BRYAN, GARNIER & CO

INDEPENDENT RESEARCH

Grifols

¡El consenso al borde de un ataque!

17th October 2016

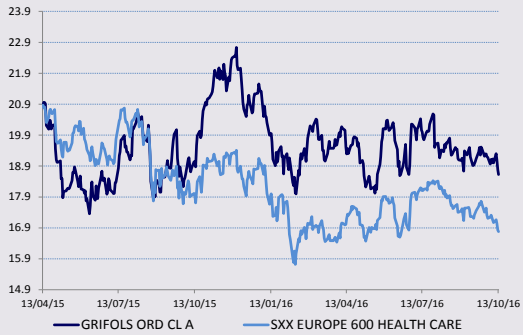
Healthcare

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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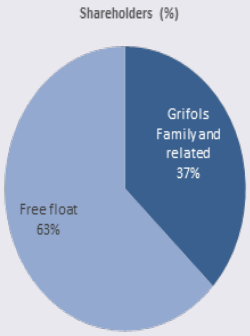
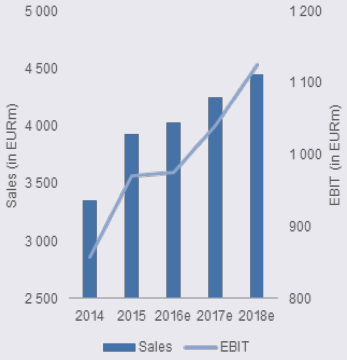




Company description

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.

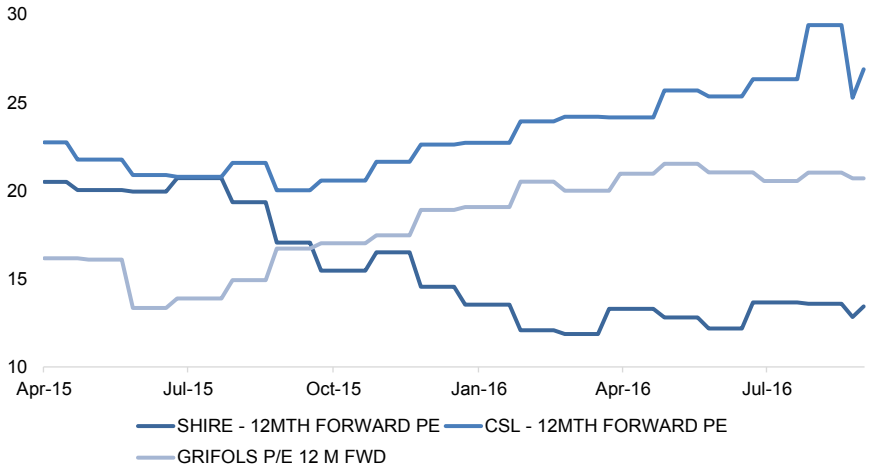
2. The reason for writing this report

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

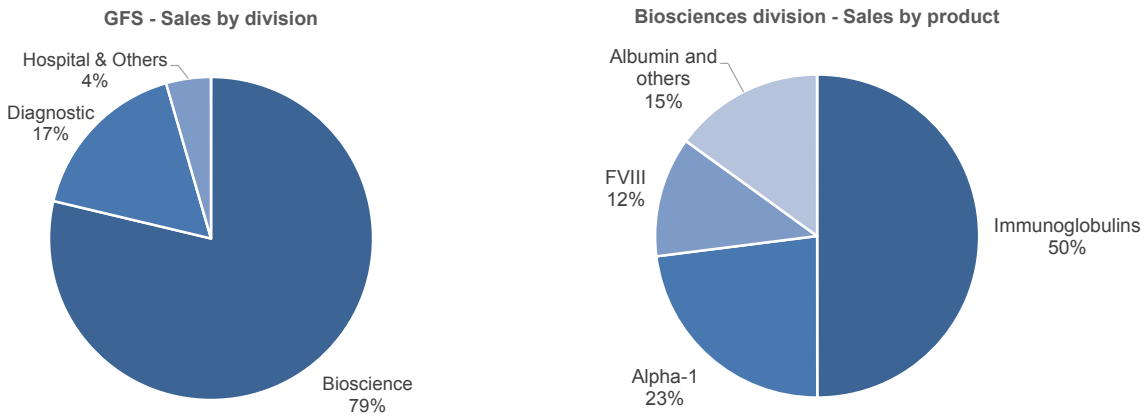


Source: Thomson Reuters; Bryan, Garnier & Co. ests.

