thrombasthenia

NovoSeven® RT key dynamics

- First and only recombinant bypassing agent
- Market value share leader, ~75%
- Small CHwI patient population, impacted by Immune Tolerance Induction (ITI) and clinical trial enrollment

Source: Novo Nordisk

Fig. 19: NovoSeven – BG vs consensus sales estimates

(DKKm)	2015	2016e	2017e	2018e	2019e	2020e	2021e
NovoSeven - consensus estimates	10,064	10,825	11,017	10,675	10,138	9,619	9,483
% yoy change		8%	2%	-3%	-5%	-5%	-1%
NovoSeven - BG estimates	10,064	9,306	8,613	7,955	7,248	6,386	5,633
% yoy change		-8%	-7%	-8%	-9%	-12%	-12%
BG vs consensus	**0%**	**-14%**	**-22%**	**-25%**	**-29%**	**-34%**	**-41%**

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

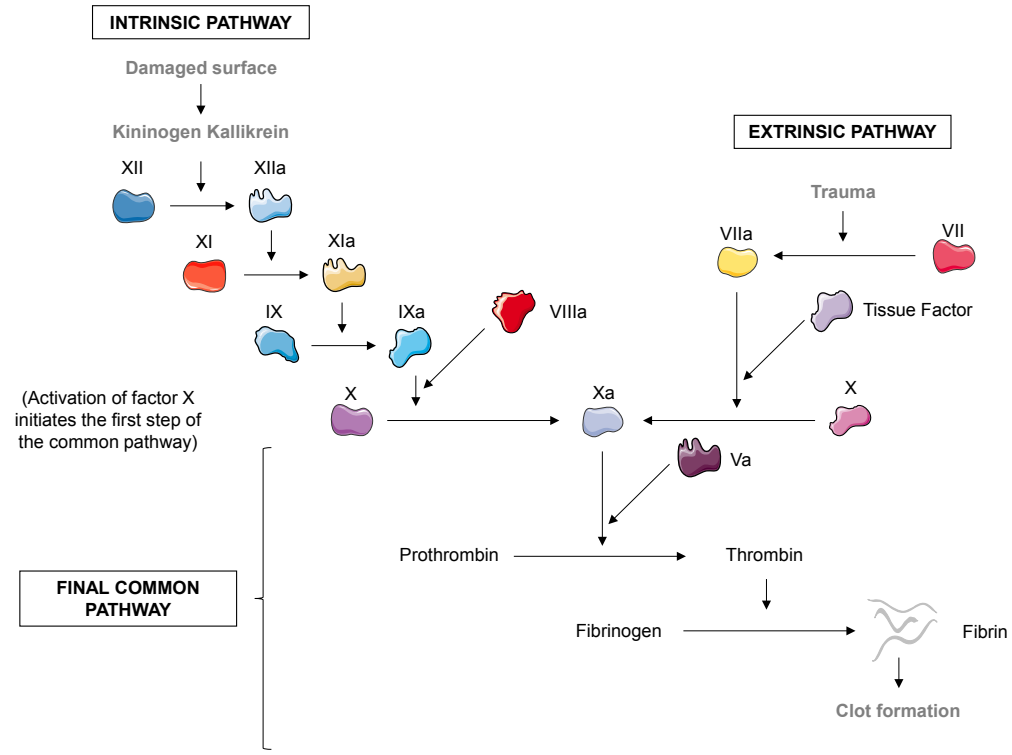
Whatever the case, the impact of ACE910 could be significant for Novo's EPS. Indeed, NovoSeven should account for around 8% of the group's sales this year, although we estimate that its contribution to EBIT should stand more at between 10% and 15%e. In a backdrop where pressure on prices is constantly rising in the diabetes segment, operating leverage is likely to come under pressure in coming years.

2.3. Other early-stage approaches to watch

The market and various brokers have placed particular importance on ACE910, but we estimate that other early-stage molecules (including Fitusiran and the various gene therapies in development) deserve just as much attention.

Fitusiran by Alnylam is a small molecule that interferes with RNA production (this being a functional copy of DNA at the origin of protein production), **and more precisely that associated with anti-thrombin.** The idea behind this mechanism is fairly simple: apart from the fact that patients suffer from a lack of FVIII, it would appear that the disease is also linked to an insufficient generation of thrombin (a protein that also plays a major role in blood clotting). Rather than injecting a lacking/deficient factor, the aim here is to undermine another factor in the clotting process with the ability of inhibiting thrombin production.

Fig. 20: Coagulation pathway



Source: Bryan, Garnier & Co. ests.

Although the first clinical data obtained on this project stemmed from small cohorts, it was fairly promising. Apart from the fact that median ABR came in at zero in the C part of the study (rising dosage from 225 to 1800 mcg/kg, fixed dose of 80 mg, 18 patients), note that this rate was obtained with 1/ a monthly subcutaneous administration and 2/ in patients with/without inhibitors suffering from haemophilia A or B.

However, as for ACE910, we are fairly cautious concerning the safety of use of this candidate … and especially concerning the risk of thrombosis over a long duration and under the framework of a prophylactic treatment. We would also point out that one of the patients receiving a dose of 80 mg/kg was removed from the study following a severe case of chest pain (also accompanied by increases in ALT, AST and C-protein rates among others).

Fig. 21: Comparison of Fitusiran vs ACE910

	Fitusiran (RNA interference)	ACE910 (bispecific FIXa-FX)
Evidence for reduced ABR	Yes	Yes
Potential indications	Haemophilia A Haemophilia B Other bleeding disorders	Haemophilia A
Administration & volume	Subcutaneous <1mL	Subcutaneous >1mL
Frequency	Once monthly	Once weekly
Development of ADA	None - 0%	3/18 patients - 17%
Storage conditions	Room temperature	Refrigeration

Source: Alnylam; Bryan, Garnier & Co ests.

3. Haemophilia B

Our contact with CSL Limited showed in particular the fact that Idelvion (recombinant fusion protein linking an rFIX to albumin) could be the current best-in-class in treatment of haemophilia B (longer acting, top-notch clinical data). With the lack of a genuine first-mover advantage, we estimate that ex-US peak sales for Alprolix (and especially in territories where SOBI has rights to the product) should not be as spectacular as in the US.

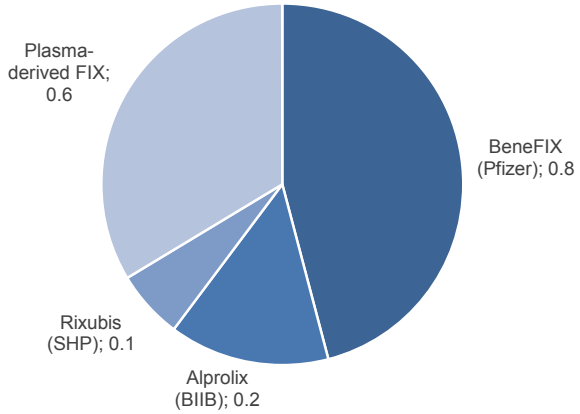
3.1. An historically less crowded market

Haemophilia B vs A: a different clotting factor involved, a less frequent prevalence and a much reduced risk of inhibitors

Haemophilia B stands out fundamentally from haemophilia A by the type of clotting factor missing (FIX vs. FVIII). However, the eventual differences do not stop there and it is important to note that 1/ its prevalence is even less frequent (only 5,000 sufferers in the US vs. 15,000 for haemophilia A), 2/ the genetic mutations underlying the pathogenesis are fairly different (and this could also explain why B cases are often less serious), 3/ the risks of developing inhibiting antibodies are far lower, even in patients the most severely affected (1-5% vs. 20-30%).

Given the differences in terms of prevalence, the market for this disease is clearly less lucrative than that of haemophilia A. Recent estimates are also fairly close to USD1.5bn, bearing in mind that 1/ BeneFIX by Pfizer was the only recombinant alternative available until 2013 (the year when Baxalta's Rixubis was approved), 2/ plasma products such as Alphanine by GFS and Octanine by OctaPharma.

Fig. 22: Haemophilia B market (2015e)



Source: Bryan, Garnier & Co. ests

3.2. A more marked advent of long-acting products

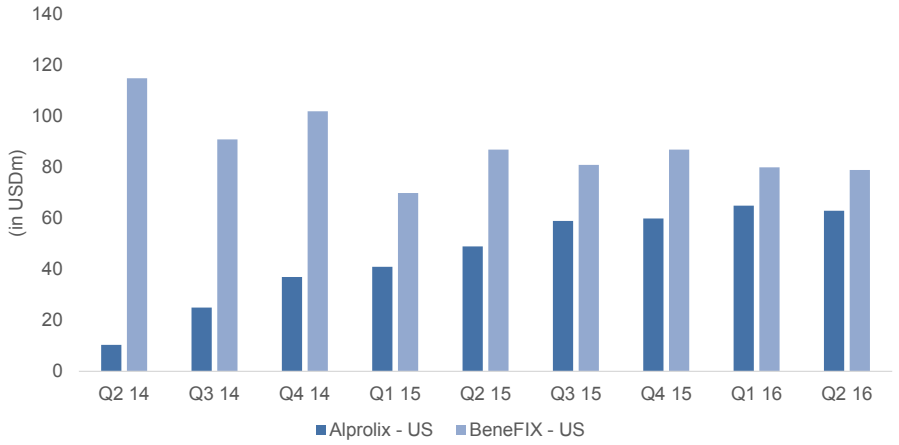
The switch to longer-acting therapies for this disease is likely to be more rapid and significant

Here again, recombinant approaches that are more or less long-acting have also been developed. However, contrary to what we have seen in haemophilia A, we estimate that patients could **switch to long-acting treatments more rapidly and more widely** given that 1/ the half-life difference is close to 5x vs. 1.5x for haemophilia A, such that the treatment intervals are far more spaced out, 2/ the annual cost for a patient under preventive treatment (which is in our view the first target for these new therapies) is fairly close to that of BeneFIX…

Proof of this lies in the fact that **Alprolix generated USD209m in sales as of its first full year of marketing in the US** (vs USD308m for Eloctate, whereas the addressable market for this drug is far narrower), and that sales of BeneFIX were under pressure in the same time-lapse.

In addition, it is not impossible that all of this could contribute to **preventive treatments becoming far more widespread,** while upside is far from negligible since 1/ almost 60% of patients suffer from a severe form (and are by definition the best candidates for this type of approach), 2/ the percentage of patients under prophylaxis still only stands at 30-40% irrespective of the type of disease.

Fig. 23: BeneFIX (short-acting) and Alprolix (long-acting) sales



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

3.3. Idelvion by CSL: the current best-in-class?

Idelvion: best-in-class clinical data, and the most flexible administration schedule

We also estimate that there is a clear winner among the various treatments developed for B haemophiliacs, namely Idelvion by CSL (rFIX linked to a recombination albumin), for which the Phase III study has provided efficacy data that we consider as best-in-class:

Fig. 24: Haemophilia B – Recombinants marketed or in development

Drug	Company	Mechanism of action	Stage	Administration	Median ABR (prophyl.)
Rixubis	Shire	Recombinant FIX	Commercialised	Twice-weekly	2.0
BeneFIX	Pfizer	Recombinant FIX	Commercialised	Twice-weekly	2.0
Alprolix	Biogen	Recombinant FIX linked with to the Fc portion of IgG1	Commercialised	Every 7 or 10 days	2.25-3.13
N9-GP	Novo	Recombinant glycoPEGylated FIX	Registration	Once-weekly	1.00-1.36
Idelvion	CSL	Recombinant FIX linked to albumin	Commercialised	Every 1, 2 or 3 weeks	0.00-1.08

Source: Company Data; Bryan, Garnier & Co ests

- **The most efficient**: the average annualised rate of haemorrhages stood at 0, 0 and 1.08 in patients under preventive treatment receiving the product every seven, 10 or 14 days (zero for all doses combined if we limit the study to spontaneous bleeding). In absolute terms, this compares more than favourably to other approaches used in this setting, and with a fairly benign toxicity profile.
- **The most flexible**: the fact that it can be administered on a twice-weekly basis is already a significant advantage relative to other alternatives on the market or in development (Alprolix

by Biogen/SOBI for example is only injected once a week). However, various analyses suggest that administration every three weeks is quite foreseeable.

We would nevertheless admit that an eventual administration every 21 days seems above all possible in older patients bearing in mind that the over-18s represent around 50% of the pool of haemophilia patients in the US. This needs to be confirmed by another wider-reaching study before being integrated into the product's label. However, the CSL product is currently the only recombinant FIX for which an interval of this length has been tested in clinical trials.

Fig. 25: Idelvion - efficacy profile (extension study)

Study 3001	**7-day regimen (n=40)**	**10-day regimen (n=7)**	**14-day regimen (n=21)**	**21-day regimen (n=0)**
Median annualised spontaneous bleeding rate	0 (0, 0)	0 (0, 0)	0 (0 ,1.0)	
Estimated mean AsBR	0.65 (0.37 - 1.13)	0.56 (0.27 - 1.17)	0.83 (0.38 - 1.77)	
Duration, median (days)	269	240	386	
Study 3003	**7-day regimen (n=19)**	**10-day regimen (n=14)**	**14-day regimen (n=39)**	**21-day regimen (n=10)**
Median annualized spontaneous bleeding rate	0.85 (0, 2.9)	0 (0, 0.5)	0 (0 ,1.24)	0 (0, 0)
Estimated mean AsBR	191 (1.09 - 3.36)	0.31 (0.14 - 0.70)	0.88 (0.47 - 1.65)	0.45 (0.07 - 2.98)
Duration, median (days)	309	650	491	442
. Patients who completed two previous studies (3001 or 3002) were included . Treatment intervals could be extended to 10 or 14 days with 50-75 IU/kg for all patients . Adult patients (≥ 18 years old) who were well controlled on a 14-day regimen could switch to a 21-day interval with a 100 IU/kg dose				

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

Fig. 26: Idelvion - toxicity profile

MedDRA standard system organ class	**Adverse reactions**	**Subjects (n=111)**
Nervous system disorders	Headache	2 (1.8%)
	Dizziness	1 (0.9%)
Immune system disorders	Hypersensitivity	1 (0.9%)
Skin and subcutaneous tissue disorders	Rash	1 (0.9%)
	Eczema	1 (0.9%)

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

3.1. Limited impact for Novo, Grifols and Shire, but more pronounced for SOBI

Novo, Grifols and Shire are not so exposed to Haemophilia B

Without going into too much detail, we would say that **Shire, Grifols and Novo have fairly little exposure to haemophilia B** thereby automatically limited the risks to their earnings. There are two reasons for this: 1/ Rixubis (SHP) and Alphanine (GFS) each generate less than USD200m in annual sales, suggesting that less than 5% of the top line at both groups is derived from the indication. 2/ N9-GP (NOVO) is not set to be marketed before 2017e, and forecasts do not look sufficiently significant to trigger eventual concerns (peak sales of around USD180m).

Fig. 27: N9-GP sales estimates - BG vs consensus

(DKKm)	2015	2016e	2017e	2018e	2019e	2020e	2021e
N9-GP - consensus estimates	0	0	298	551	824	1,035	1,202
% var y-o-y		n/s	n/s	85%	50%	26%	16%
N9-GP - BG estimates	0	0	467	771	1,001	1,124	1,170
% yoy chg		n/s	n/s	65%	30%	12%	4%
BG vs consensus	**n/s**	**n/s**	**57%**	**40%**	**21%**	**9%**	**-3%**

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

SOBI's Alprolix is at risk…

Meanwhile, SOBI seems slightly more exposed (Alprolix accounts for around 20-30% of forecasts for the entire haemophilia franchise). We even believe that consensus forecasts are slightly too high given that 1/ Idelvion and Alprolix were both approved by the European authorities in May this year, with similar labels (meaning that the SOBI product does not boast the first-mover advantage here, contrary to the US), 2/ the BIIB/SOBI candidate is objectively less attractive in terms of both efficacy and administration schedule, 3/ as of next year, the market will have to count on the contribution of N9-GP by Novo.

In any case, we believe that an eventual de-rating of the SOBI share could be triggered by 1/ the announcement of earnings guidance for 2017 (with the consensus currently expecting consolidated revenues of SEK6.3bn) and 2/ forthcoming quarterly publications by CSL, and especially if management's comments confirm aggressive market share gains.

Fig. 28: Long-acting rFIX - Timing of approvals

Company	Product	Previous approvals and labels (US and EU)	What's next?
CSL	Idelvion	- US and EU approval respectively in March 2016 and May 2016 (prophylaxis, on-demand, perioperative management in adults and children)	
Biogen / SOBI	Alprolix	- US and EU approval respectively in March 2014 and May 2016(prophylaxis, on-demand, perioperative management in adults and children)	
Novo Nordisk	N9-GP	- Filing for regulatory approval in the EU and in the US respectively in January and May 2016	- H1 2017: European and US approval

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

4. Gene therapies: still too early to say

On paper, gene therapies are treatments that very clearly carry the highest breakthrough potential, whether from a therapeutic viewpoint (given that they could potentially help to cure the disease whereas drugs currently available are merely palliative), or from a medico-economic stance (making prophylactic and repetitive treatments redundant). Contrary to what some may think, they could be commercially available as of the beginning of the next decade (as of 2020 or 2021 in haemophilia B).

That said, we also believe that these new therapies cannot become widespread given the toxicity profile caused by the use of a viral vector. Even if development focuses have been clearly identified, we struggle to see a genuine shake-up in the therapeutic landscape prompted by the eventual arrival on the market of the most advanced projects. For this reason, **we have preferred not to factor them into our forecast models for the companies concerned (Shire especially),** or at least pending data for a large number of patients over a long period of time.

4.1. A genuine source of hope...

Gene therapy is a fairly old concept, the scientific and industrial interest of which has above all emerged in recent years, probably following the approval of the first two therapies of this type (Gencidine in 2004 and Glybera by GSK in 2012), combined with various stages of progress (development of new vectors, greater ability/flexibility in terms of manufacturing, accumulation of clinical data etc.).

