

Shire PLC

Price 4,590p

Feedback from SHP's ASH call. Questions remain about ACE910's safety profile

Fair Value: 6,800p (+48%)

BUY

Bloomberg	SHP LN
Reuters	SHP.L
12-month High / Low (p)	5,323 / 3,480
Market Cap (GBPm)	41,490
Ev (BG Estimates) (GBPm)	58,446
Avg. 6m daily volume (000)	2,751
3y EPS CAGR	14.0%

	1 M	3 M	6 M	31/12/15
Absolute perf.	3.6%	-4.4%	3.2%	-2.3%
Healthcare	0.9%	-8.6%	-10.1%	-15.5%
DJ Stoxx 600	2.4%	-3.2%	-1.4%	-7.2%

YEnd Dec. (USDm)	2015	2016e	2017e	2018e
Sales	6,100	10,953	14,821	15,765
% change		79.6%	35.3%	6.4%
EBITDA	2,924	4,609	6,695	7,371
EBIT	2,785	4,334	6,250	6,851
% change		55.6%	44.2%	9.6%
Net income	2,310	3,305	4,646	5,321
% change		43.1%	40.6%	14.5%

	2015	2016e	2017e	2018e
Operating margin	45.7	39.6	42.2	43.5
Net margin	37.9	30.2	31.4	33.8
ROE	23.5	11.0	14.0	14.3
ROCE	16.2	5.1	7.2	8.2
Gearing	14.7	71.6	55.1	37.6

(USD)	2015	2016e	2017e	2018e
EPS	3.89	4.25	5.04	5.77
% change	-	9.0%	18.7%	14.5%
P/E	14.9x	13.7x	11.5x	10.1x
FCF yield (%)	6.4%	NM	6.2%	8.6%
Dividends (USD)	0.23	0.20	0.22	0.30
Div yield (%)	0.4%	0.3%	0.4%	0.5%
EV/Sales	8.8x	6.8x	4.8x	4.2x
EV/EBITDA	18.5x	16.1x	10.6x	9.0x
EV/EBIT	19.4x	17.1x	11.3x	9.7x

SHP held a sell-side call last Friday afternoon, during which they discussed data presented at the ASH Congress, and involving the combination of Feiba with a biosimilar of ACE910. Overall, we note that 1/ such combo might lead to a strong increase in thrombin, which might explain some recent side effects seen in ROG's Phase III trial a few weeks ago); 2/ TMA is not an AE that could be explained by the latter mechanism, and rather by the mAb nature of ACE910 (but that remains to be confirmed)... Thus strengthening our cautious stance regarding its safety profile.

ANALYSIS

- **Feiba and ACE910's combo might lead to an excessive thrombin generation.** SHP held a sell-side call last Friday afternoon during which they discussed data regarding the combination of Feiba with a biosimilar of ACE910/Emicizumab. Obviously, their reading has to be done with cautious due to the lack of clarity about the biosimilar nature of the FIXa and FX antibody that was used, or more simply because they are based on *in vitro* experiments... But we would note that 1/ the cocktail might lead to an excessive dose-related thrombin generation (peak values of > 500nM while the normal range is c.50-120nM); 2/ this might explain the thromboembolic events seen in ROG's Phase III trial in Hemophilia A with inhibitors. Of note, rVIIa is also known to affect thrombin generation (Aljamali *et al*, 2009); so such complications can be expected with the different bypassing therapies commercially available.
- **Questions also remain about the potential causes of thrombotic microangiopathies** (the other types of severe adverse events detected in ROG's study – which, in concrete terms, are small vessels occlusions), as such AEs cannot be related to a rise in thrombins. One of the presenters noted that some monoclonal antibodies are known to induce TMAs, and raised the potential role of the complement cascade... Admittedly, complement hyperactivation is a pathogenic effector known to lead to endothelial damage microvascular thrombosis in different diseases (Noris *et al*, 2012), but we would not draw hasty conclusions about this without any confirmatory clinical data.
- **Caution is still warranted.** Detailed data from a large pivotal trial, and preferably over a long period, remain the sole judge. But recent events call for a degree of caution, in our view. As a reminder, we see ACE910 as a potential game-changer in Haemophilia with inhibitors given the strong efficacy observed in a small Phase Ib study... But we are quite cautious about its safety profile due to some weaknesses in its mechanism of action (lower binding affinity to FIX and X relative to a natural or recombinant FVIII, etc.).

VALUATION

- **BUY reiterated with a FV of GBP6,800.** We leave our estimates unchanged knowing 1/ we currently expect a strong decline in Feiba's sales starting from 2018 (i.e. ACE910's first year on the market); 2/ we believe sales from FVIII therapies are also to suffer, though to a much lesser extent... Which could prove to be conservative if the different safety issues were to be confirmed.

NEXT CATALYSTS

- Q4 16/Q1 17: Phase III results of ROG's ACE910 in Haemophilia A patients with inhibitors.

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Analyst :
Mickael Chane Du
33(0) 1 70 36 57 45
mchanedu@bryangarnier.com

Sector Team :
Eric Le Berrigaud
Marion Levi
Hugo Solvet

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London	Paris	New York	Munich	New Delhi
Beaufort House	26 Avenue des Champs Elysées	750 Lexington Avenue	Widenmayerstrasse 29	The Imperial Hotel Janpath
15 St. Botolph Street	75008 Paris	New York, NY 10022	80538 Munich	New Delhi 110 001
London EC3A 7BB	Tel: +33 (0) 1 56 68 75 00	Tel: +1 (0) 212 337 7000	Germany	Tel +91 11 4132 6062
Tel: +44 (0) 207 332 2500	Fax: +33 (0) 1 56 68 75 01	Fax: +1 (0) 212 337 7002	+49 89 2422 62 11	+91 98 1111 5119
Fax: +44 (0) 207 332 2559	Regulated by the	FINRA and SIPC member		Fax +91 11 2621 9062
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Financial Conduct Authority (FCA)	Autorité de Contrôle prudentiel et de			rue de Grenus 7
	resolution (ACPR)			CP 2113
				Genève 1, CH 1211
				Tel +4122 731 3263
				Fax+4122731 3243
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