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

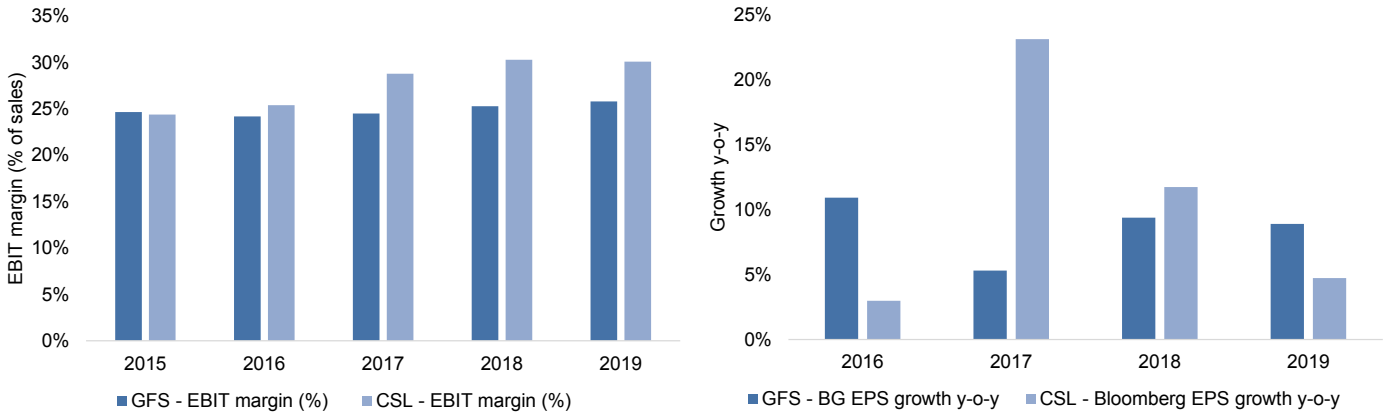
Some players might say however that Grifols is trading on a significant discount relative to CSL (around 20%) whereas the two companies share a number of similarities (high exposure to the immunoglobulins field, predominance of plasma FVIIIs in its haemophilia business etc.). However, this reasoning 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

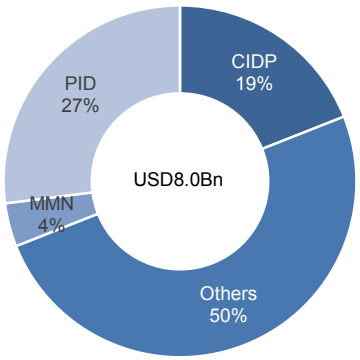
3.1. Exposure to IG: a key factor for investor appeal

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

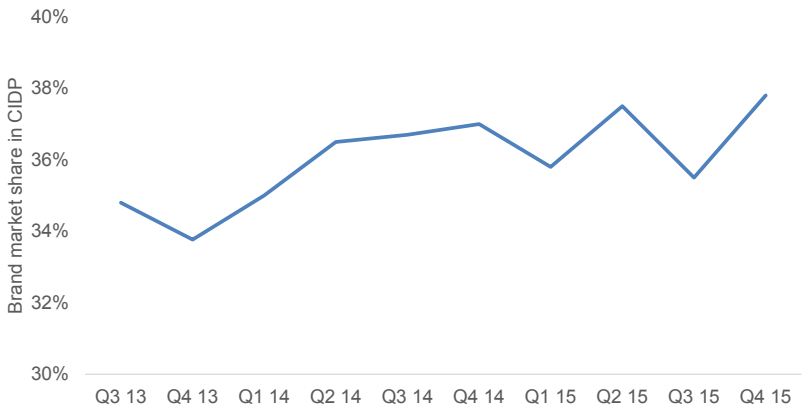
The main growth driver for Grifols in this segment is undoubtedly Gamunex (for which the majority of sales is generated with the IV form). While the drug's very comprehensive label is a top factor underlying its success, we would say that the main reason is especially its long-standing exposure to the 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.