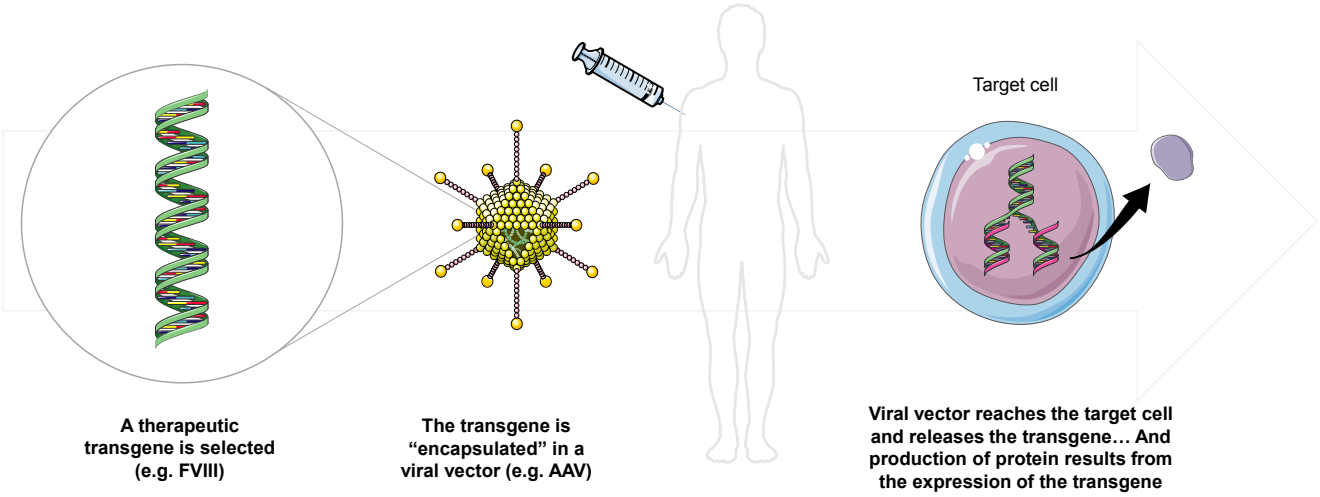
From a purely theoretical viewpoint, diseases characterised by genetic deficiency (unique or not) could be cured on a more or less lasting basis. The aim is relatively simple, namely to deliver the missing or deficient gene to the sick cells (*ex vivo* or *in vivo*). Given the relative simplicity of the procedure (since it is monogenic), haemophilia is one of the few areas for which pharmaceutical companies have expressed clear interest alongside opthalmology (retinopathies).

Fig. 29: Gene therapies developed in haemophilia

Company	Candidate	Clinical stage	Vector
Haemophilia A			
Shire/Baxalta	BAX 888	Preclinical	AAV8
Biomarin	BMN 270	Phase I/II	AAV?
Spark/Pfizer	SPK-H1	Preclinical	AAV8
Dimension	DTX201	Preclinical	AAV?
Biogen	No name	Preclinical	Lentivirus
Haemophilia B			
Shire/Baxalta	BAX335	Phase I/II (discontinued)	AAV8
Spark/Pfizer	SPK-FIX	Phase I/II	AAV?
Dimension	DTX101	Phase I/II	AAV?
UniQure	AMT-060	Phase I/II	AAV5

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

Fig. 30: Gene therapy - action mechanism

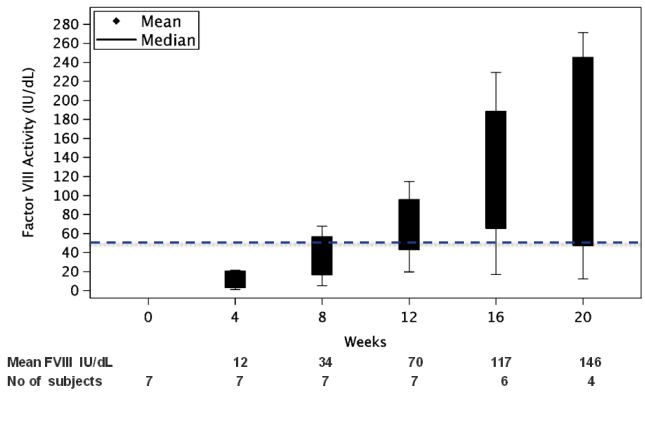


Source: Bryan, Garnier & Co. ests

The theory is now being put into practice, 1/ numerous candidates are already being tested in humans, and 2/ a number of big pharmas and biotechs have signed agreements with smaller companies in order to get their hands on this type of project. One of the most noticeable examples was Pfizer's partnership with Spark Therapeutics in haemophilia B (upfront payment of USD20m and milestones of up to USD260m).

Biomarin recently presented clinical data implying BMN 270 (which uses adeno-associated viruses or AAV) in haemophilia A, and showing more than encouraging efficacy results in that 1/ the level of FVIII should theoretically be higher than 50 IU/dL for articular bleeding to be generally minimised (Den Uijl *et al*, Hemophilia 2011), 2/ BMN270 clearly exceeded this threshold at the highest doses and we would even note that responses improved over time (see Fig. 31).

Fig. 31: BMN270 (high dose) – FVIII levels



Source: BioMarin; Bryan, Garnier & Co. ests

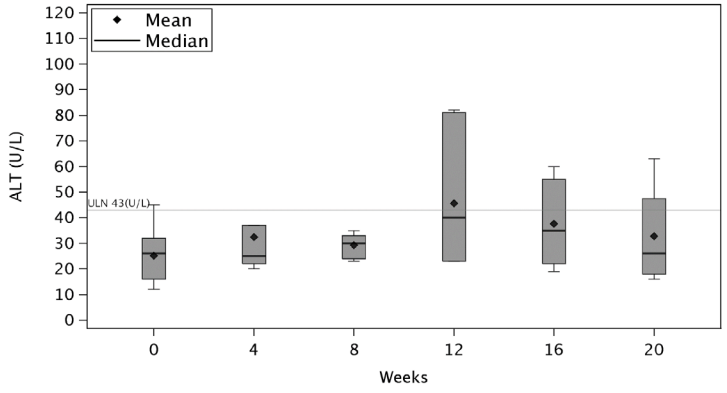
4.2. But a still unsatisfactory safety profile

Admittedly, these new therapies present numerous theoretical advantages and a number of candidates have generated very encouraging clinical data. However, we believe that the practice is still set to face a number of issues associated with the very construction of these compounds.

The use of a viral vector is and will remain the main subject in coming years, whether for haemophilia treatment or other indications. On the one hand, we know that this type of vector is fairly immunogenic, such that 1/ a CD8+ immune response can be initiated against the vector itself, but also cells in the liver that have been infected/transduced (hence an increase in ALT type hepatic enzymes), and that, 2/ in certain cases, patients have pre-existing antibodies limiting transduction, especially if the vector is an adeno-associated (AAV) virus.

We understand that the issue of neutralising antibodies was partly addressed by the choice of AAV sub-types to which the vast majority of patients are unlikely to react given the lesser exposure to a wild-type virus (Mingozzi *et al*, 2013). Although the majority of candidates in development use AAV sub-types, note that Biogen made the original choice of focusing on lentiviruses. On paper these viruses could be a good alternative to the extent that 1/ they penetrate fairly well the cells characterised by a low division such as neurones and hepatocytes (contrary to retroviruses), 2/ expression levels for the target protein can theoretically be more stable. That said, no real solution has so far been provided for that of immune response beyond the simple monitoring of hepatic enzymes and administration of immuno-suppressants (which is also not viable over a long period due to the risks associated with them).

Fig. 32: BMN270 (high dose) – impact on ALT levels



Source: BioMarin; Bryan, Garnier & Co. ests

Last but not least, these new therapies theoretically present the same risk of development inhibitors as classic substitutive treatments, and especially in haemophilia A. Admittedly, AAV's benefit from greater capacity in terms of DNA transport than other vectors, and especially relative to retroviruses. However, it would seem that this is not enough to transport an FVIII gene similar to the native form, such that the genes inserted are smaller in size. For the moment, this risk has not really been confirmed/observed in clinical trials, but we would note that the various trials did not include patients already treated with FVIIIs.

BRYAN, GARNIER & CO

INDEPENDENT RESEARCH UPDATE

19th October 2016

Shire PLC

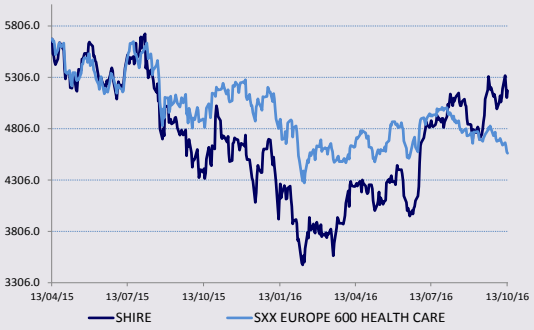
Re-rating still underway!

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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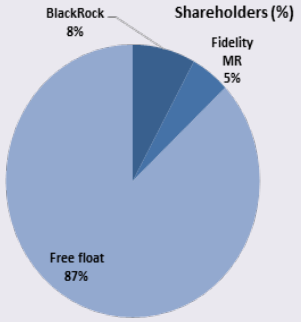

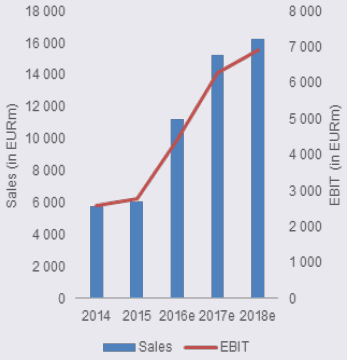

Company description

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).

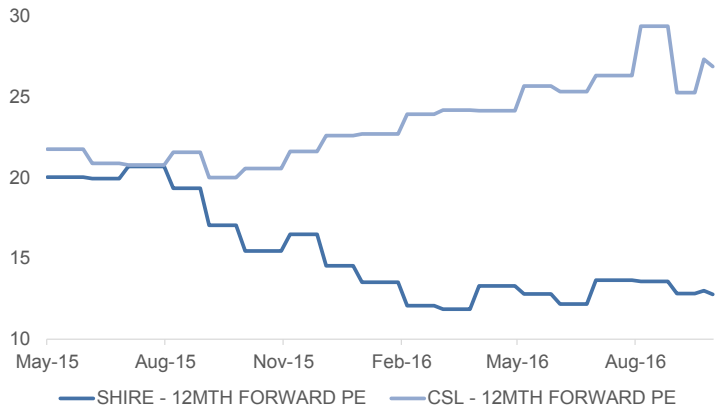
We also remain convinced that the discount relative to CSL is not only unjustified but also that it should gradually narrow in favour of SHP given that the two companies' fundamentals do not seem significantly different as a whole. From our viewpoint, three catalysts should participate especially in 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

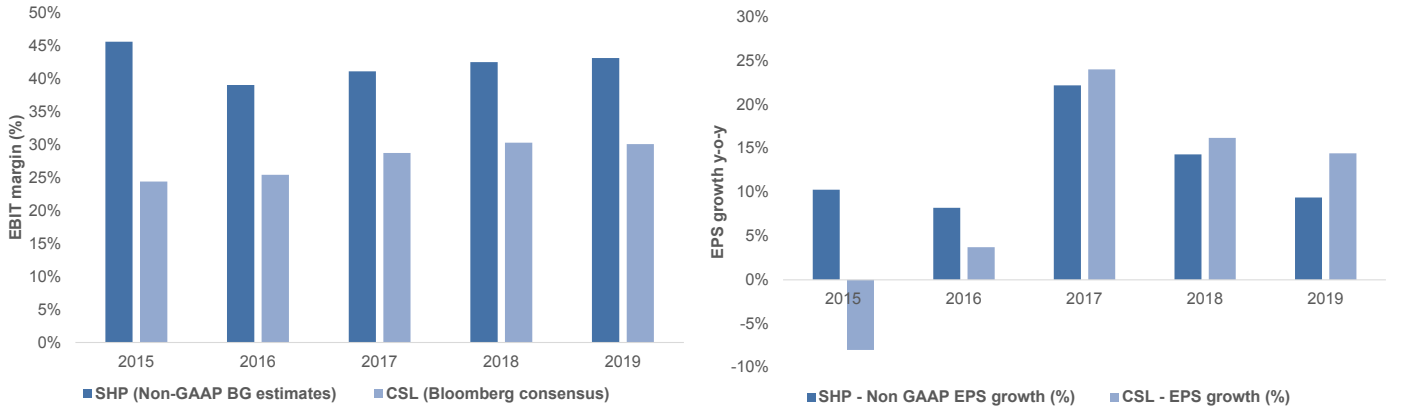


Source: Thomson Reuters; Bryan, Garnier & Co. ests.

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),

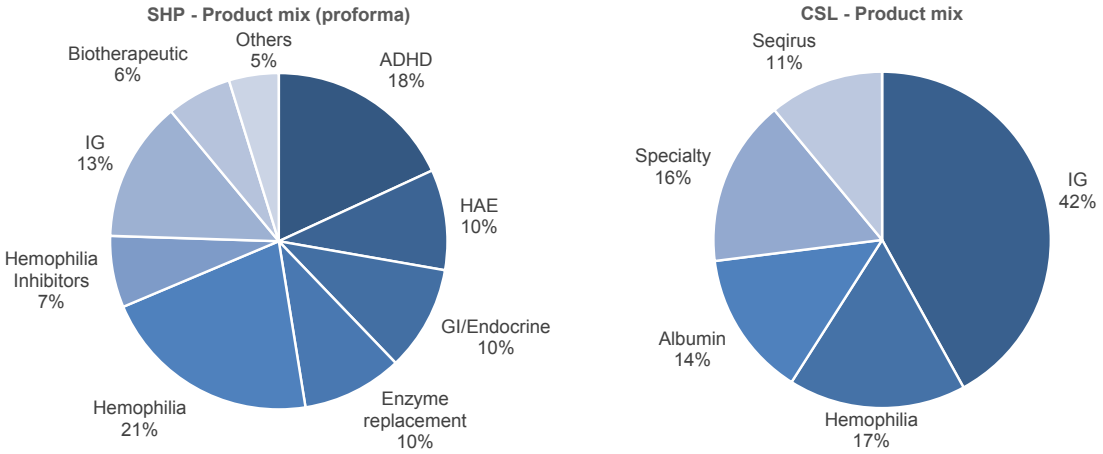
including Hizentra, and 2/ growth in historical franchises such as ADHD and HAE (see our initiation report here for further details).

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

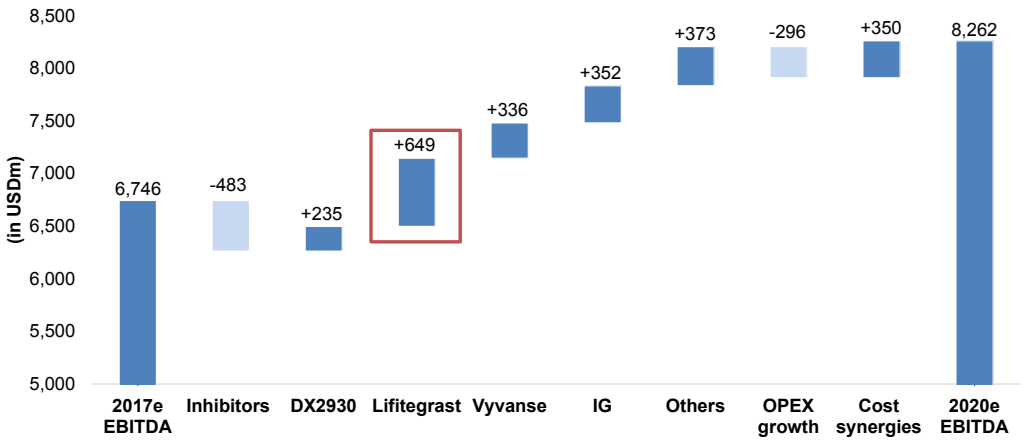
ACE910 is clearly set to have a substantial impact on sales in the inhibitors franchise and the fact that Feiba is a high-margin product (gross margin of around 90%) makes it a palpable source of concern for investors. However, we should not under-estimate the diversity in the group's pipeline, its positioning 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%

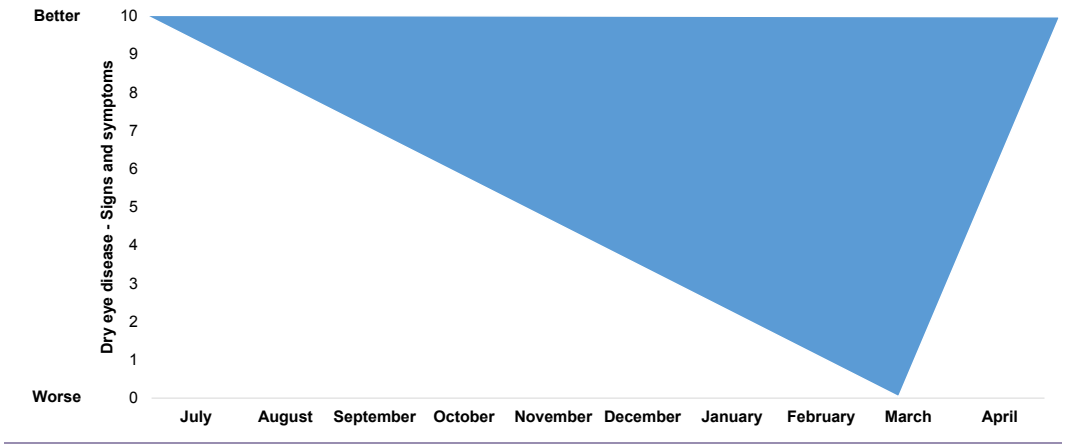
Source: Bryan, Garnier & Co ests.

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

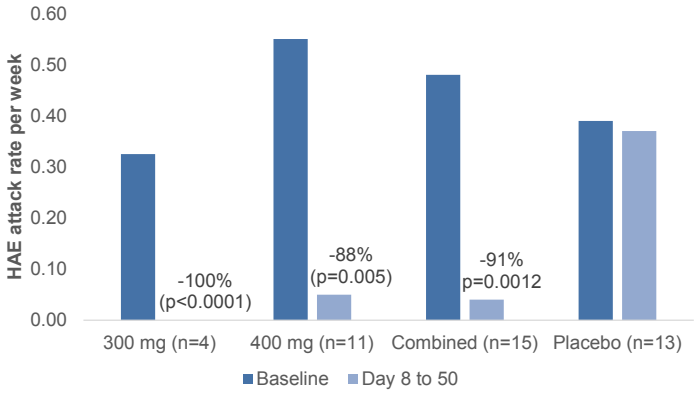
- **A potential new best-in-class in HAE**

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).

