Fabry pipeline leaves less room for Pharming

Similarly to Pompe, Fabry disease results from the accumulation of globotriaosylceramide in the cells, leading to symptoms that affect many parts of the body, causing pain, angiokeratomas, hypohidrosis, corneal opacity, GI problems, tinnitus, and hearing loss. Fabry disease also involves potentially life-threatening complications such as progressive kidney damage, heart attack, and stroke. The accumulation results from the deficient activity of alpha-galactosidase A (a-Gal A), which breaks down the glycolipids. The disease is caused by an X-chromosome mutation and affects around 1 in 40,000 men and 1 in 60,000 women.

Several options approved

Currently, patients with Fabry disease receive two ERTs with recombinant human a-galactosidase proteins: Fabrazyme (agalsidase beta) commercialized by Sanofi-Genzyme and produced in CHO cells, and Replagal (agalsidase alfa) commercialized by Shire and produced in a human cell line. In addition, in 2016 Amicus launched a chaperone protein that binds to the misfolded enzyme and promotes proper folding, processing, and trafficking. Galafold is now indicated for the treatment of patients above 16 years with an amenable mutation. Unlike in Pompe, the immunogeneicity with current ERTs is less of an urgent issue compared to Fabry. Pharming is working on the development of a recombinant version of the a-galactosidase, and the company believes that it would be a less immunogenetic and compare favorably with Fabrazyme on efficacy and ease of administration. The candidate is expected to enter clinical development in 2020.

Busy late-stage pipeline

The late-stage development pipeline includes phase III trials with the further development of Galafold, with a chemically modified version of a-Gal A from Protalix, and a glucosylceramide synthase inhibitor from Idorsia. The early stage pipeline includes a gene therapy from Avrobio in phase I/II trial, and an epigenetic drug from Resverlogix in phase IIa.

Table 10 - Clinical candidates for Fabry disease

Phase	Company	Candidate / Trial	Description
MA	JCR Pharmaceuticals	Application for Japanese marketing approval of biosimilar JR-051 for Fabry Disease	Biosimilar recombinant alpha-galactosidase A
III	Protalix	BRIGHT: Safety, efficacy, & PK of pegunigalsidase alfa (PRX-102) administered every 4 Weeks in Fabry disease Extension study of 1 mg/mL pegunigalsidase alfa Safety and efficacy in patients currently treated with Replagal BALANCE: safety and efficacy of PRX-102 compared to agalsidase beta on renal function	PRX-102: pegunigalsidase alfa is a plant cell culture expressed, and a chemically modified version of, the recombinant alpha-Galactosidase-A protein
III	Amicus Therapeutics	Extension study of the long-term effects of Migalastat HCL	-
III	Idorsia	MODIFY: Efficacy and safety of Lucerastat oral monotherapy in adults	Lucerastat: a glucosylceramide synthase inhibitor for neuropathic pain
II	Genzyme	Long-term safety, PD and exploratory efficacy of GZ/SAR402671 in treatment-naïve adult male patients	GZ/SAR402671: a glucosylceramide synthase inhibitor, which blocks the formation of glucosylceramide (GL-1), a key intermediate in the synthesis of GL-3
I/II	Resverlogix	Safety and effect of oral RVX000222	RVX000222: a BET inhibitor which modulates the expression of a variety of genes, with effects on pathways downstream of substrate accumulation
I/II	AvroBio	Open-label study of efficacy and safety of AVR-RD-01 for treatment - naive subjects	Gene therapy: infusing the patient's own genetically modified stem cells that express the enzyme α-galactosidase A