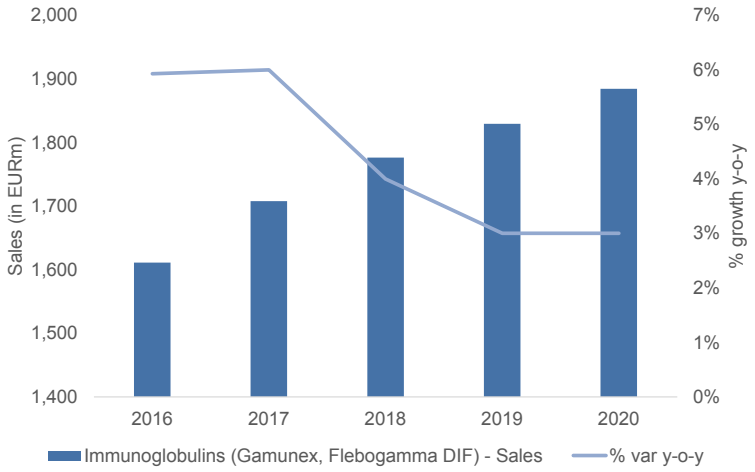
Fig. 9: Gamunex market share in CIDP



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



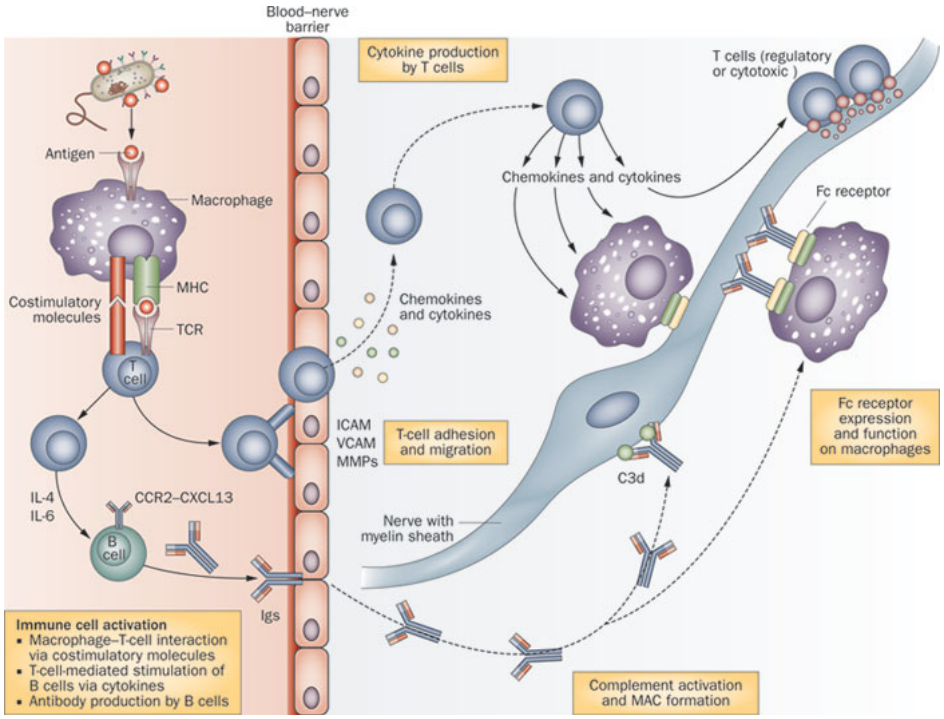
Source: Grifols; Bryan, Garnier & Co. ests

- **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.