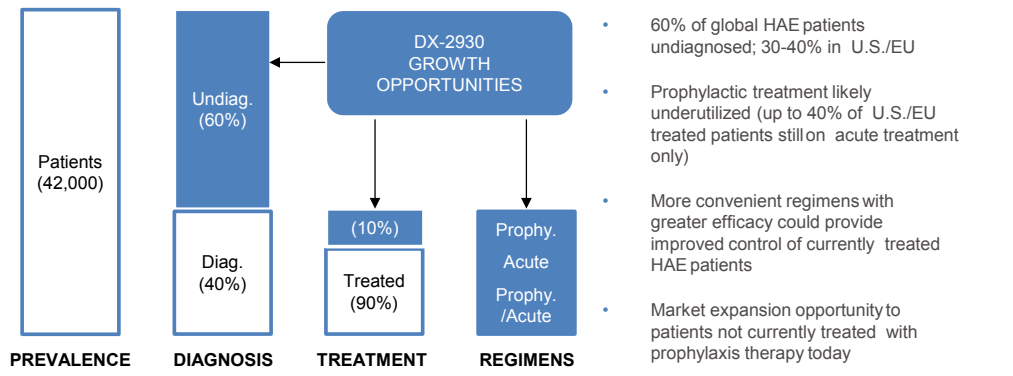
Given this, we estimate that a large portion of patients treated with Cinryze could rapidly be switched to this new approach (which would be positive for margins, since a monoclonal antibody is far less complex and expensive to produce than a plasma derivative). More efficient and more convenient, it 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

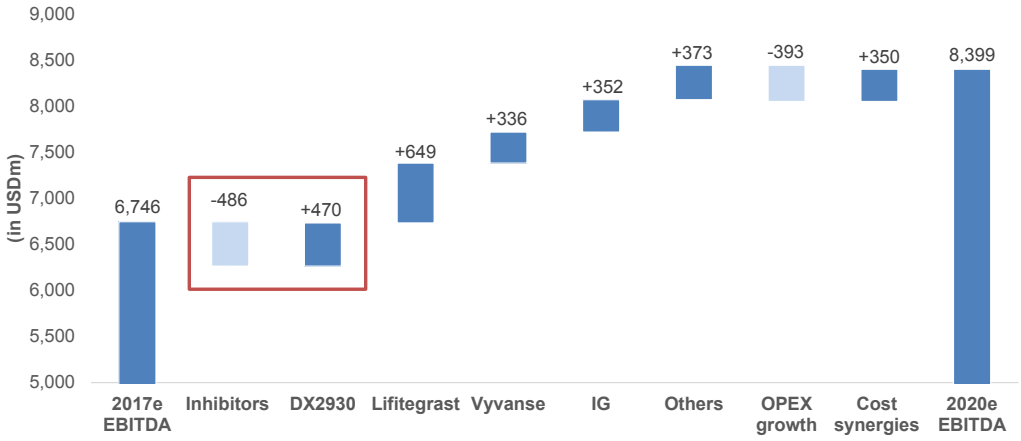
An important point to note: our sales assumptions for this project are currently adjusted for clinical risk, and more precisely, we only take into account 50% of its potential pending its approval (BG: 2018e). If it is approved, we estimate that its commercial launch should enable the group to fully 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.

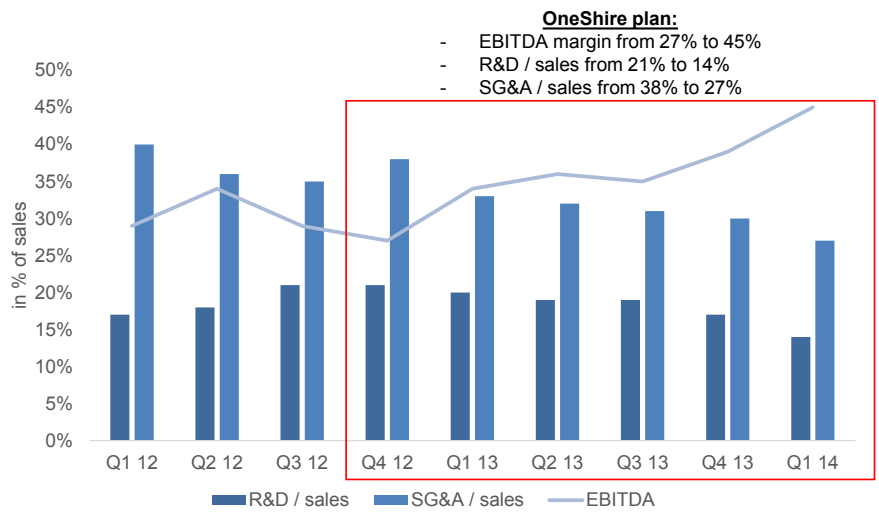
2.2. Remember OneShire…

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



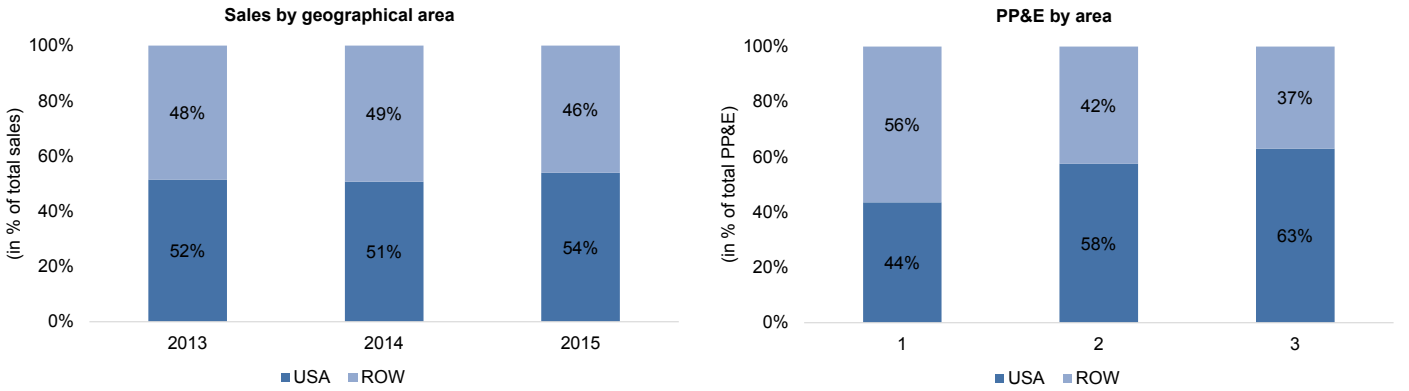
Source: Shire; Bryan, Garnier & Co. ests

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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BRYAN, GARNIER & CO

INDEPENDENT RESEARCH

17th October 2016

Grifols

¡El consenso al borde de un ataque!

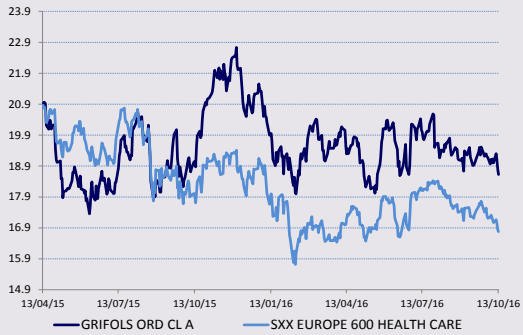
Healthcare

Fair Value EUR20 (price EUR18.63)

NEUTRAL
Coverage initiated

Bloomberg	GRF SM
Reuters	GRF.MC
12-month High / Low (EUR)	22.7 / 18.0
Market capitalisation (EURm)	11,509
Enterprise Value (BG estimates EURm)	15,083
Avg. 6m daily volume ('000 shares)	801.3
Free Float	63.0%
3y EPS CAGR	8.5%
Gearing (12/15)	113%
Dividend yields (12/16e)	1.66%

YE December	12/15	12/16e	12/17e	12/18e
Revenue (EURm)	3,935	4,033	4,250	4,447
EBIT(EURm)	970.34	976.04	1,041	1,125
Basic EPS (EUR)	0.78	0.86	0.91	0.99
Diluted EPS (EUR)	0.78	0.86	0.91	0.99
EV/Sales	3.87x	3.74x	3.49x	3.26x
EV/EBITDA	13.1x	12.8x	11.8x	10.7x
EV/EBIT	15.7x	15.5x	14.2x	12.9x
P/E	24.0x	21.6x	20.6x	18.8x
ROCE	6.9	7.5	7.8	8.4



We are initiating coverage of Grifols with a Neutral recommendation and a Fair Value of EUR21. The company is far from lacking in qualities but 1/ its valuation looks demanding (2017e P/E of 20x), and 2/ forthcoming newsflow is not particularly exciting (readout in Alzheimer's, clinical announcements by rivals in haemophilia and immunoglobulins). Hence our caution…

- **An under-estimated risk of deceleration.** Although our forecasts are generally in line with those of the consensus for the current year, we are nevertheless far more cautious on growth prospects as of 2017e. In addition to the fact that we are probably more cautious on the recovery in the diagnostics segment, we believe that the market under-estimates 1/ the impact of the label extension in subcutaneous immunoglobulins for the treatment of chronic inflammatory demyelinating polyneuropathy or CIDP (to which GFS is significantly exposed), and especially as of 2018e, and 2/ the risk of market share losses for Alphanate and other plasma-derived FVIIIs in favour of ROG's ACE910 (and eventually Eloctate/Elocta by SOBI/BIIB).

- **Operating leverage will have to wait.** While the outlook is generally positive, we believe EBITDA margin should remain under pressure (around 29-30% in 2017e vs. 31-33% in normal average terms) given 1/ the expansion in the group's activities, and 2/ persistent pressure on US revenues in the diagnostics business.

- **Neutral with a FV of EUR20.** With 2017e P/E of 20x, GFS is trading on a premium of 10% relative to the European pharma segment. This leaves little room for an eventual disappointment. In addition, given the news flow we anticipate (Phase III for Hizentra in CIDP and ACE910 in haemophilia with inhibitors in Q4 2016, readout of Albutein in Alzheimer's, etc.), we prefer to take a cautious stance on the share.

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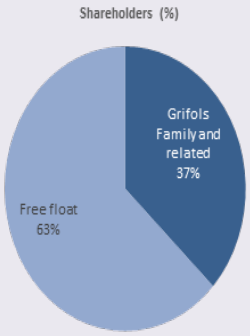
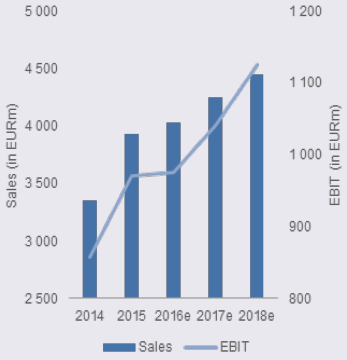




Company description

Grifols is a Spanish healthcare company which develops, manufactures and markets plasma derivatives. These are human proteins extracted from the blood of donors that are used to treat various diseases such as immune deficiencies or haemophilia.

Simplified Profit & Loss Account (EURm)	2014	2015	2016e	2017e	2018e	2019e	2020e
Revenues	3,355	3,935	4,033	4,250	4,447	4,625	4,825
Change (%)	*-%*	*17.3%*	*2.5%*	*5.4%*	*4.6%*	*4.0%*	*4.3%*
Adjusted EBITDA	1,047	1,163	1,178	1,258	1,356	1,438	1,491
EBIT	858	970	976	1,041	1,125	1,193	1,231
Change (%)	*-%*	*13.1%*	*0.6%*	*6.7%*	*8.0%*	*6.1%*	*3.1%*
Financial results	(261)	(272)	(244)	(232)	(228)	(217)	(204)
Pre-Tax profits	590	690	769	809	897	977	1,026
Exceptionals	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tax	123	159	177	186	215	234	246
Profits from associates	NM	NM	NM	NM	NM	NM	NM
Minority interests	NM	NM	NM	NM	NM	NM	NM
Net profit	470	532	592	623	682	742	780
Restated net profit	470	532	592	623	682	742	780
Change (%)	*-%*	*13.2%*	*11.2%*	*5.3%*	*9.4%*	*8.9%*	*5.1%*
Cash Flow Statement (EURm)							
Operating cash flows	638	721	793	840	913	987	1,041
Change in working capital	(341)	(21.4)	(67.5)	58.5	53.1	48.1	54.1
Capex, net	252	266	226	255	267	278	290
Financial investments, net	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Dividends	156	217	213	237	249	273	297
Other	(201)	(206)	(461)	(105)	(105)	(415)	(154)
Net debt	3,270	3,718	3,574	3,314	3,001	2,642	2,271
Free Cash flow	727	476	635	526	593	662	697
Balance sheet (EURm)							
Tangible fixed assets	1,148	1,644	1,669	1,707	1,742	1,775	1,804
Intangibles assets	4,243	4,694	4,694	4,694	4,694	4,694	4,694
Cash & equivalents	1,079	1,143	1,104	1,288	1,527	1,501	1,747
current assets	1,834	1,947	1,896	1,998	2,090	2,174	2,268
Other assets	1,225	1,316	1,556	1,770	2,039	2,043	2,320
Total assets	8,450	9,602	9,814	10,169	10,566	10,686	11,085
L & ST Debt	3,270	3,718	3,574	3,314	3,001	2,642	2,271
Others liabilities	2,517	2,583	2,560	2,788	3,066	3,075	3,362
Shareholders' funds	2,663	3,301	3,680	4,067	4,499	4,969	5,452
Total Liabilities	8,450	9,602	9,814	10,169	10,566	10,686	11,085
Capital employed	6,486	7,669	7,904	8,031	8,149	8,260	8,373
Financial Ratios							
Operating margin	25.56	24.66	24.20	24.50	25.30	25.80	25.50
Tax rate	20.79	23.01	23.00	23.00	24.00	24.00	24.00
Net margin	14.01	13.52	14.67	14.66	15.33	16.05	16.17
ROE (after tax)	17.66	16.12	16.08	15.32	15.15	14.94	14.31
ROCE (after tax)	7.25	6.94	7.49	7.76	8.36	8.99	9.32
Gearing	123	113	97.11	81.50	66.70	53.17	41.66
Pay out ratio	33.18	40.74	35.97	37.99	36.57	36.74	38.05
Number of shares, diluted	686	686	688	688	688	688	688
Data per Share (EUR)							
EPS	0.69	0.78	0.86	0.91	0.99	1.08	1.13
Restated EPS	0.69	0.78	0.86	0.91	0.99	1.08	1.13
% change	*-%*	*13.2%*	*10.9%*	*5.3%*	*9.4%*	*8.9%*	*5.1%*
EPS bef. GDW	NM	NM	NM	NM	NM	NM	NM
BVPS	3.88	4.81	5.35	5.91	6.54	7.23	7.93
Operating cash flows	0.93	1.05	1.15	1.22	1.33	1.44	1.51
FCF	1.06	0.69	0.92	0.77	0.86	0.96	1.01
Net dividend	0.23	0.32	0.31	0.34	0.36	0.40	0.43

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

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

Table of contents

1. Investment Case

Why the interest now?

The reason for writing now

We believe the time is right to initiate coverage of the stock as the haemophilia market seems to have attracted considerable investor attention.

Cheap or Expensive?

Valuation

The share's valuation is fairly demanding in our view (2017e P/E of 20x vs. 17x for European pharma sector and 20x for medtech stocks). In addition, our EUR20 FV based on a DCF valuation only points to upside of 5-10%.

When will I start making money?

Catalysts

We have identified four catalysts that could affect the share price over the next 12 months: 1/ the publication of Phase III data for Hizentra by CSL in CIDP during Q4 2016, 2/ the likely announcement of a Phase IV trial aimed at assessing Eloctate/Elocta as an immune tolerance inductor in haemophilia A, 3/ results of the AMBAR trial (Albutein in Alzheimer's), and 4/ the publication of Phase III data assessing Pulmaquin in bronchiectasis in cystic fibrosis.

What's the value added?

Difference from consensus

Our growth estimates are more at the low end of the consensus average range. Apart from the fact that we are more cautious on the recovery in the diagnostics segment, we believe the market under-estimates 1/ the impact of the label extension in subcutaneous IGs in CIPD, especially as of 2018e, and 2/ the risk of market share losses for Alphanate and other pdFVIIIs in favour of Eloctate/Elocta.

Could I lose money?

Risks to our investment case

The main risks to our call would be 1/ the clinical failure of Hizentra and Hyqvia in CIDP, 2/ a clinical and commercial success for Albutein as a treatment for Alzheimer's, 3/ a faster-than-expected return to growth in the diagnostic franchise.

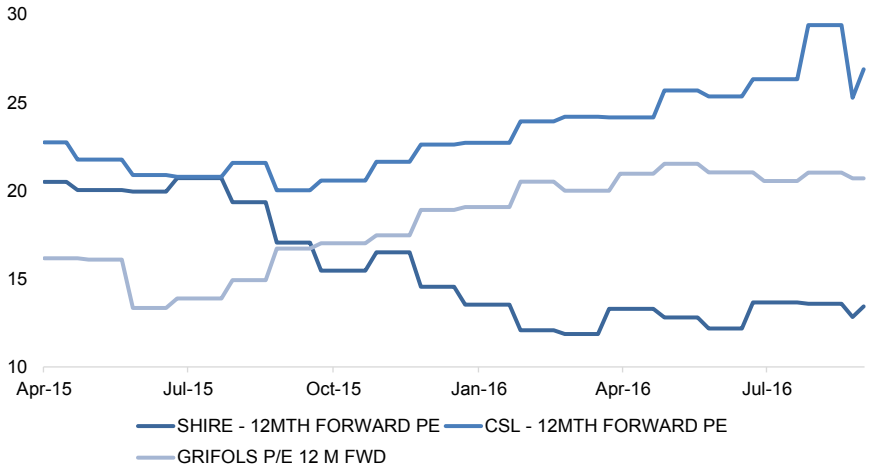
2. The reason for writing this report

2.1. A demanding valuation

A premium of 10% relative to European pharma groups

With 2017e P/E at 20x, Grifols is trading on a premium of 10% relative to the STOXX Europe 600 Healthcare. The fact that growth in EPS should be close to 10% over 2015-18e and that it stems especially from a defensive and buoyant segment (IGs) could potentially explain this fact. However, we also believe that this valuation level leaves fairly little room to manoeuvre in the event of eventual disappointments (and we are likely to see that the risks are far from zero in coming months).

Fig. 1: GFS vs SHP and CSL – P/E 12m forward

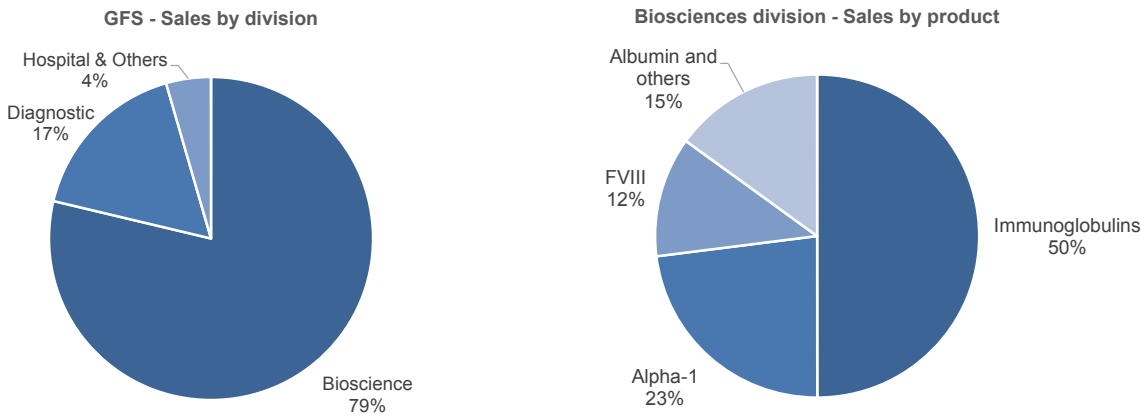


Source: Thomson Reuters; Bryan, Garnier & Co. ests.

A significant discount vs CSL…explained by differences in mix and momentum

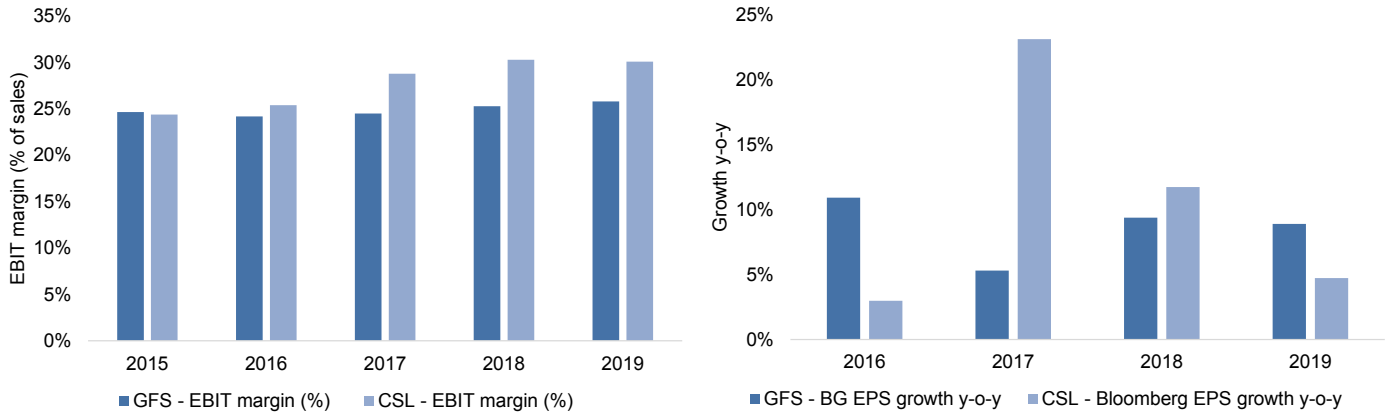
Some players might say however that Grifols is trading on a significant discount relative to CSL (around 20%) whereas the two companies share a number of similarities (high exposure to the immunoglobulins field, predominance of plasma FVIIIs in its haemophilia business etc.). However, this reasoning does not take account of the fundamental differences that characterise the groups and which are likely to affect short and medium-term growth and margin prospects: 1/ lower exposure to the subcutaneous IG sub-segment and to long-acting recombinant factors, 2/ a low level of diversification beyond diagnostics (bearing in mina demanding d that the contribution to this business is fairly dilutive for margins).

Fig. 2: GFS – Sales mix



Source: GFS; Bryan, Garnier & Co. Ests

Fig. 3: GFS vs CSL – Change in EBIT margins/EPS growth



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

2.2. Under-estimated risks

Our forecasts differ from the consensus mainly as of 2018e

Although our forecasts are generally in line with those of the consensus for the next two years, we are nevertheless far more cautious on growth prospects as of 2018e (see Fig. 4).

Indeed, we estimate that growth in the immunoglobulins franchise (around 40% of sales) should slow substantially as of 2018e. Gamunex 10% remains one of the highest-selling intravenous IGs in the world (sales estimated at EUR1-1.5bn) and this success probably lies in its very comprehensive label and its high exposure to an indication such as CIDP (less competitive and more lucrative than PID). Although this positioning has been beneficial to the group in the past, it could now become a disadvantage once the best two subcutaneous alternatives on the market have obtained label extensions (in 2017e for Hizentra and potentially in 2018-19 for Hyqvia). At the same time as this, **we consider that the pdFVIII franchise and its focus on ITI is likely to be threatened by the arrival of ACE910 (that we also expect in 2018).**

Fig. 4: BG estimates vs consensus (2015-2018e)

	2015	2016e	2017e	2018e
Total revenues (in EURm)	**3,935**	**4,033**	**4,250**	**4,447**
% growth y-o-y	17%	3%	5%	5%
% Δ vs Bloomberg consensus	0.0%	-0.8%	-0.6%	-1.5%
Bloomberg consensus	3,935	4,065	4,276	4,513
% growth y-o-y	17%	3%	5%	6%
Reported EBIT (in EUR)	**970**	**976**	**1,041**	**1,125**
% growth y-o-y		1%	7%	8%
% Δ vs Bloomberg consensus		-1.1%	-3.2%	-4.4%
EBIT Bloomberg consensus	970	986	1,075	1,177
% growth y-o-y		1.7%	9.0%	9.4%
Reported EPS (in EUR)	**0.78**	**0.86**	**0.91**	**0.99**
% growth y-o-y		11%	5%	9%
% Δ vs Bloomberg consensus		6.3%	-3.6%	-7.4%
EPS Bloomberg consensus	0.78	0.81	0.94	1.07
% growth y-o-y		3.8%	16.0%	13.8%

Source: Bloomberg; Bryan, Garnier & Co ests.

The likelihood also exists that FVIII sales could be affected by the arrival of Eloctate/Elocta (around 12%e of sales in the biosciences division), especially if its efficacy profile in an ITI setting (immune tolerance induction) should be confirmed in a Phase III/IV trial. For the moment, we admit that this scenario remains theoretical, but our contacts with SOBI/BIIB seem to confirm the prospect. If this is the case, we would probably end up reducing our EPS estimates.

2.3. Initiation at Neutral with a FV of EUR20

We are initiating coverage of the stock with a Neutral recommendation and a FV of EUR20. As for SOBI and SHP, our FV is based on a DCF valuation, using the following main assumptions:

Fig. 5: BG valuation – DCF

(in EURm)	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Revenues	4,033	4,250	4,447	4,625	4,825	5,002	5,162	5,337	5,498	5,658
% chg yoy		5.4%	4.6%	4.0%	4.3%	3.7%	3.2%	3.4%	3.0%	2.9%
(+) Current EBIT	**976**	**1,041**	**1,125**	**1,193**	**1,231**	**1,276**	**1,316**	**1,361**	**1,402**	**1,443**
in % of sales	24.2%	24.5%	25.3%	25.8%	25.5%	25.5%	25.5%	25.5%	25.5%	25.5%
% chg yoy		6.7%	8.0%	6.1%	3.1%	3.7%	3.2%	3.4%	3.0%	2.9%
(-) Taxes	224	239	270	286	295	306	316	327	336	346
(+) D&A	202	217	231	245	261	275	289	304	319	339
in % of sales	5.0%	5.1%	5.2%	5.3%	5.4%	5.5%	5.6%	5.7%	5.8%	6.0%
= Net operating income after tax	**953**	**1,019**	**1,086**	**1,152**	**1,196**	**1,245**	**1,289**	**1,339**	**1,384**	**1,436**
(-) CAPEX	226	255	267	278	290	300	310	320	330	339
(-) Change in WCR	-67	59	53	48	54	48	43	47	43	43
= Free Cash Flows	**795**	**705**	**766**	**826**	**852**	**897**	**937**	**971**	**1,011**	**1,053**

= Enterprise Value (EURm)	**17,499**
(-) Minority interests	0
(-) Net debt	3,718
= Equity value (EURm)	**13,782**
Number of diluted shares	687.6
= Fair Value per share (EUR)	**20**
DCF implied P/E 2017e	22.1x

Source: Bryan, Garnier & Co ests.

- **Our WACC: 7%**. Apart from a risk-free rate of 1.6% and an equity risk premium of 7.0%, we have retained a beta of 0.9 (which is very slightly lower than the level applied to Shire and other big pharmas).

- **We are also assuming an EBITDA margin close to 30% over a long period,** corresponding to the peak levels reached by the company. However, we should not forget that Grifols has expanded massively on the back of acquisitions (especially that of Talecris in 2011) from which considerable synergies were generated.
  However, in the very short term, gross margins should remain under pressure in view of 1/ the rising momentum of the new fractionation plant in Clayton (with capacity often at a surplus initially, and the launch implying additional costs), and the opening of new collection centres, and 2/ pressure on sales in the diagnostics business.

- We have a **growth rate to infinity** of +2.0%.

3. Immunoglobulins: under-estimated competitive pressure

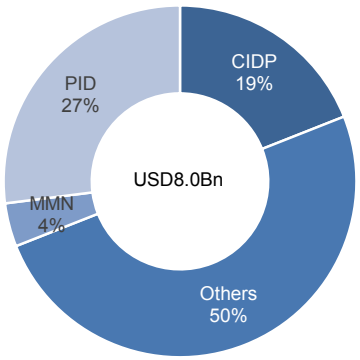
3.1. Exposure to IG: a key factor for investor appeal

Fairly fundamentally, we believe that investor appeal for companies specialised in plasma derivatives lies in certain differences that these products can have with more classic pharmaceuticals products: 1/ generic risks are inexistent since no bioequivalence can be shown for products with components as variable as human proteins, 2/ entry barriers are high and are not limited to know-how or the ability to invest in R&D, but go as far as the complexity of manufacturing, the need to build collection centres and the development of a trust capital for a brand.

Significant exposure (40% of sales) and a buoyant segment

However, we believe this appetite could be strengthened by the fact that Grifols is **particularly exposed to the immunoglobulins segment (around 40% of total sales and 50% of the biosciences division).** While the market is clearly small (around USD8bn), it continues to grow in high single digits thanks to the rising diagnosis of the various diseases addressed (and especially primary immunodeficiency) and a greater use of IGs outside the US. Alongside this, the risk of a significant change in therapeutic paradigm (except for in haemophilia eventually) is actually fairly low in the short term.

Fig. 6: IG – Use depending on indication (volumes)



Indication	2015-2020 growth	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: Companies Data; Bryan, Garnier & Co ests.

Fig. 7: GFS – Market share in plasma products segment

Product	Market share (%)	GFS global position
Immunoglobulins (Intravenous)	**49%**	**Number 1**
Alpha-1	26%	Number 1
Plasma-derived Factor VIII	11%	Number 1
Albumin	15%	Number 2

Source: Grifols; Bryan, Garnier & Co ests.

3.2. But clouds are looming in CIDP

Gamunex IVIG: a comprehensive label and exposure to CIDP the main factors for success

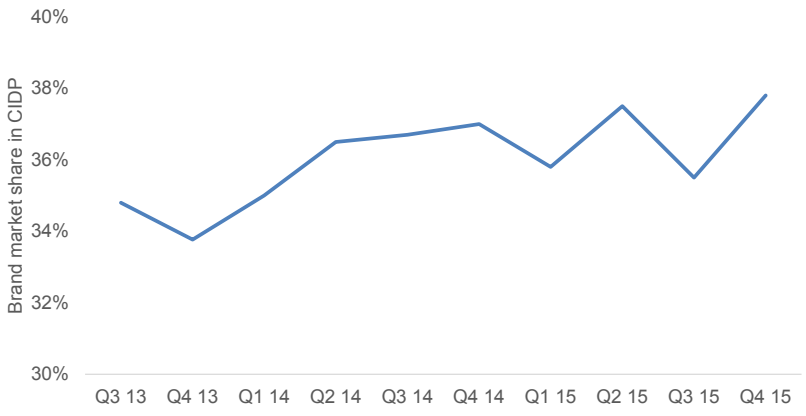
The main growth driver for Grifols in this segment is undoubtedly Gamunex (for which the majority of sales is generated with the IV form). While the drug's very comprehensive label is a top factor underlying its success, we would say that the main reason is especially its long-standing exposure to the Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) market (around 30-40%e du CA), in which competitive intensity looks less pronounced than in PID (where all other IGs are approved and marketed).

Fig. 8: Gamunex – On-label indications in the US

Indication	Gamunex	Privigen	Hizentra	Hyqvia	Gammagard	Flebogamma
Primary humoral immunodeficiency (PI)	x	x	x	x	x	x
Idiopathic Thrombocytopenia Purpura (ITP)	x	x				x
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	x	x				
Multifocal motor neuropathy (MMN)					x	

Source: FDA; Bryan, Garnier & Co ests.

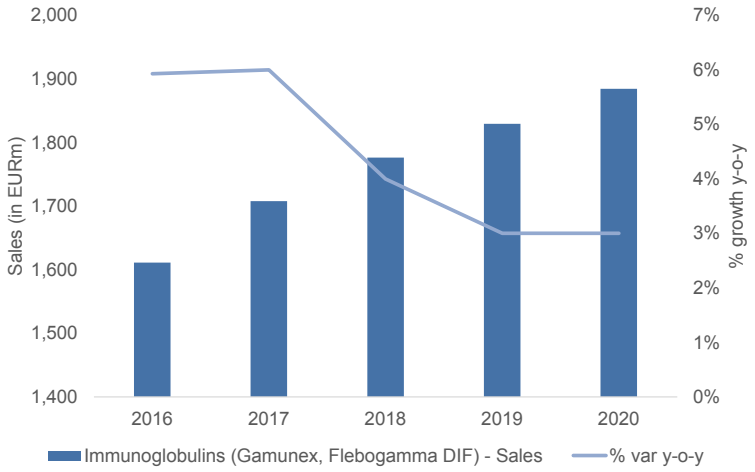
Fig. 9: Gamunex market share in CIDP



Source: Grifols; Bryan, Garnier & Co. ests

That said, we estimate that the landscape could change soon, especially in view of the marketing of the latest generations of subcutaneous IGs such as Hizentra (CSL) and Hyqvia (SHP), against a backdrop in which Grifols is unlikely to have its own alternative SC format on the market before 2018 or 2019 (not to mention the fact that we have no real details on its characteristics).

Fig. 10: IG - sales estimates



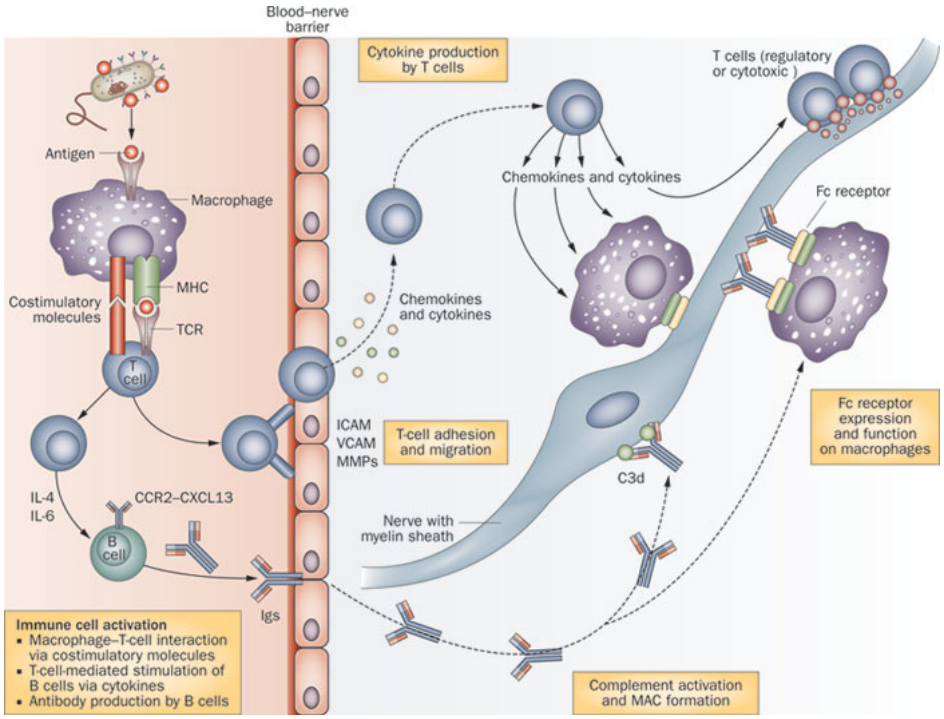
Source: Grifols; Bryan, Garnier & Co. ests

- **CIDP: an auto-immune disease for which IGs will remain the standard**

CIDP: a rare neurological disease

Before setting out our scenario for the development of Gamunex, we consider it important to take a look at CIDP and its therapeutic environment. CIDP is a fairly rare indication (prevalence of only 10,000 in the US), characterised by attacks on the myelin sheathes located in the peripheral nervous system. In concrete terms, this leads to weakness in the lower limbs and arms, a loss of reflex and difficulties in walking that only become worse etc.

Fig. 11: Mechanisms underlying development of CIDP



Source: Dalakas, M. C. (2011) Advances in the diagnosis, pathogenesis and treatment of CIDP Nat. Rev. Neurol.

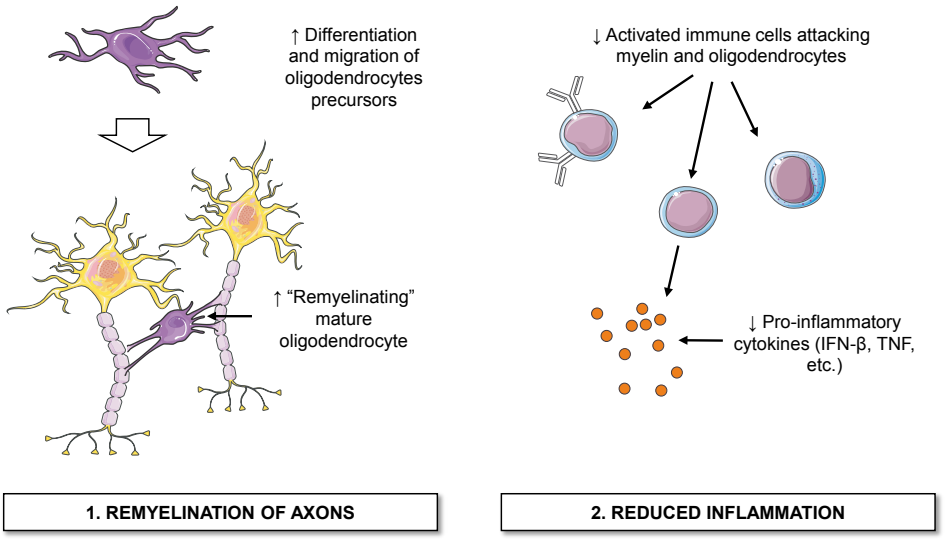
We believe that IGs should remain one of the standard treatments for the disease

Administration of immunoglobulins plays and will continue to play a dominant role in treatment of patients suffering from modest or severe forms of the disease, alongside anti-inflammatory drugs such as prednisone (although the latter are not necessarily recommended for patients with a pure motor deficiency).