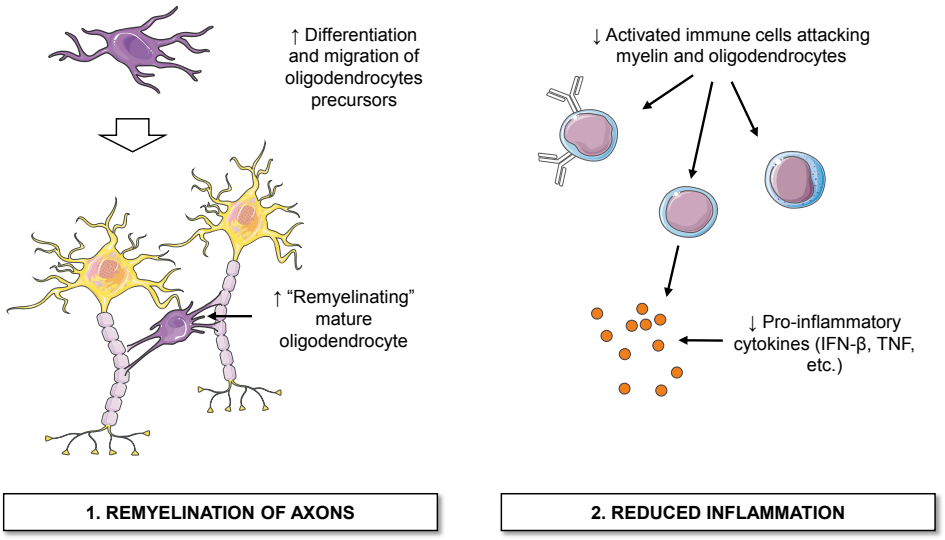
We believe that IGs should remain one of the standard treatments for the disease

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.

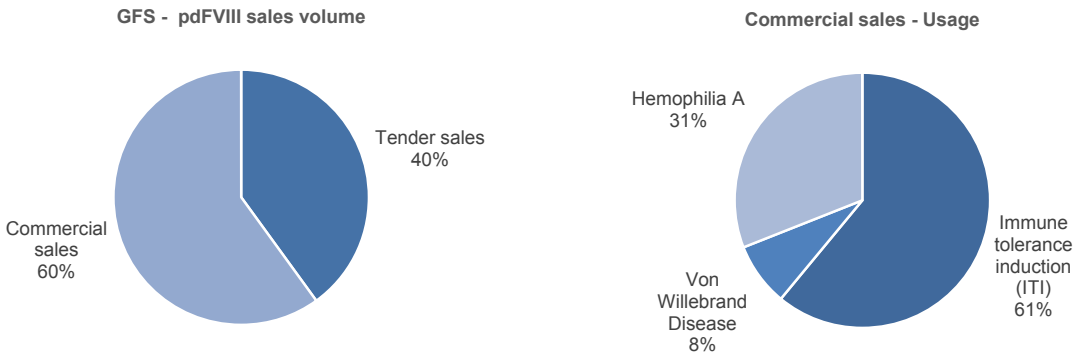
4. FVIIIs potentially under pressure as of 2018e

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

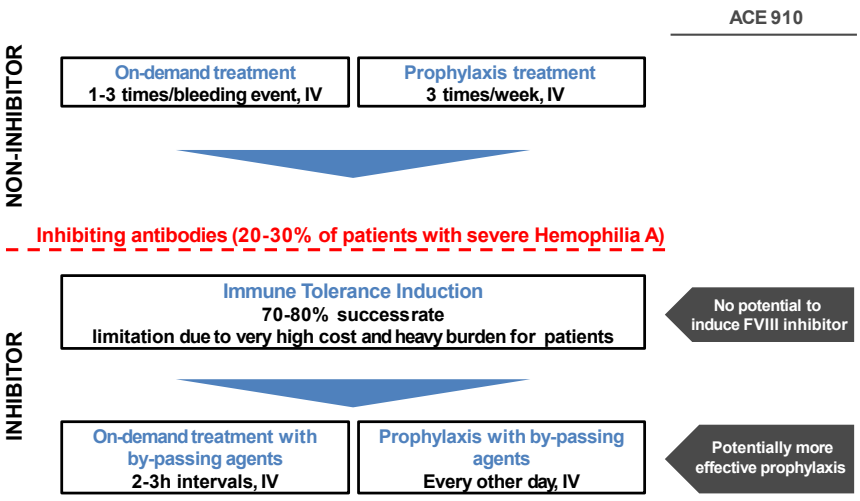
Admittedly for the moment, we assume that the ROG molecule is likely to struggle to penetrate the market of haemophilia A without inhibiting antibodies, although we estimate that its efficacy profile and administration schedule make it particularly attractive for patients with inhibiting antibodies. 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