Potentially disease-modifying approaches are currently being developed in this disease, among which Gilenya by NVS. However, without questioning an eventual clinical success, we are fairly sceptical concerning the ability of Gilenya (fingolimod) to penetrate the CIDP market, especially in view of the toxicity profile associated with its action mechanism. Note indeed that S1Ps aim to retain the T-lymphocytes responsible for the destruction of axons in lymphoid organs and this results in 1/ an increased risk of brain infections (due to the decline in the number of protective cells in the brain) and 2/ a strong rebound effect when the treatment is stopped (Hatcher et al, 2016).

GNbAC1 (an anti-MSRV Env) by Geneuro could be a potential game changer given its theoretical ability to remyelinate axons (see our initiation report here for further details). However, 1/ the current lack of clinical data on proof of concept, and 2/ the small amount of literature concerning the eventual role of this protein in the pathogenesis means we have no sure opinion on its potential (and for this reason, we have not yet factored it into our valuation). We should know far more once the results of the current Phase II trial are published (probably in 2018), but for the moment, we assume that IGs will remain the benchmark treatment for CIDP.

Fig. 12: GNbAC1 – Action mechanism



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

- **Extension of SC immunoglobulins label likely to redeal the cards**

A slowdown in the franchise due to 1/ the arrival of two differentiated sub-cutaneous IGs, and 2/ the lack of an equivalent option

We expect growth in Grifols' IG franchise to slow following approval of two subcutaneous IGs in CIDP: Hizentra and Hyqvia (potentially in 2018e and 2019e respectively). Indeed, we believe that patients should fairly rapidly switch to the latter more user-friendly alternatives (possibility of being treated at home rather than in hospital etc.), the cost of which is nevertheless substantially different from that of IV options (with a premium of close to 30%). Some would probably say that this price difference could play in favour of subcutaneous IGs, but this would be forgetting that they boast a better safety profile, with far fewer systemic side effects (Haddad et al, 2012) and that they help reduce the cost per patient for the health system (Martin et al, 2013).

Admittedly, we do not expect a massive change in habits and practices, as for the PID framework (certain patients prefer to be treated in an hospital environment, while others could be put off by the fact that the SCIGs require several injection sites). However, we think that two main trends are currently emerging in this latter indication and that they should be reproduced in CIDP: 1/ IVIGs are currently growing far less quickly than SCIGs (+5% vs. +15% on average), 2/ since the arrival of Hizentra, appeal for subcutaneous administration has increased and especially for a once fortnightly administration (bringing it slightly closer to the monthly injection for IVs). This effect has apparently been amplified with the arrival of Hyqvia (once-monthly administration).

Fig. 13: Comparison of Gamunex vs main SCIGs and IVIGs on the market

Product	Product	Label	Administration schedule	Infusion time	Sites for infusion
Shire	Hyqvia SC	PID	Once a month	2-3 hours	1
Shire	Gammagard IV	PID, MN	Once a month	2-3 hours	1
CSL	Hizentra SC	PID	Once a week or twice a month	1-2 hours	2
CSL	Privigen IV	PID, ITP	Once a month	2-3 hours	1
Grifols	Gamunex IV	PID, CIDP	Once a month	2-3 hours	1
Grifols	Gamunex SC	PID, CIDP	Once a week	1-2 hours	4

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

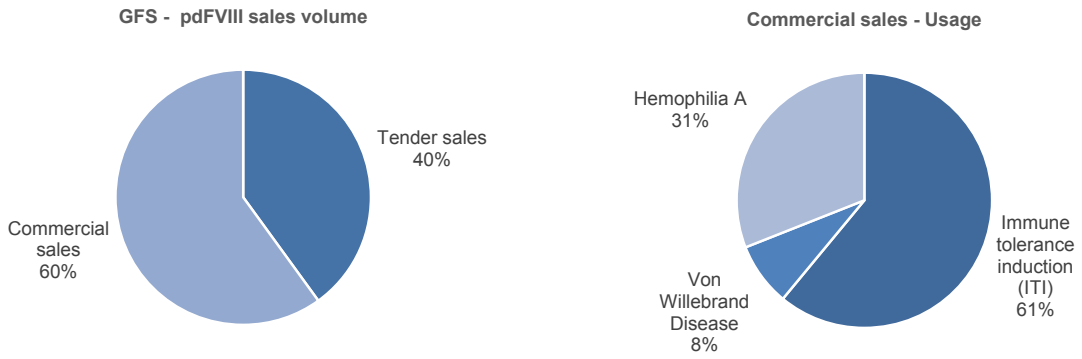
4. FVIIIs potentially under pressure as of 2018e

4.1. Eloctate and ACE910: potential negative impact under-estimated

ACE910 likely to win market share from Grifols' pdFVIIIs given the extent of revenues generated in ITI

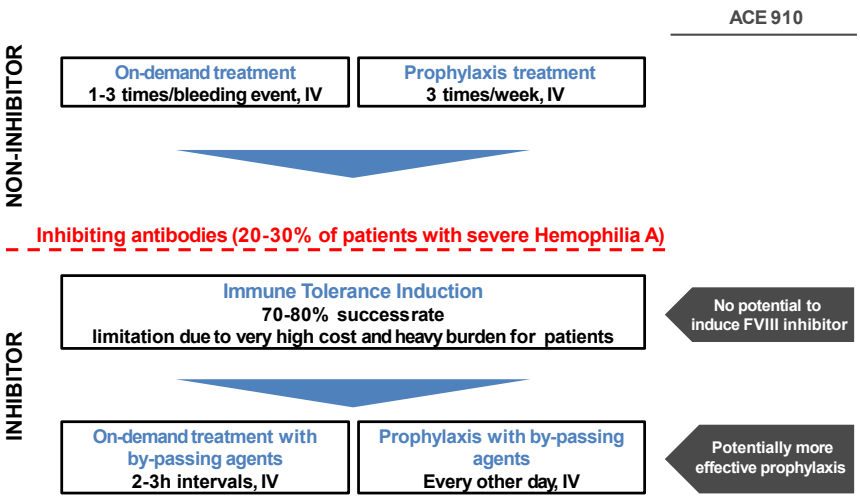
Admittedly for the moment, we assume that the ROG molecule is likely to struggle to penetrate the market of haemophilia A without inhibiting antibodies, although we estimate that its efficacy profile and administration schedule make it particularly attractive for patients with inhibiting antibodies. However, note that 1/ Alphanate derives a quite significant share of its revenues from immune tolerance induction (ITI) in patients suffering with inhibitors, 2/ a share of patients with high titers (those with a level varying between 5 and 10 BU) use ITI and these should theoretically be addressed by ACE910.

Fig. 14: GFS – pdFVIII – usages



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

Fig. 15: Potential positioning of ACE910



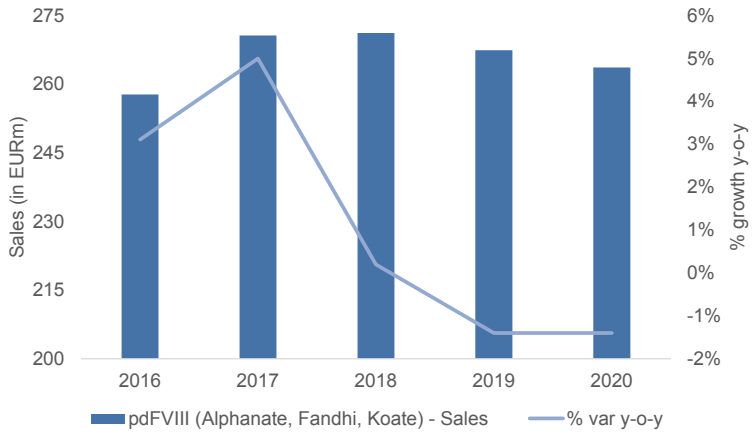
Source: Roche; Bryan, Garnier & Co. ests.

Confirmation of ACE910's safety profile is of course essential for fully appreciating the eventual decline in the FVIII franchise. However, ROG's pricing strategy should be just as important a factor to take into account (bearing in mind that the monthly cost of ITI can vary from EUR20,000 to EUR70,000 with pdFVIIIs, with the variation depending on the protocol used and the weight of the patient). In our scenario for a monthly cost of USD50,000 per patient for a prophylactic treatment, ACE910 would be fairly competitive in our view.

We are forecasting a slight deterioration in pdFVIII sales as of 2018e

Knowing this, we have decided to integrate a slight deterioration in revenues generated in ITI (around 4-5%) as of the first year of marketing of ACE910, while continuing to expect mid-single digit growth for the rest of the business.

Fig. 16: GFS – Change in pdFVIII franchise



Source: Bryan, Garnier & Co. ests.

We could reduce our estimates if Eloctate confirms its efficacy profile in ITI

Another factor could also accentuate this deterioration: as described in the section of this report on SOBI, **Eloctate/Elocta produced very promising data in immune tolerance induction.** It is still too early to estimate the drug's potential in this specific segment (and hence to integrate an eventual negative impact for GFS), especially since SOBI and BIIB have still not unveiled their intentions concerning the potential initiation of Phase IV trials aimed at confirming the data noted under the framework of a small study.

That said, the likelihood of a development being launched in coming months is higher than 50%e in our view. Especially in a context where 1/ several other long-acting rFVIIIs are now on the market and we believe that the product's ramp-up could be more difficult in Europe, 2/ a superiority in ITI would make Eloctate the molecule in its class that could make this claim. Otherwise, we will probably have to wait for data publications in 2018e at the latest.

4.2. SIPPET study: limited upside?

For a few months now, Grifols has placed a specific focus on the publication of results from the SIPPET randomised prospective study that showed a more significant risk (+87%) of developing inhibitors with rFVIIIs compared with pdFVIIIs containing Von Willebrand's factor (vWF). With the latter also being cheaper, it therefore looks highly likely that this data has an impact on practices and sales of products such as Alphanate. That said, we also believe that the eventual benefit could be limited for at least two reasons:

- **Other wide-scale studies, and especially RODIN, came to a totally different conclusion,** showing that 1/ the risks of developing inhibitors were fairly similar between recombinant products and plasma derived products, irrespective of whether they were associated with vWF (Gouw et al, 2013), 2/ third generations of rFVIII (e.g. Advate, etc.) are safer than the first ones. As such, it seems fairly unlikely that the guidelines will be modified drastically, especially since the most widely-sold rFVIIIs are notably third-generation ones.

- **The results of SIPPET were fairly straightforward, but the study only implied treatment-naïve patients.** As such, we estimate that patients already treated with recombinant approaches and (above all) who are well controlled, will be unlikely to want to change their therapeutic cocktail.

Fig. 17: Results of RODIN study

	Recombinant products				Plasma derived	All types (n=574)
	Third generation (n=157)	Second generation (n=183)	First generation (n=59)	2nd gen B-domain deleted (n=183)		
Median age (years)	4.6	6.1	9.3	9.1	6.4	6.4
Family history of haemophilia						
No	45%	64%	46%	55%	50%	53%
Yes - Negative for inhibitors	41%	27%	36%	27%	27%	33%
Yes - Positive for inhibitors	14%	9%	19%	18%	23%	15%
F8 genotype - High risk	61%	55%	59%	48%	64%	58%
Median age at first exposure to FVIII (in months)	9.9	10.2	9.7	8.8	7.9	9.8
History of surgical procedure	29%	18%	31%	36%	18%	25%
Inhibitor development - Clinically relevant	28%	38%	29%	30%	33%	32%
Inhibitor development - High titer	18%	25%	25%	18%	26%	22%

Source: Gouw et al, NJEM (2013); Bryan, Garnier & Co ests.

5. Albutein in Alzheimer's disease: a difficult call…

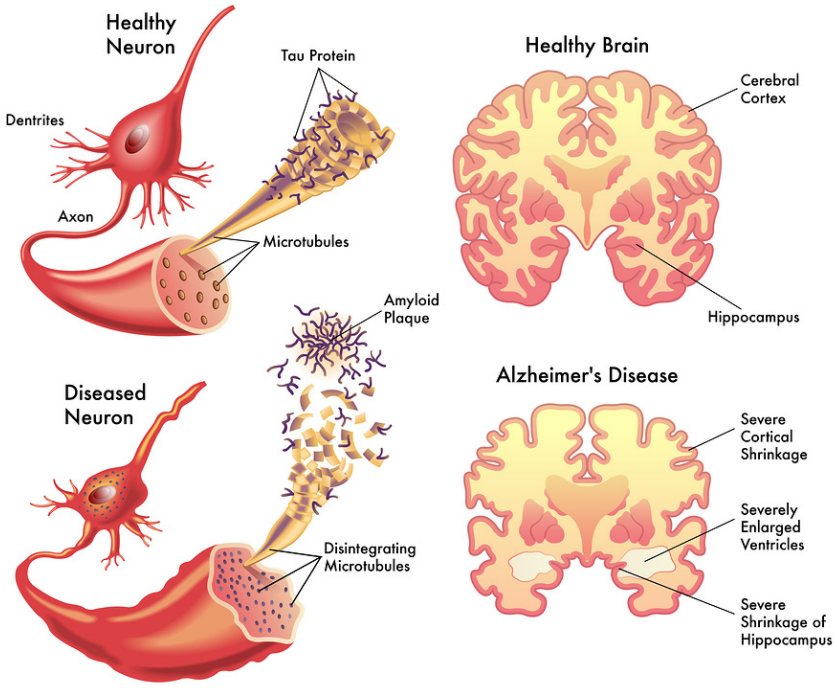
5.1. A significant and rational medical need…

- **What is albumin and what is its potential role in the pathogenesis?**

Albumin: the most abundant protein in human plasma…

Albumin is the most abundant protein in human plasma (60%). Synthesised in liver cells it is 1/ the **main transport protein in blood** (whether for endogenous factors such as hormones, coagulation factors, calcium or fatty acids, or also exogenous factors such as medicines), 2/ essential for balancing fluids in the body. Traditionally, this plasma protein is used for plasma exchanges or in the treatment of hypo-albuminemia, cirrhosis etc. However, Grifols and other companies have tried or are trying to extend the application field to other diseases and especially Alzheimer's disease.

Fig. 18: Alzheimer's disease –Tau and β-amyloid proteins



Source: Adapted from Morreale et al, 2012

… with the ability to join to β-amyloid proteins and carry them out of the brain

The rationale behind this development is based on a theory concerning the genesis of the disease and one observation. For a number of years, a theory seems to be gaining in importance: β-amyloid protein which is naturally present in the brain, is thought to build up abnormally in Alzheimer patients to the extent that it creates plaques, that also favour an over-phosphorylation/accumulation of another protein (Tau) and consequently, a disorganisation and degeneration of neuronal structures.

Alongside this a double-observation has been made: 1/ clearance of β-amyloid in the brain is apparently far less fluid in these patients, and at the same time as this, 2/ plasma concentrations of albumin also tend to be lower when compared with healthy subjects (Yamamoto et al, 2014). Since

these proteins are known for their ability to transport β-amyloid towards the periphery, several researchers have questioned a possible relationship between the two phenomena and their eventual role in the genesis of the disease.

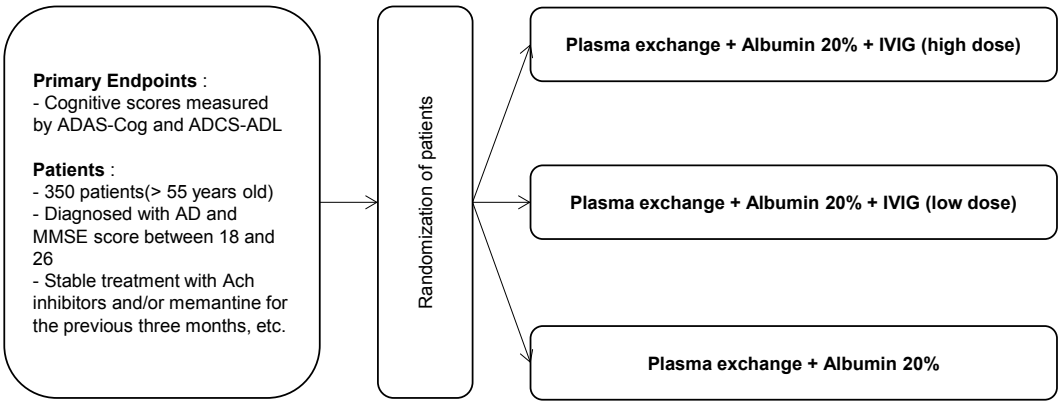
- **A Phase III underway and results expected by H1 2017 at the latest**

Results of Phase III study expected in H1 2017

Based on this, Grifols initiated a clinical programme (AMBAR) assessing its albumin in this disease 1/ in combination with an IVIG, and 2/ after a plasmapheresis (the aim of which is to withdraw albumins and other plasma proteins associated with β-amyloid). In April 2016, almost 94% of patients in the study were recruited.

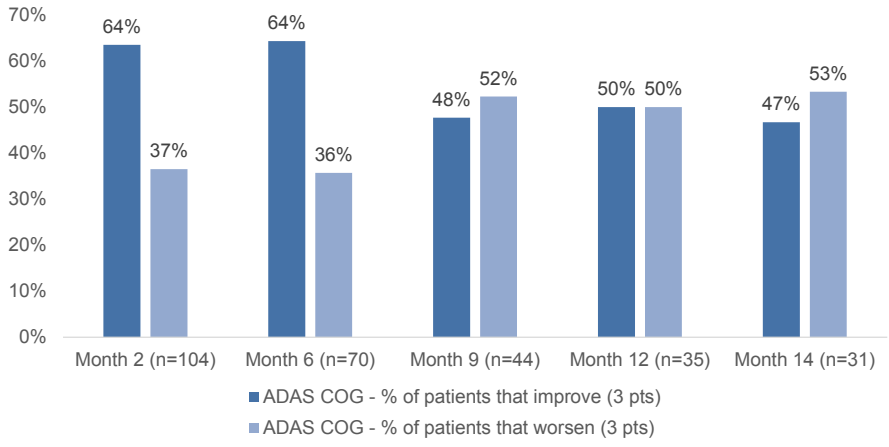
The definitive results should be published in early 2017 at the latest, bearing in mind that intermediary results for 170 patients were presented at a congress and that these were fairly intriguing. Randomisation codes were not broken (thereby signifying that we do not know to which groups the eventual responding patients were assigned). However, note that a number of patients saw their situation improve, even several months after the start of the treatment, on the basis of scales such as ADAS-Cog and ADCS-ADL (two criteria widely used in trials implying Alzheimer's disease.