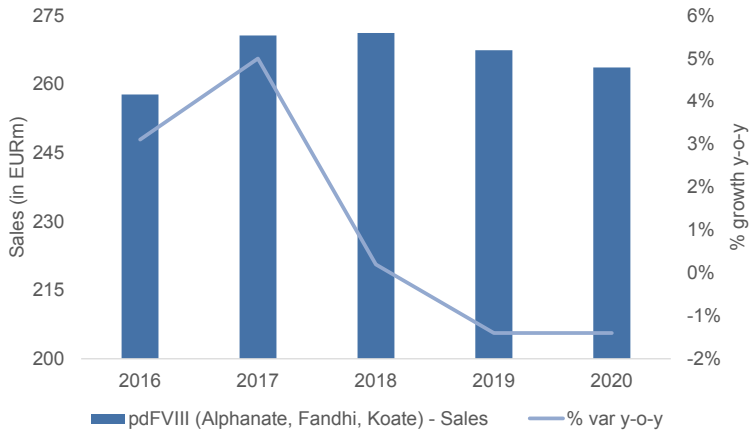
Source: Roche; Bryan, Garnier & Co. ests.

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…

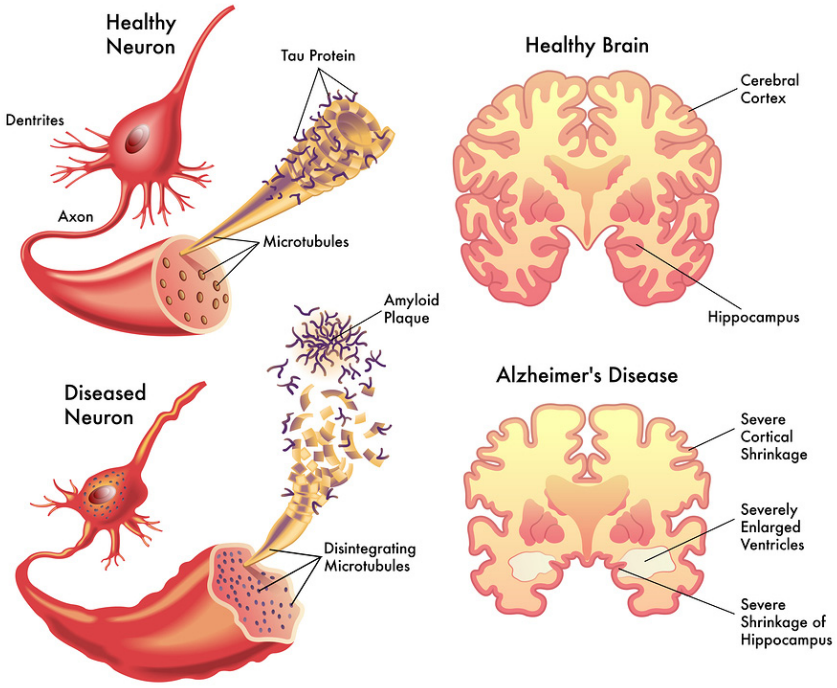
5.1. A significant and rational medical need…

- **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.