Fig. 19: Design of AMBAR trial



Source: ClinicalTrials.gov; Bryan, Garnier & Co. Ests

Fig. 20: Intermediary results of the AMBAR study



Source: Grifols; Bryan, Garnier & Co. Ests

5.2. … However numerous factors warrant caution

However, caution is necessary. A large number of failures have been noted in this indication and we have doubts on the design of the study and the market access of the approach.

We have decided not to integrate growth prospects relative to an eventual use of albumins for treatment of Alzheimer's disease (and the consensus is very likely not to have done so), thereby suggesting that upside can only stem from positive results. However, we believe caution is necessary. And the fact that numerous therapies and especially those targeting β-amyloid, have never succeeded in showing a therapeutic benefit in patients suffering from a light/modest disease is a first factor warranting caution. However, this reflection could apply to any other candidate developed in the indication. In the case of GFS, we believe that the issue could above all be that of market access.

- **Alzheimer: a genuine cemetery for R&D**

Alzheimer is among the few indications on which we are clearly cautious, if only because the failure rate is far higher than for other indications. Less than five molecules have been approved since the end of the 1990s out of more than 100 assessed (for which efficacy results are also far from being a panacea). A number of factors could also explain this trend, but we would highlight three in particular: 1/ the disease is extremely complex, implying numerous pathways (and we do not know which is the most significant) such that the triggers are unknown, 2/ the significant patient heterogeneity that characterises the disease could be at the root of numerous failures in late-stage trials, 3/ maybe we are not looking at the right targets (this point is particularly true for β-amyloid).

- **Uncertain market access**

Whereas the subject of financing social security systems is constantly centre stage, we would like to remind that plasmapheresis is an expensive treatment (around USD1,000-2,000 per procedure) and the fact of adding in albumin and immunoglobulins could in our view lift the annual cost to USD50-100,000 per patient depending on their weight (without counting the expenses associated with acquiring the machine necessary to exchange the plasma).

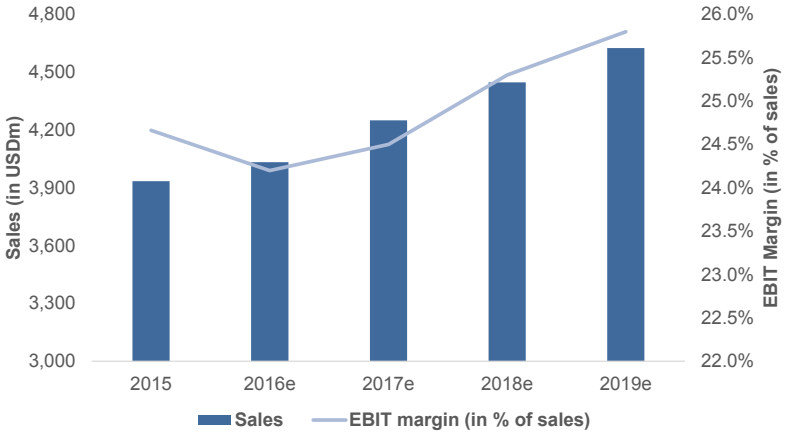
Last but not least, we understand that the regulatory road to take has not been entirely clarified with the authorities and especially with the FDA. Beyond this aspect, we ask ourselves whether the design of the trial is really satisfactory and especially, with a population of patients as small as this (< 500 whereas millions of people are affected with a pathology otherwise characterised by a large inter-patient heterogeneity).

6. Operating leverage will have to wait

EBITDA margin set to be below normal average levels in 2016e and 2017e

For slightly more than a year, the group's margins have tended to narrow for a number of reasons. The first factor, and not the least important, was the mid-single digit decline in immunoglobulin prices in the US following the arrival of new entrants in the market (Biotest?), which luckily did not last. That said, we believe that other factors should continue to weigh on EBITDA margin (around 29-30% in 2017e whereas normal average levels are close to 31-33%e) and especially: 1/ the current expansion in the group's production capacity, but also the 2/ pressure persisting on the top-line in the diagnostics business, and the lack of visibility on an eventual breath of air in this respect prompts us to remain fairly cautious.

Fig. 21: GFS - Change in margins



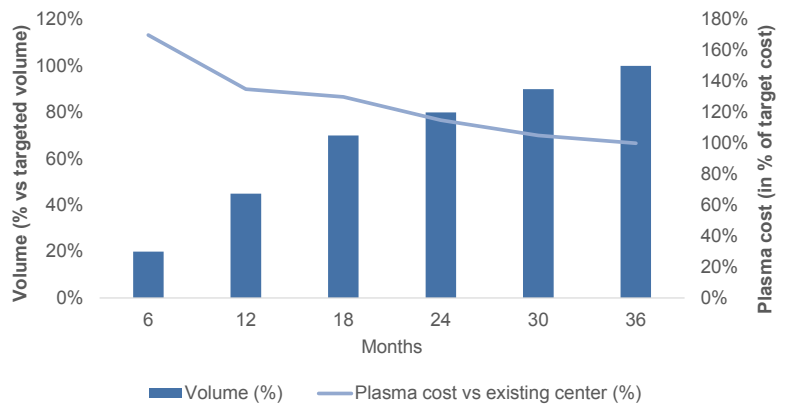
Source: Bryan, Garnier & Co. ests.

6.1. Capacity extension (still) taking a toll

A situation of overcapacity in the short term following the construction of fractioning plants and collection centres

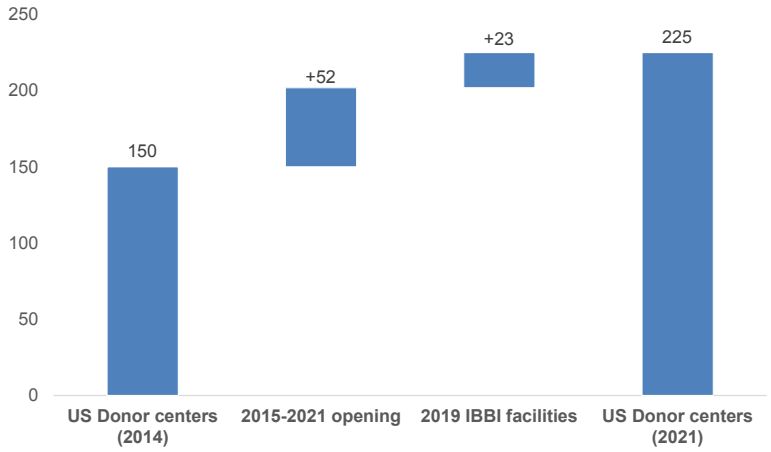
The first factor concerning pressure on margins in the short term remains extension of production capacity for plasma derivatives (opening of new fractioning sites and collection centres), with a double effect on EBIT margin as well: 1/ capacity is not entirely used over the first three years of use, especially since the transfer of production from other plants is only gradual, 2/ depreciation costs are set to rise with the use of the new units.

Fig. 22: Theoretical change in the cost of plasma from a new collection centre



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

Fig. 23: Theoretical change in the cost of plasma from a new collection centre



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

In absolute terms, all companies in the plasma industry are faced with this type of issue on a recurring basis. However, the ability to turn around margins is far from the same for everyone. The efficiency of manufacturing is one thing (but this is difficult to quantify from an outside viewpoint), however, the product mix and growth prospects also play a very important role. As it happens, we believe that Grifols could suffer from its absence from segments such as subcutaneous IGs and recombinant coagulation factors (for which margins are by definition not dependent on the yield of production plants).

6.2. Diagnostics franchise under pressure

Pressure on sales and margins due to plunge in transfusion volumes

Grifols' diagnostic division (c.20% of sales) stems from its acquisition from Novartis dating back to 2013 (EUR1.2bn). Focused especially on transfusional diagnostics and more precisely, guarantee of the safety of blood donations destined for transfusions or the plasma fractioning industry (90% of sales), we estimate that this business could weigh on the group's margins in coming quarters. The fact that it carries far lower margins than the rest of the group (EBIT margin standing at around 10%e whereas companies such as BIM and QIA are closer to 15-20%e) is clearly not an argument in its favour. However, it is above all top-line trends that make us fairly cautious.

Fig. 24: Diagnostic business – breakdown of sales

	Nucleic acid testing	Immunoassay	Blood typing and other
Products	Assays, instruments	HCV and HIV antigens	Genotyping, instruments
Partner	Hologic (50-50% revenue sharing)	Ortho Clinical (50-50% profit sharing)	None
in % of sales	c.55%	c.25%	c.20%

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

For six years now, blood transfusion volumes have not stopped falling (including -24% between 2009 and 2013) for reasons that we consider structural: blood demand is pretty much on a downtrend. The development of mini-invasive techniques for various surgical operations and the advent of new treatments clearly play a role in this, although, an increasing number of doctors are also taking more conservative positions following the 1/ publication of a number of large studies showing that the outcome could be similar, if not better, by reducing the volumes of blood transfused (Yang et al, 2015; Holst et al, 2014; Robertson et al, 2014; etc.); and 2/ changes in certain guidelines (for heart bypasses for example).

We expect no stabilisation before 2018e

When will this spiral stop? This is difficult to say in a backdrop where the decline in volumes is also encouraged by the aim to save costs by hospitals (whether in terms of the raw material or its storage etc.). In these conditions, **we have opted for a cautious scenario and are forecasting a slight decline in sales in the division before a stabilisation in 2018e**.

Fig. 25: BG estimates – sales and margins in the diagnostics division

(in EURm)	2015	2016e	2017e	2018e	2019e
Diagnostics Revenues	**691**	**645**	**638**	**638**	**645**
% var y-o-y	12%	-8%	-1%	0%	1%
% CER	-1%	-6%	-1%	0%	1%
in % of total sales	18%	16%	15%	14%	14%
Diagnostics EBIT	**69**	**68**	**70**	**77**	**84**
EBIT margin (%)	10.0%	10.5%	11.0%	12.0%	13.0%
in % of total EBIT	7.1%	6.9%	6.7%	6.8%	7.0%

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

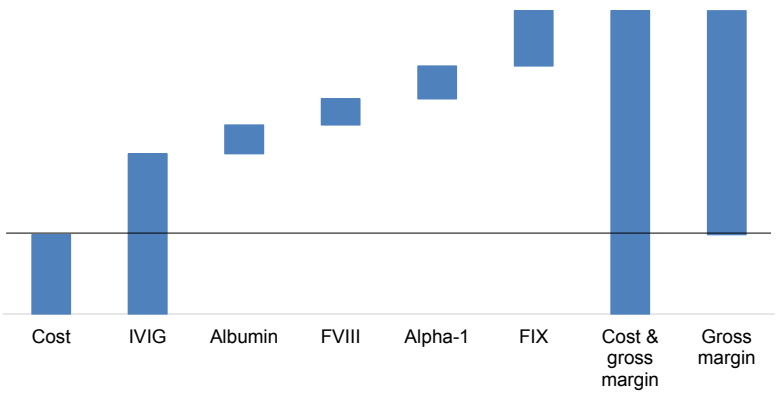
the international side of transfusion (especially since transfusions in the rest of the world are more on an uptrend) as well as 2/ supply of HIV and HCV antigens to immunoassy producers such as Abbott, Siemens and OCD. However, the importance of the US transfusion business means that it is likely to remain the main factor underpinning margin growth.

6.3. Risks to medium-term leverage

For the moment, we estimate that the group should be capable of restoring more aggressive operating leverage as of 2018. More specifically, 1/ once the new fractioning units and collection centres are running at full pace, whereas all of the biosciences business should continue to grow (whether in the historical business or thanks to the launch of new products such as Pulmaquin – for which we estimate 2020e sales at EUR250m).

Note however, that **we have not factored a further decline in the pdFVIII business into our estimates along with confirmation of a best-in-class status for Eloctate in ITI.** If this scenario should materialise, we estimate the negative impact on our 2018-20e EPS estimates could be close to 6-7% in a first approach, especially if we assume 1/ a double digit decline in revenues in the franchise and consequently a c.5% decline in sales on the group scale, 2/ the loss of margin associated could be even higher since the volumes used in ITI are higher in patients without inhibitors.

Fig. 26: Plasma economics (illustrative)



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

BRYAN, GARNIER & CO

INDEPENDENT RESEARCH

SOBI

17 Octobre 2016

« Préparez-vous, l'hiver vient ! »

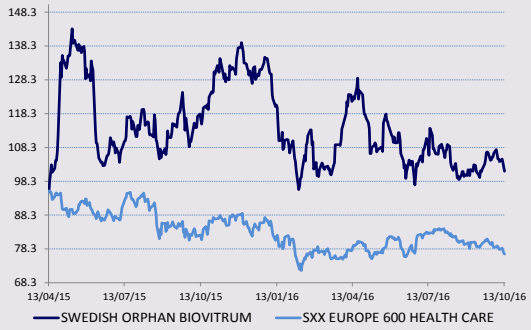
Santé

Fair Value 90SEK (cours 101,30SEK)

VENTE
Initiation de couverture

Bloomberg	SOBI SS
Reuters	SOBIV.ST
+Haut /+Bas 12 mois (SEK)	139,3 / 95,9
Capitalisation Boursière (MSEK)	27 391
Valeur d'Entreprise	28 557
Volume moyen 6 mois (000 actions)	1 234
Flottant	60,4%
TMVA BPA (3 ans)	ns
Gearing (12/15)	35%
Rendement (12/16e)	NM

Fin Décembre	12/15	12/16e	12/17e	12/18e
C. d'affaires (MSEK)	3 228	5 066	5 966	7 243
EBIT (MSEK)	146,04	860,05	1 290	1 995
BPA Publié (SEK)	0,25	2,38	3,62	5,65
BPA dilué (SEK)	0,25	2,38	3,62	5,65
EV/CA	9,00x	5,64x	4,60x	3,60x
EV/EBITDA	62,5x	23,9x	16,5x	10,9x
EV/EBIT	198,9x	33,2x	21,3x	13,1x
P/E	NS	42,6x	28,0x	17,9x
ROCE	1,0	9,4	14,6	22,2



Nous initions le suivi de SOBI avec une recommandation VENTE et une FV de 90SEK. Bien qu'elles soient globalement positives, nos prévisions d'EPS sont notoirement en deçà de celles du consensus, et en particulier du fait de notre prudence vis-à-vis d'Eloctate/Elocta… Du moins tant que son potentiel dans la « désensibilisation » des patients avec inhibiteurs n'a pas été confirmé. En attendant, nous estimons que les prochaines publications trimestrielles se traduiront par de fortes révisions à la baisse des attentes.

- **Trop d'optimisme sur la franchise Hémophilie** ? Nous admettrons bien volontiers qu'Elocta et Alprolix sont d'assez belles réussites commerciales aux Etats-Unis, et c'est sans doute pour cette raison que les attentes du consensus sont aussi élevées sur les territoires de SOBI (*peak sales* combiné : entre 700 MUSD et 1 MdUSD vs BG : 500 MUSD)… Mais ce serait oublier que 1/ ces deux molécules de BIIB étaient sans concurrents directs pendant plus d'un an aux US ; 2/ les autres zones géographiques ont historiquement préféré les options plasmatiques ; 3/ a contrario, le paysage concurrentiel est déjà beaucoup moins favorable du côté de l'Europe.

- **Elocta dans l'ITI : un potentiel significatif… Encore incertain**. Notons néanmoins qu'Elocta pourrait potentiellement se différentier des autres FVIII à action prolongée en démontrant un bénéfice dans l'induction d'une tolérance immunitaire (impact potentiel sur notre *peak sales* : +400MUSD)… Si les premières données sont plutôt prometteuses, nous soulignerons néanmoins le fait que 1/ cette preuve de concept n'a été obtenu que sur un petit nombre de patients (n=3) ; 2/ pour le moment, aucune étude clinique n'a été initiée afin de confirmer ce positionnement.

- **Initiation à la VENTE avec une FV de 90 SEK.** La dynamique bénéficiaire devrait être globalement positive au cours de ces prochaines années, mais les attentes nous semblent un peu trop élevées, et en particulier 1/ pour 2017e et 2/ en l'absence de confirmation du potentiel d'Eloctate dans l'ITI.

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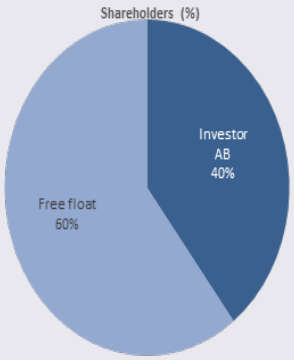
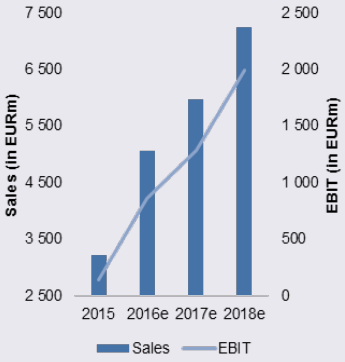




Company description

SOBI is a Swedish healthcare company developing and commercializing rare disease-oriented drugs

Simplified Profit & Loss Account (USDm)	2014	2015	2016e	2017e	2018e	2019e	2020e
Revenues	2,607	3,228	5,066	5,966	7,243	8,435	9,158
Change (%)	*-%*	*23.8%*	*57.0%*	*17.8%*	*21.4%*	*16.5%*	*8.6%*
Adjusted EBITDA	257	465	1,194	1,666	2,394	2,934	3,429
EBIT	(325)	146	860	1,290	1,995	2,512	3,008
Change (%)	*-%*	*-%*	*489%*	*50.0%*	*54.7%*	*25.9%*	*19.8%*
Financial results	6.4	(58.4)	(36.6)	(36.6)	(35.8)	(35.8)	(35.8)
Pre-Tax profits	(319)	87.7	823	1,254	1,960	2,476	2,972
Exceptionals	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tax	(50.7)	19.3	181	276	431	545	654
Net profit	(268)	68.4	642	978	1,529	1,931	2,318
Restated net profit	(268)	68.4	642	978	1,529	1,931	2,318
Change (%)	*-%*	*-%*	*839%*	*52.3%*	*56.3%*	*26.4%*	*20.0%*
Cash Flow Statement (USDm)							
Operating cash flows	299	411	977	1,354	1,927	2,353	2,740
Change in working capital	65.6	(96.0)	290	21.8	276	617	145
Capex, net	183	146	203	239	290	337	366
Financial investments, net	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Dividends	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other	19.6	24.9	(480)	(495)	(400)	(379)	0.0
Net debt	345	1,651	1,167	73.3	(1,288)	(2,686)	(4,915)
Free Cash flow	50.6	361	484	1,093	1,361	1,398	2,229
Balance Sheet (USDm)							
Tangible fixed assets	115	109	194	297	435	604	794
Intangibles assets	4,247	5,787	5,672	5,550	5,448	5,364	5,302
Cash & equivalents	519	904	908	1,507	2,467	3,487	5,716
current assets	1,416	1,413	1,705	1,677	1,996	2,294	2,475
Other assets	592	1,003	906	1,385	2,201	3,052	5,097
Total assets	6,371	8,311	8,476	8,909	10,081	11,314	13,668
L & ST Debt	864	2,555	2,075	1,580	1,180	801	801
Others liabilities	983	1,067	1,070	1,020	1,063	743	779
Shareholders' funds	4,523	4,689	5,332	6,310	7,838	9,770	12,088
Total Liabilities	6,371	8,311	8,476	8,909	10,081	11,314	13,668
Capital employed	5,153	6,662	6,820	6,704	6,872	7,405	7,495
Ratios							
Operating margin	(12.47)	4.52	16.98	21.63	27.55	29.78	32.85
Tax rate	15.93	22.01	22.00	22.00	22.00	22.00	22.00
Net margin	(10.27)	2.12	12.68	16.39	21.10	22.90	25.32
ROE (after tax)	(5.92)	1.46	12.05	15.50	19.50	19.77	19.18
ROCE (after tax)	(5.20)	1.03	9.42	14.59	22.24	26.08	30.93
Gearing	7.63	35.21	21.88	1.16	(16.43)	(27.49)	(40.66)
Pay out ratio	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Number of shares, diluted	270	270	270	270	270	270	270
Data per Share (USD)							
EPS	(0.99)	0.25	2.38	3.62	5.65	7.14	8.57
Restated EPS	(0.99)	0.25	2.38	3.62	5.65	7.14	8.57
% change	*-%*	*-%*	*839%*	*52.3%*	*56.3%*	*26.4%*	*20.0%*
BVPS	16.73	17.34	19.72	23.34	28.99	36.13	44.71
Operating cash flows	1.11	1.52	3.61	5.01	7.13	8.70	10.13
FCF	0.19	1.34	1.79	4.04	5.03	5.17	8.24
Net dividend	0.0	0.0	0.0	0.0	0.0	0.0	0.0

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

Table of contents

1. Investment Case

Pourquoi investir maintenant?

Pourquoi s'intéresser au dossier maintenant :

The fact that Biogen announced the spin-off of its haemophilia business helped highlight the products for which SOBI has rights outside the US, namely Eloctate/Elocta and Alprolix. That said, our analysis of the segment suggests that short-term disappointment risk is far from negligible.

Attractif ou non?

Valorisation

It is difficult to base ourselves on multiples given that the company has only exceeded breakeven point very recently. Note however that our FV stands at SEK100 per share implying slight downside risk.

Horizon d'investissement?

Catalyseurs

Recent publications by BIIB have already shown a slowdown in growth at Eloctate and Alprolix in the US… And we have the feeling that coming quarters are very likely to show similar trends. We estimate that European revenues, which concern SOBI especially, could disappoint as of Q3 2016.

Valeur ajoutée?

Différentiation face au consensus *:*

Although our EPS estimates are generally positive, they are noticeably lower than the consensus figures (around 10% as of 2017e), especially in view of our caution on Eloctate, at least until its "desensitisation" potential in patients with inhibiting antibodies against FVIII has been confirmed.

Quels risques?

Risques

The main risk to our investment case would be higher than expected growth by Elocta and Alprolix in Europe.

2. Why initiate coverage now?

2.1. A call on the European ramp-up of Elocta and Alprolix

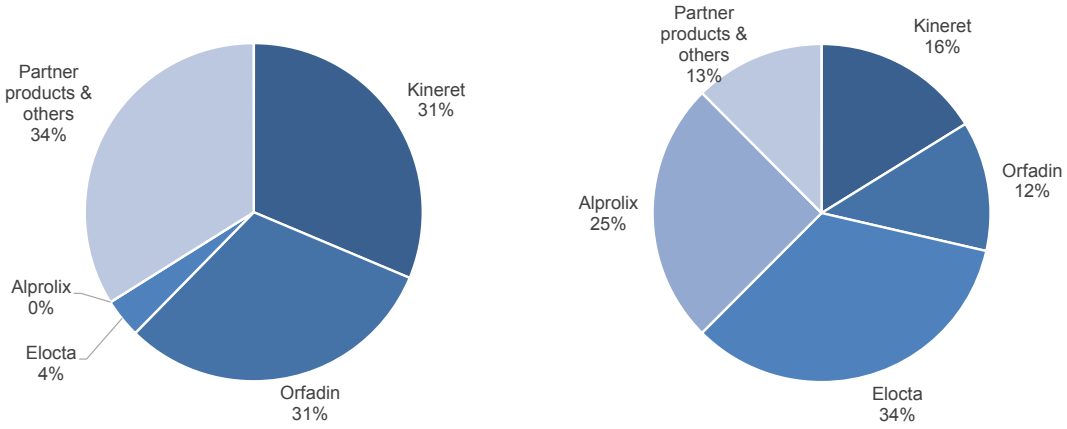
Since 2014, SOBI has been Biogen's partner in the development and marketing of Elocta and Alprolix in a well-established zone including Europe, North Africa, Russia and a part of the Middle-East (with BIIB nevertheless keeping the rights to North America). Thanks to this agreement, we would say that **SOBI could become the Swedish counterpart to Shire, namely a group focused on rare diseases field and also with high exposure to the haemophilia field.**

Fig. 1: SOBI - Commercial and clinical portfolio

Project	Indication	Partner	Clinical stage
Elocta (rFVIII Fc)	Haemophilia A	Biogen	Registered
Alprolix (rFIX Fc)	Haemophilia B	Biogen	Registered
Orfadin oral suspension	Hereditary Tyrosinaemia Type 1	Proprietary	Registered
Orfadin 20 mg capsule	Hereditary Tyrosinaemia Type 1	Proprietary	Registered
Nitisinone	Alkaptonuria	DevelopAKUre	Phase III
SOBI003	Enzyme replacement therapy	Proprietary	Preclinical
IL-1 Affibody	IL-1 driven disease	Affibody	Preclinical
C5 inhibitor	Complement C5 driven disease	Affibody	Preclinical
XTEN	Haemophilia	XTEN	Preclinical

Source: SOBI; Bryan, Garnier & Co. ests

Fig. 2: Sales - change in mix from 2015 to 2020e



Source: Bryan, Garnier & Co. ests

Today still, this franchise only plays a small role in earnings generation in that the two products that make up the division were only very recently approved by the European watchdog (November 2015 for Elocta and May 2016 for Alprolix). However, we estimate that it should represent almost 60% of the group's revenues in 2022e (excluding royalties and revenues linked to manufacturing as is the case with PFE's Refacto), with combined sales of almost EUR500m. Note also that the two companies pay each other royalties as a percentage of sales and net profit generated in their respective regions, according to the following scheme:

Fig. 3: Financial terms of the SOBI-Biogen agreement

% Royalties/Reimbursement between companies	Method	Before 1st sales in SOBI's territory	Base rate	After 1st sales in SOBI's territory
From SOBI to BIIB based on net sales in SOBI's territories	Royalty on sales	n/a	12%	17%
BIIB to SOBI based on net sales in North America	Royalty on sales	2%	12%	7%
BIIB to SOBI based on net sales in BIIB's territory ex-North Am.	Royalty on sales	2%	17%	12%
BIIB to SOBI based on net profit from BIIB's distribution territory*	Royalty on net profit	10%	50%	35%
** BIIB's distribution territory pertains to the territory in which sales are conducted through a third party*				

Source: SOBI; Bryan, Garnier & Co ests.

Fig. 4: Haemophilia - SOBI's addressable market

	Haemophilia A pop.	Haemophilia B pop.
Central and eastern Europe	6,839	1,155
Germany, Austria and Switzerland	4,616	876
Belgium, Netherlands and Luxembourg	1,875	379
Italy and Greece	4,651	980
Nordics and Baltics	1,670	384
France	5,400	1,201
UK and Ireland	6,229	1,394
Spain and Portugal	2,217	388
TOTAL Europe	**33,497**	**6,757**
Middle East	16,770	3,632
North Africa	2,959	610
Russia	5,801	992
TOTAL SOBI's territory	**59,027**	**11,991**

Source: SOBI; Bryan, Garnier & Co ests.

While these two projects look fundamentally promising, we nevertheless believe that consensus forecasts are slightly too optimistic, whether in terms of peak sales or ramp-up. Admittedly Biogen's figures are very attractive: barely a year after approval in the US market, Eloctate (Elocta's commercial name in the region) and Alprolix generated combined sales of USD500m. We ask ourselves to what extent these figures have inspired analysts' forecasts whereas underlying momentum on either side of the Atlantic is very different (the appeal for recombinant approaches and the share of patients under prophylactic treatment in Europe are well below US standards for example).

2.2. Caution for the short term as well

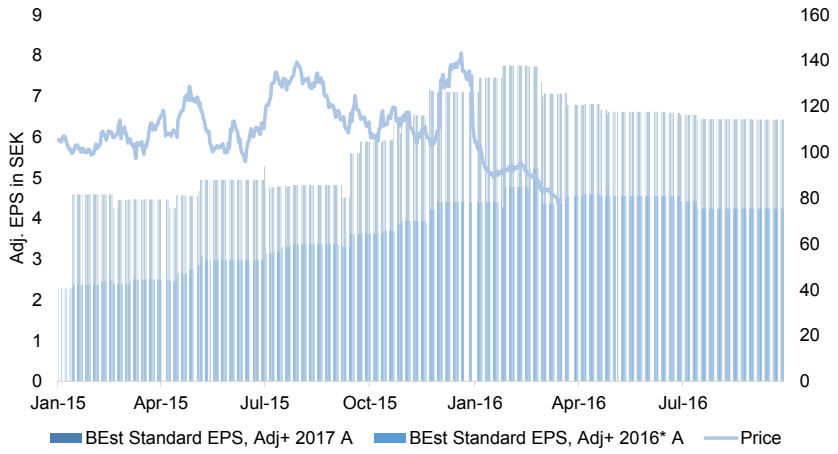
We will focus especially on Elocta's ramp-up in view of its relative weight in valuations (around 30-40% in our case). And as we stated in the first part of this study, the risk of disappointment should not be underestimated, especially in view of 1/ the recent change in the competitive backdrop (Kovaltry having been approved recently, and we believe that it should benefit from the large base of patients built up by Bayer with Kogenate), and 2/ the lower appetite for recombinant factors in Europe.

Fig. 5: 2016 guidance vs BG and consensus estimates

(in SEKm)	SOBI Guidance	Consensus	BG
Revenues (including royalties, manufacturing income, etc.)	4,800-5,000	5,178	4,850
Gross margin (%)	68% -70%	71%	70%
EBITA	1,200-1,300	1,134	1,161
in % of revenues	25-26%	22%	24%

Source: Bloomberg; Bryan, Garnier & Co ests.

Fig. 6: Change in 2016e and 2017e EPS since January 2015



Source: Bloomberg; Bryan, Garnier & Co. ests

2.3. Initiation at SELL with a FV of SEK100

We are initiating coverage of SOBI with a Sell recommendation and a FV of SEK100. Growth momentum that we expect for the company is generally very positive, since Elocta and Alprolix are two projects that should enable the group to double in size by the start of the next decade. However 1/ in our humble opinion, short-term market forecasts are slightly too high concerning the ramp-up of this franchise, 2/ the risk of disappointment during upcoming publications is far from zero, whether for SOBI or BIIB, and this is likely to result in a downgrade to the consensus average.

Fig. 7: BG estimates vs the consensus (2015-2019e)

(in SEKm)	2015	2016e	2017e	2018e	2019e
Total revenues (in EURm)	**3,228**	**5,065**	**5,868**	**7,006**	**8,173**
% growth y-o-y	0%	57%	16%	19%	17%
% Δ vs Bloomberg consensus	0.0%	-2.2%	-6.7%	-10.5%	-10.4%
Bloomberg consensus	3,228	5,178	6,286	7,830	9,120
Reported EBITA (in EUR)	**433**	**1,161**	**1,612**	**2,268**	**2,762**
% growth y-o-y		n/s	39%	41%	22%
% Δ vs Bloomberg consensus		2.3%	-8.0%	-13.4%	-18.0%
EBITA Bloomberg consensus	433	1,135	1,753	2,620	3,367

Source: Bloomberg; Bryan, Garnier & Co ests.

Our DCF valuation also points to a Fair Value of SEK100 and based on the following factors:

- A discount rate (WACC) of 9% based on 1/ a risk-free rate of 1.6%, 2/ an equity risk premium of 7% and 3/ a beta of 1.1.

- We have assumed that the group's EBIT margin should be close to 30-35% over a long period thanks to the rising momentum of Elocta and Alprolix (for which we estimate a net gross margin at almost 80%e).

- Given SOBI's status as a growth stock and the various factors set to underpin the development of its various target markets, we have assumed a growth rate to infinity of 3%.

Fig. 8: SOBI – DCF valuation

(in USDm)	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Revenues	5,065	5,962	7,237	8,427	9,149	9,558	9,639	9,462	9,169	8,914
% chg yoy		17.7%	21.4%	16.4%	8.6%	4.5%	0.8%	-1.8%	-3.1%	-2.8%
(+) Current EBIT	**860**	**1,289**	**1,994**	**2,509**	**3,005**	**3,150**	**3,178**	**3,115**	**3,009**	**2,916**
in % of sales	17.0%	21.6%	27.5%	29.8%	32.8%	33.0%	33.0%	32.9%	32.8%	32.7%
% chg yoy		50.0%	54.6%	25.9%	19.7%	4.8%	0.9%	-2.0%	-3.4%	-3.1%
(-) Taxes	189	284	439	552	661	693	699	685	662	642
(+) D&A	334	376	398	421	421	411	395	378	367	357
= Net operating income after tax	**1,005**	**1,381**	**1,953**	**2,379**	**2,765**	**2,868**	**2,874**	**2,808**	**2,714**	**2,631**
(-) CAPEX	203	238	289	337	366	382	386	378	367	357
(-) Change in WCR	289	21	276	617	144	82	16	-35	-59	-51
= Free Cash Flows	**513**	**1,122**	**1,388**	**1,425**	**2,254**	**2,404**	**2,473**	**2,465**	**2,406**	**2,326**

= Enterprise Value (EURm)	**29,005**
(-) Minority interests	0
(-) Net debt	1,651
= Equity value (SEKm)	**27,354**
Number of diluted shares	270.4
= Fair Value per share (SEK)	**101**

Source: Bryan, Garnier & Co ests.

2.4. A FV of SEK150 in a more optimistic scenario

The main risk to our recommendation would clearly be higher than expected growth in the haemophilia franchise. Forthcoming quarterly publications should obviously help assess this aspect, but we would nevertheless highlight the fact that a **re-rating on our part could also stem from the confirmation of Elocta's ability to rapidly induce immune tolerance in haemophilia A patients with inhibitors** (which would really help the product stand out from all the other long-acting drugs on the market).

SOBI and BIIB have not yet decided whether to launch trials aimed at validating this assumption and for this reason, we have only factored in low upside potential associated with this development (especially since the data we have stems from a fairly small sample of patients). However, if a trial is indeed launched, 1/ we understand that results could be obtained during 2018 and 2019, if it is

initiated in the next few months, and 2/ we estimate that this data would be a key part of the process to differentiate the product and its growth.

For all useful purposes, **note that our FV would stand at SEK150 if we were to integrate this prospect without adding any probability of success ratio.** Note also that if this scenario were to materialise it would have a clear impact on Grifols' EPS and valuation.

Fig. 9: BG valuation – Best-case scenario

(in USDm)	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Revenues	5,065	5,962	7,724	9,412	11,031	12,356	13,369	14,033	13,786	13,577
% chg yoy		17.7%	29.6%	21.8%	17.2%	12.0%	8.2%	5.0%	-1.8%	-1.5%
(+) Current EBIT	**860**	**1,289**	**2,136**	**2,817**	**3,656**	**4,123**	**4,477**	**4,718**	**4,628**	**4,551**
in % of sales	17.0%	21.6%	27.7%	29.9%	33.1%	33.4%	33.5%	33.6%	33.6%	33.5%
% chg yoy		50.0%	65.7%	31.9%	29.8%	12.8%	8.6%	5.4%	-1.9%	-1.7%
(-) Taxes	189	284	470	620	804	907	985	1,038	1,018	1,001
(+) D&A	334	376	425	471	507	531	548	561	551	543
= Net operating income after tax	**1,005**	**1,381**	**2,091**	**2,668**	**3,359**	**3,747**	**4,040**	**4,242**	**4,161**	**4,093**
(-) CAPEX	203	238	309	376	441	494	535	561	551	543
(-) Change in WCR	289	21	373	716	324	265	203	133	-49	-42
= Free Cash Flows	**513**	**1,122**	**1,409**	**1,575**	**2,594**	**2,988**	**3,303**	**3,547**	**3,659**	**3,592**

= Enterprise Value (EURm)	**41,442**
(-) Minority interests	0
(-) Net debt	1,651
= Equity value (SEKm)	**39,791**
Number of diluted shares	270.4
= Fair Value per share (SEK)	**147**

Source: Bryan, Garnier & Co ests.

3. Haemophilia A: the need to stand out from the crowd

3.1. Eloctate slowing in the US…

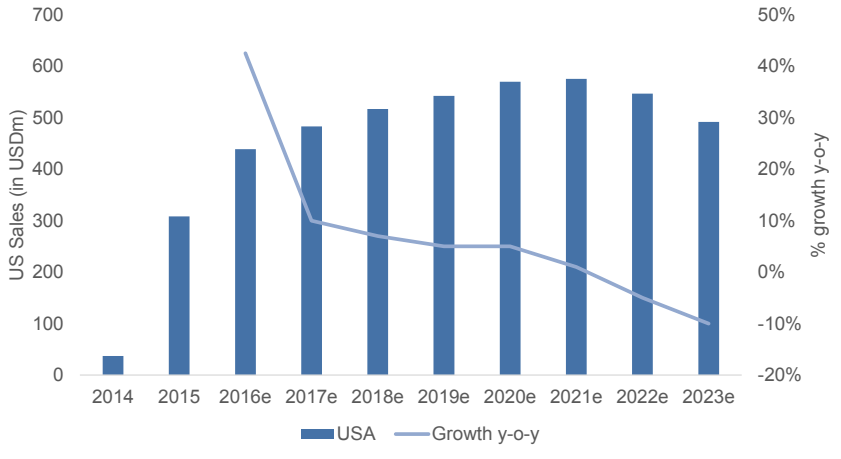
Eloctate has undeniably benefited from its status as the first entrant in the much-coveted segment of long-acting FVIIIs. Proof of this is the fact that it should generate more than USD400m in revenues in the US this year (just two years after its approval by the FDA).