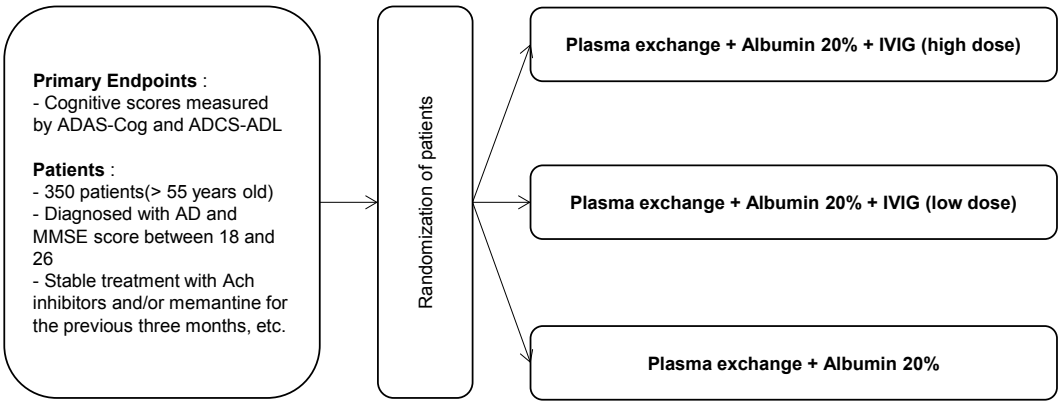
- **A Phase III underway and results expected by H1 2017 at the latest**

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.

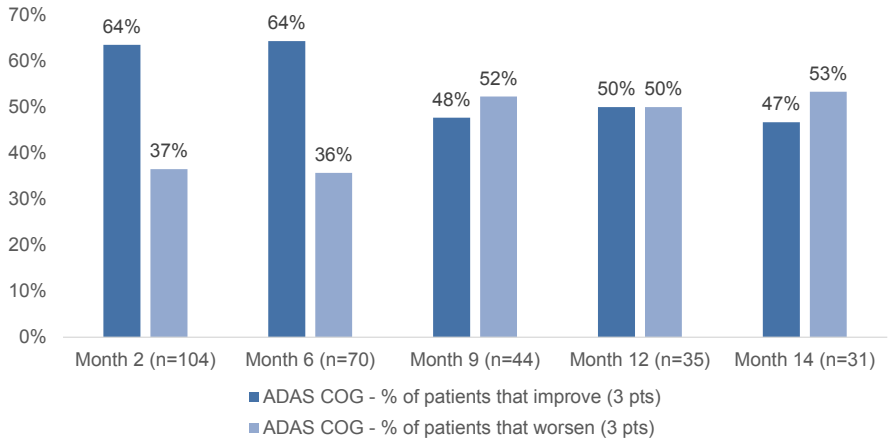
The definitive results should be published in early 2017 at the latest, bearing in mind that intermediary results for 170 patients were presented at a congress and that these were fairly intriguing. Randomisation codes were not broken (thereby signifying that we do not know to which groups the eventual 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).

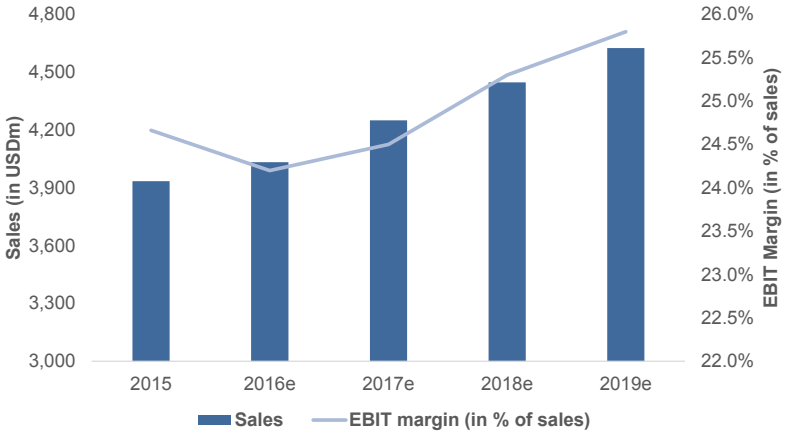
Last but not least, we understand that the regulatory road to take has not been entirely clarified with the authorities and especially with the FDA. Beyond this aspect, we ask ourselves whether the design of the trial is really satisfactory and especially, with a population of patients as small as this (< 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