That said, we would note that **recent quarterly publications have shown a clear slowdown in growth from one quarter to the next** and this has also had an impact on SOBI which is paid 12% in royalties on these sales. Contrary to the consensus on BIIB/Bioverativ, which is still forecasting growth of 20-30% in 2017e, we believe the trend is unlikely to improve for a large number of reasons:

- **Three other long-acting rFVIIIs have come onto the US market in recent months** (Adynovate, Kovaltry, Afstyla). While the data obtained from pivotal studies show no major differences in terms of efficacy and toxicity (at least in haemophilia A patients without inhibitors), we nevertheless consider that these new therapies could provide leverage to the patient bases created by the companies that have developed them (Shire, Bayer and CSL).

- **The reduction in the number of weekly injections is actually fairly low and we believe that this puts a significant brake on the prospect of a mass switchover by patients undergoing prophylactic treatment** to this first generation of long-acting solutions. In addition, a portion of these patients (also difficult to quantify) fear the possibility of developing inhibitors due to a possible change in product or brand.

Fig. 10: Eloctate –BG sales estimates for the US



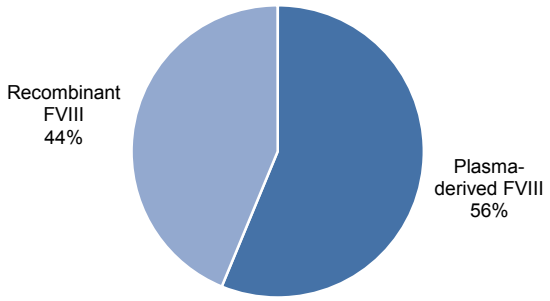
Source: Bryan, Garnier & Co. ests

3.2. … and the risk of disappointment in Europe is far from zero

We are also fairly reserved about the ramp-up of Elocta in Europe. The fact that it is the first entrant is obviously positive, but this does not mask the fact that a **second product (Kovaltry by Bayer) was launched a few months after its approval by the watchdog,** and more precisely in March of this year.

We should also bear in mind that **Europe as a whole is far less keen on recombinant approaches** and this is probably due to the additional costs involved compared with pdFVIIIs, which are nevertheless 20-30% less expensive. We believe this situation is unlikely to change radically, especially in a backdrop whereby the SIPPET study showed that the risk of developing inhibitors is far less important 1/ with plasma derivatives containing vWF, and 2/ in treatment-naive patients.

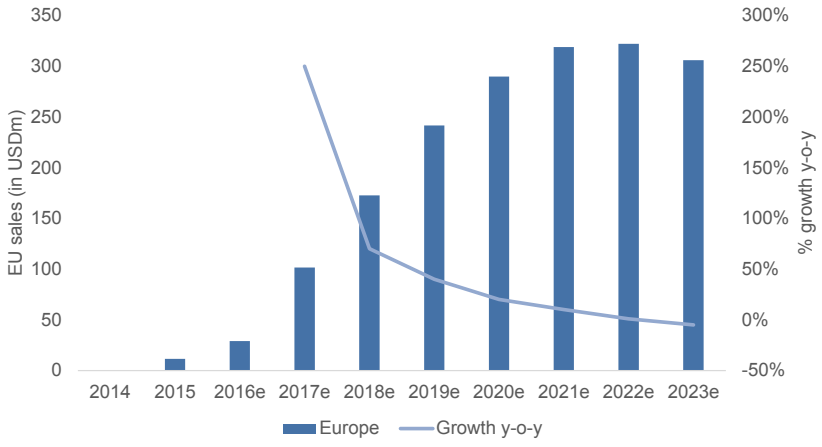
Fig. 11: FVIII - Volumes depending on the factor's origins (Europe)



Source: MRBI; Bryan, Garnier & Co. ests

Under these conditions, we estimate that Elocta's European sales should be closer to USD300-350m at the start of the next decade, rather than the USD700m that the low end of the consensus is currently pointing to.

Fig. 12: Eloctate –BG sales estimates for Europe



Source: Bryan, Garnier & Co. ests

3.3. An opportunity in ITI… to be confirmed!

It is fairly difficult to find exact figures concerning the market's forecasts for Elocta out to 2020, although our interactions with BIIB and SOBI nevertheless suggest that we are at the low-end of the consensus range, and it is highly likely that this difference stems especially from our cautious position on the advent of the project.

However, nothing is set in stone and we admit that we could revise our figures upwards if Eloctate were to confirm the first clinical results generated as a "desensitisation treatment" for haemophilia A patients with inhibitors. For the moment, data here is very few and far between, and neither BIIB nor SOBI have confirmed their intention to launch a confirmatory clinico-marketing trial. All of this therefore remains very theoretical, although the likelihood of this type of development being initiated is high in our view, since without it, we do not see how the product could genuinely stand out from other rival products.

■ What proof is there?

A few months ago, retrospective data implied the use of Eloctate and Elocta in three young children having developed high levels of inhibiting antibodies. The results were admittedly very promising, especially in terms of efficacy.

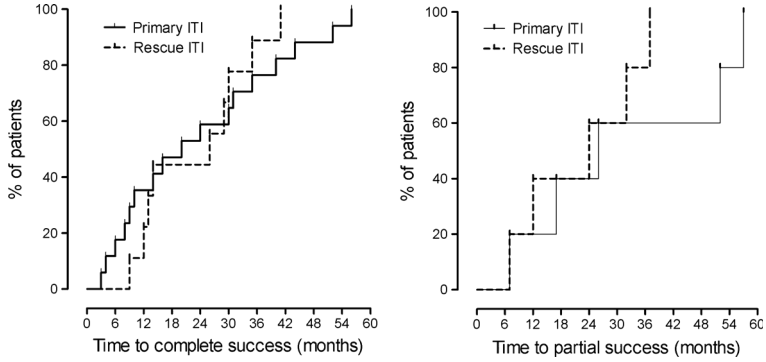
These three patients were able to be desensitised in less than three months (and even within four weeks for the patient that was refractory to a previous ITI based on rFVIII), whereas the duration of the treatment before a complete or even partial response is generally far higher than 12 months with pdVIIIs containing vWF (Oldenburg et al, 2014).

Fig. 13: Eloctate - Immune tolerance induction (ITI) – preliminary results

Patient	1	2	3
Haemophilia severity	< 0.01 IU/ml	< 0.01 IU/ml	< 0.01 IU/ml
F8 gene mutation	Intron 22 inversion	Nonsense	Not available
Age at anti-FVIII detection	13 months	9 months	10 years
Peak anti-FVIII titer	32 BU	422 BU	16 BU
Prior ITI	No	Yes	No
Initial ITI dose	200 IU/kg QOD	200 IU/kg 3x / week	100 IU/kg QOD
Time to anti-FVIII = 0	**12 weeks**	**4 weeks**	**11 weeks**
Current anti-FVIII	0 BU	0 BU	0 BU

Source: Biogen; Bryan, Garnier & Co ests.

Fig. 14: ITI with vWF/pdFVIII - time to complete/partial success



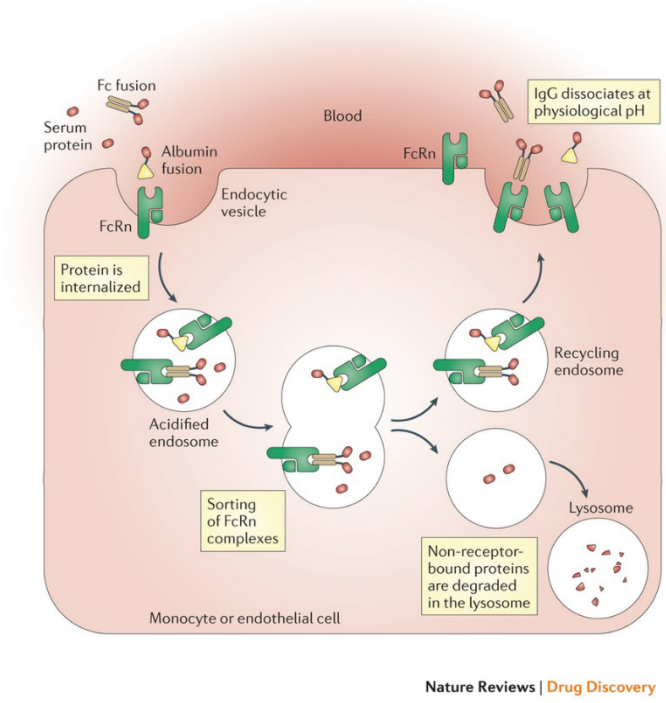
Source: Oldenburg et al (2014)

■ **The possibility of differentiation thanks to a unique action mechanism**

The fact that Eloctate is potentially more efficient from a desensitisation stance could stem from its very construction (fusion protein associating an rFVIII with an Fc fragment from a recombinant human IgG1 immunoglobulin), which enables not only a reduction in lysosomal deterioration in the coagulation factor, but also an induction in regulatory T-cells.

For those that would like to go into further detail on the mechanism, note that Fc is the constant part of an antibody and plays a key role in 1/ initiating effector functions (such as ADCC after joining up with its receptor, or activation of the complement after joining up with the antigen), and 2/ transport/intra-cellular survival, by protecting from an enzymatic deterioration and enabling their recycling (and this is what helps explain the extension in the half-life).

Fig. 15: Fc fusion or how to reduce intra-cellular deterioration



Source: Nature; Bryan, Garnier & Co. ests

In addition, the fact that Eloctate/Elocta is an Fc fusion protein also seems to have immuno-modulating/tolerogenic virtues given its ability to induce Tregs (De Groot et al, 2008; Lei et al, 2005). This is what could explain Eloctate's ability to induce a desensitisation more quickly than a native FVIII, especially since the formation of inhibiting antibodies is the result of an immune response mediated by T-cells.

■ **What impact on our figures and the rest of the sector in an optimistic scenario?**

However, caution is the mother of safety, especially since prospective data on a sufficiently large number of patients is missing. For this reason, we have decided not to factor the opportunity into our forecasts, or at least until conclusive results are presented.

For all useful purposes, we have nevertheless factored in the impact that the success of a large multi-centric study focused on patients with inhibitors could have (ideally the study would be randomised with several arms including Eloctate and other types of FVIIIs). The result is that our sales forecasts for SOBI territories could be increased by around USD400m by 2023e if the results were to be published in 2018 or 2019 (although this would depend on the trial design) and on the basis of the following assumptions:

Fig. 16: Eloctate – additional sales potential in ITI

	2016e	2017e	2018e	2019e	2020e	2021e	2022e	2023e
Congenital haemophilia A - Prevalence	**30,000**	**30,300**	**30,603**	**30,909**	**31,218**	**31,530**	**31,846**	**32,164**
- US	15,000	15,150	15,302	15,455	15,609	15,765	15,923	16,082
- Europe (SOBI territory)	15,000	15,150	15,302	15,455	15,609	15,765	15,923	16,082
- RoW	9,000	9,090	9,181	9,273	9,365	9,459	9,554	9,649
% Severe haemophilia A (FVIII levels < 1%)	70%	70%	70%	70%	70%	70%	70%	70%
% Diagnosed & treated	65%	65%	65%	65%	65%	65%	65%	65%
% Incidence of inhibitors	30%	30%	30%	30%	30%	30%	30%	30%
% Market penetration - US	0%	0%	10%	20%	30%	40%	50%	50%
% Market penetration - Europe	0%	0%	5%	10%	20%	30%	40%	50%
% Market penetration - RoW	0%	0%	5%	10%	20%	30%	40%	50%
Pricing per patient - US (in USD)	500,000							
Pricing per patient - Europe (in USD)	400,000							
Eloctate - Non-risk adjusted sales (in USDm)	**0**	**0**	**171**	**346**	**592**	**844**	**1,100**	**1,251**
% var y-o-y		n/s	n/s	102%	71%	42%	30%	14%
- US	0	0	104	211	320	430	543	549
- Europe	0	0	42	84	170	258	348	439
- ROW	0	0	25	51	102	155	209	263

Source: Bryan, Garnier & Co. ests

- We base ourselves on the principle that the time-to-complete/partial response is around 15 weeks and that during this time-lapse, Eloctate would be administered five times a week (rather than every four days) at a dose of 100 IU/kg (vs 50 IU/kg under a prophylactic treatment and without inhibitors). This more or less points to an overall cost of USD400-500,000 per patient.

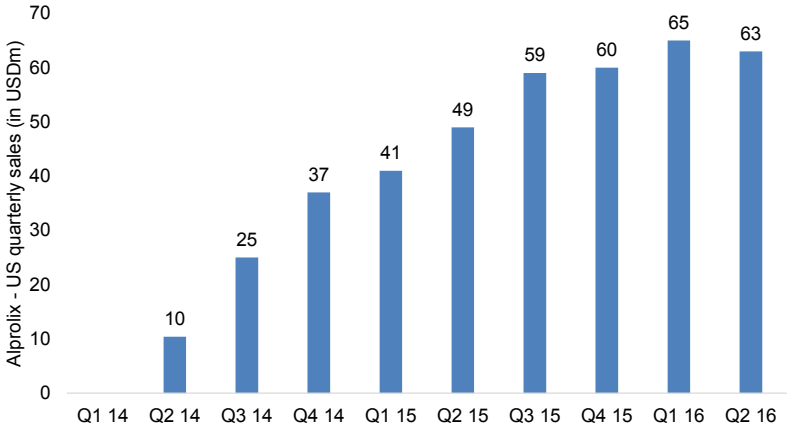
- Given the time gain provided, and for a potentially lower cost than current alternatives, it seems likely that 40% of patients developing inhibitors (whatever their title count) would switch to Eloctate as a first intention therapy as of 2022e.

- As we said in the part of our study dedicated to Grifols, it is highly likely that this would impact sales of pdFVIIIs, but also those of ACE910, Feiba and NovoSeven in view of their second intention positioning.

4. Idelvion set to weigh on Alprolix ramp-up

Alprolix is the counterpart to Eloctate in haemophilia B in that it is a long-acting recombinant FIX with an Fc fusion protein enabling the extension of its half-life. Here again, its ramp-up has been more encouraging in the US thanks to its position as a first-entrant and the lack of direct competition for two years.

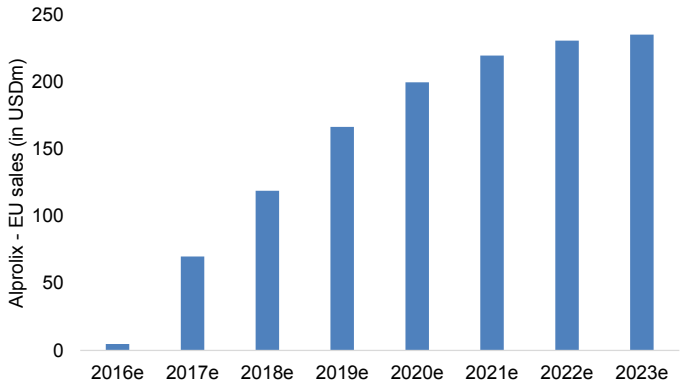
Fig. 17: Alprolix – Quarterly sales in the US



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

However, as for Elocta, we believe that growth in Europe is unlikely to be as high as in the US given the simultaneous launch of rival alternatives. As it happens, the risk is even greater given that 1/ the said rival is actually a best-in-class, whether in terms of efficacy or administration schedule (every 10-14 days or 21 in certain cases, vs. every 7-10 days for Alprolix), 2/ development of inhibitors is far less significant in haemophilia B patients (< 5%e) and the eventual increase in sales associated with a positioning in ITI would only be very limited.

Fig. 18: Alprolix –BG sales estimates for Europe



Source: Bryan, Garnier & Co. ests.

5. Appendix

Fig. 19: Product sales estimates (2015-2021e)

Fig. 20: (in SEKm)	2015	2016	2017	2018	2019	2020	2021
Product sales	**1,841**	**3,748**	**4,653**	**5,932**	**7,125**	**7,847**	**8,254**
% var y-o-y	41%	104%	24%	27%	20%	10%	5%
- Elocta - Hemophilia A	96	244	854	1,451	2,032	2,438	2,682
% var y-o-y		154%	250%	70%	40%	20%	10%
- Alprolix - Hemophilia B	0	40	589	1,001	1,401	1,682	1,850
% var y-o-y	n/s	n/s	1370%	70%	40%	20%	10%
- Hemophilia - Royalty and one-off payment		1,477	973	1,062	1,126	1,185	1,211
% var y-o-y			-34%	9%	6%	5%	2%
- Kineret - Inflammation (RA & others)	805	1,047	1,203	1,312	1,404	1,333	1,267
% var y-o-y	32%	30%	15%	9%	7%	-5%	-5%
- Orfadin - Hereditary Tyrosinemia Type 1	796	796	876	937	984	1,023	1,054
% var y-o-y	45%	0%	10%	7%	5%	4%	3%
- Others	144	144	158	169	178	185	191
% var y-o-y	21%	0%	10%	7%	5%	4%	3%

Source: Bryan, Garnier & Co ests.

Fig. 21: Eloctate & Alprolix sales estimates (2014-2021e)

(in USDm)	2014	2015	2016e	2017e	2018e	2019e	2020e	2021e
Eloctate/Elocta	**37**	**331**	**528**	**662**	**783**	**887**	**970**	**1,010**
% var y-o-y			59%	25%	18%	13%	9%	4%
- US	37	308	439	483	517	543	570	575
% var y-o-y			43%	10%	7%	5%	5%	1%
- Europe	0	11	29	102	173	242	290	319
% var y-o-y				250%	70%	40%	20%	10%
- ROW	0	12	60	78	94	103	110	116
% var y-o-y		n/s	n/s	30%	20%	10%	7%	5%
Alprolix	**80**	**234**	**325**	**434**	**515**	**587**	**641**	**673**
% var y-o-y		n/s	39%	34%	19%	14%	9%	5%
- US	76	209	260	286	306	321	337	348
% var y-o-y		175%	24%	10%	7%	5%	5%	3%
- Europe	0	0	5	70	119	167	200	220
% var y-o-y		n/s	n/s	n/s	70%	40%	20%	10%
- ROW	4	25	60	78	90	99	104	106
% var y-o-y		n/s	n/s	30%	15%	10%	5%	2%

Source: Bryan, Garnier & Co ests.

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