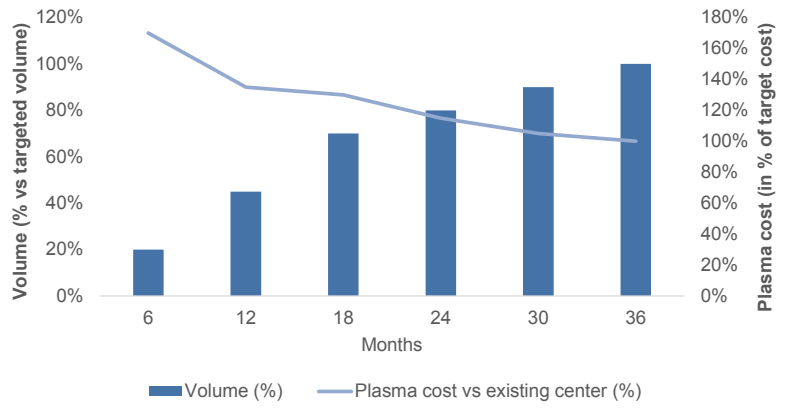
Source: Bryan, Garnier & Co. ests.

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

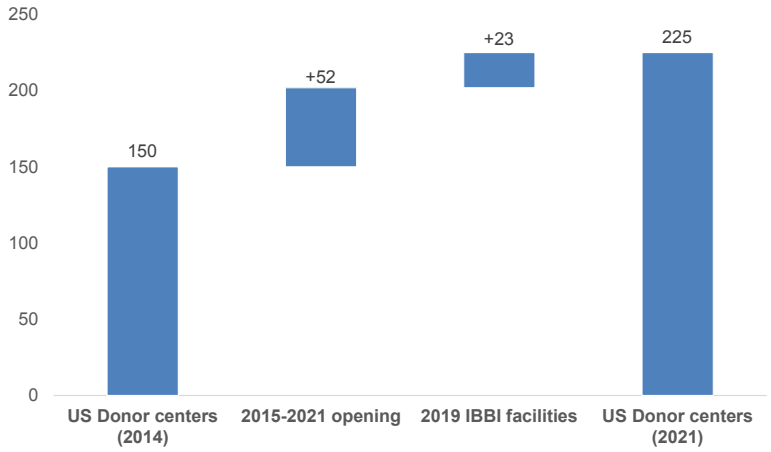
The first factor concerning pressure on margins in the short term remains extension of production capacity for plasma derivatives (opening of new fractioning sites and collection centres), with a double effect on EBIT margin as well: 1/ capacity is not entirely used over the first three years of use, 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.

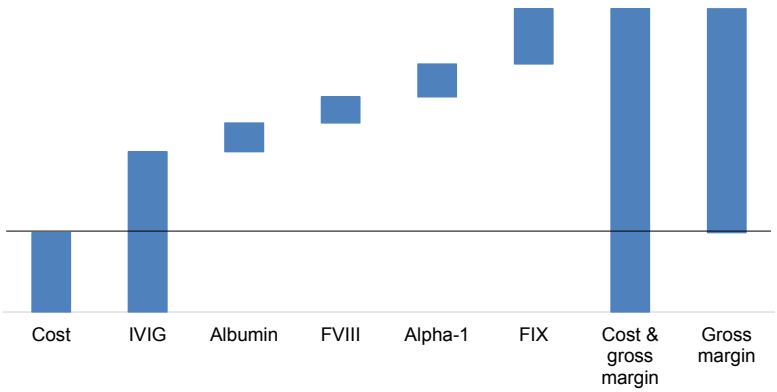
the international side of transfusion (especially since transfusions in the rest of the world are more on an uptrend) as well as 2/ supply of HIV and HCV antigens to immunoassy producers such as Abbott, Siemens and OCD. However, the importance of the US transfusion business means that it is likely to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

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