Source: clinicaltrials.gov

Figure 35 - Overview Ruconest commercialization activities

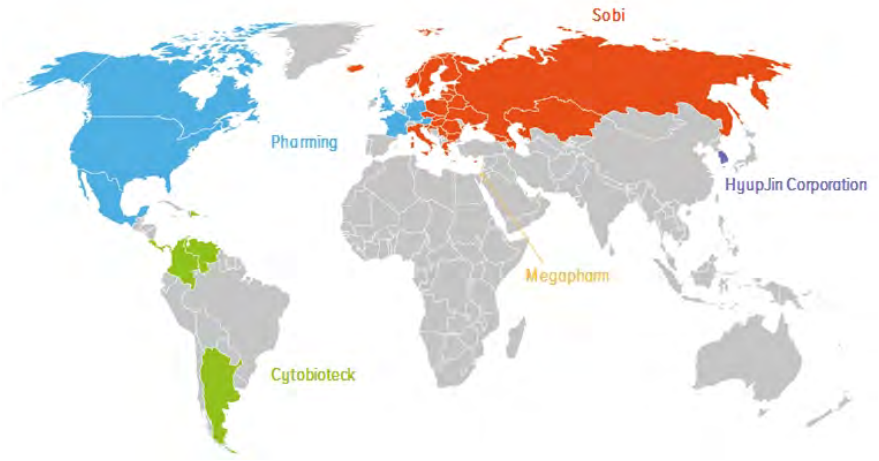


Table 11 - Overview HAE trials

Company	Drug	Action	Adm.	Phase	Details
Acute					
BioCryst	BCX7353	Kallikrein inhibitor	Oral	II Ongoing	ZENITH-1: randomized, double-blind, placebo-controlled, dose-ranging trial of the efficacy, safety and tolerability of BCX7353, in 60 subjects
KalVista	KVD900	Kallikrein inhibitor	Oral	II Expected	KDV900 for acute HAE attacks Expected by YE'18
Prophylaxis					
Shire	Cinryze (SHP616)	Plasma-derived C1-INH	SC	III Concluded	Subcutaneous formulation of Cinryze for the prophylaxis of HAE
CSL	CSL312	Antibody anti-factor XIIa	SC	II	Expected in 2018
Pharming	Ruconest	Recombinant C1-INH	IV	sBLA	PDUFA date: September 21, 2018.
BioCryst	BCX7353	Kallikrein inhibitor	Oral	III Ongoing	APeX-2: randomized, double-blind, placebo-controlled, testing two doses of BCX7353 in 100 patients during 24 weeks
BioCryst	BCX7353	Kallikrein inhibitor	Oral	III Ongoing	APeX-S: an open label trials evaluating two doses of BCX7353, in 160 patients over 48 weeks
BioCryst	BCX7353	Kallikrein inhibitor	Oral	III Ongoing	Efficacy and safety of BCX7353 for the prevention of attacks in HAE (Japanese registration)
Attune Pharma	ATN-249	Plasma kallikrein inhibitor	Oral	I Ongoing	A randomized, double-blind, placebo-controlled, single-ascending–dose study to determine the safety, tolerability, pharmacokinetics and food effect of ATN-249 in healthy male participants
Pharvaris	PHA121	Bradykinin B2 receptor antagonist	Oral	Pred.	IND preparation for H2'18 Clinical trial expected in YE'18
Ionis	IONIS-PKKrx	Reduce prekallikrein production	-	I/II Completed	Study evaluating IONIS-PKKRx in healthy volunteers
Ionis	IONIS-PKK-LRx	Reduce prekallikrein production	SC	I Ongoing	Dose-escalation study in healthy volunteers for single and multiple doses administered subcutaneously
Adverum	ADVM-053	Viral gene therapy	Gene therapy	Pred.	IND preparation for Q4'18
Acute/prophylaxis (not disclosed)					
KalVista	KVD818	Kallikrein inhibitor	Oral	I Completed	Trial in healthy volunteers to evaluate safety, tolerability, exposure and PD.
KalVista	KVDXXX	Kallikrein inhibitor	Oral	Pred.	Expected to enter clinic in 2018
Rezolute	-	-	Oral	Pred.	IND filling planned for Q1'19
Verseon	-	-	Oral	Pred.	Phase I in the near term
Pediatric					
Shire	Lanadelumab (SHP643, DX-2930)	Antibody inhibitor of kallikrein	SC	III	HAE pediatric
Pharming	Ruconest	Recombinant C1 inhibitor	IV	II Concluded	Safety, PK and efficacy of Ruconest for the treatment of acute HAE in patients from 2 up to 13 y.o.
Dyax Corp.	Kalbitor (Ecallantide)	Kallikrein antagonist	SC	II Recruiting	Study to Assess the Tolerability and Safety of Ecallantide in Children and Adolescents With Hereditary Angioedema
Other					
Pharming	-	Recombinant C1-INH	-	Observational Recruiting	C1 Inhibitor Registry in the Treatment of HAE Attacks
Shire	Firazyr	-	-	Observational Recruiting	The Firazyr Patient Registry is a study designed to document the routine clinical outcomes over time in patients treated with Firazyr.
University Hospital, Grenoble	Biomarker	Blood sample	-	N/A Recruiting	Determination of Specific Biomarkers of Acute Attack Within Pediatric Population (BRADYKID)
University of Rostock, Centogene	Biomarker	-	-	Observational Recruiting	Biomarker for Hereditary Angioedema Disease Type 1 (BioHAE)

Pharming - Company Profile

Company description

Pharming is a Dutch biotech company commercializing a recombinant C1-INH, Ruconest, for the treatment of hereditary angioedema (HAE)

SWOT analysis

Strength

Cash generating biotech company

Ruconest is safe and has reliable supply

Available internal funds to invest in pipeline

Weakness

Ruconest is a single source revenue streatm

New compounds pipeline pre-clinical

Potential pricing pressure in the US HAE market

Opportunities

Recurring supply issues with plasma-derived C1-INH

Phase III failure of oral BCX7353 in Q2'19

Ruconest investigator-initiated trails are positive

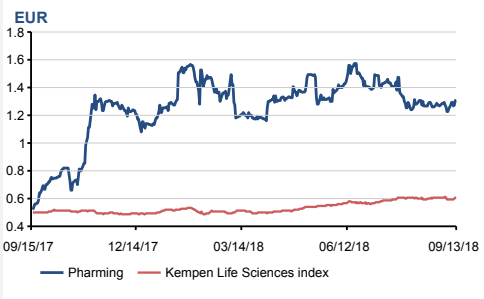
Threats

Shire launch of more convenient lanadelumba in HAE

Phase III success of oral BCX7353 in Q2'19

Phase II success of oral KVD9000 in mid-19

Rating	SELL
Price Target	€0.60
Closing price (13 Sep 2018)	€1.30
Date	14 September 2018, 15:15



Source: Bloomberg

Company data

Bloomberg	PHARM NA
Market capitalization	$1,098.9m
52-week range	€0.47 - €1.62
Number of shares	616.7m
Free float	91.6%
Avg. daily volume (20d)	6,918,458
Avg. daily turnover (20d)	€8,783,637
Daily turnover	€11,462,450
Next announcement date	25 October 2018
Reporting Period	Q4 2018 Results

Major shareholders	8.4%
FMR	3.1%
Polar Capital	3.0%
G-J Hageman	2.4%

Source: Company data, AFM

Alex Cogut
alex.cogut@kempen.com +31 20 348 8517

Source: Kempen estimates

Income Statement (FY 31-Dec, EUR m)	2017A	2018E	2019E
Total revenues	**89.6**	**148.1**	**180.4**
COGS	-12.4	-14.8	-18.0
Gross profit	**77.2**	**133.3**	**162.3**
SG&A	-31.4	-41.3	-38.1
R&D	-18.7	-18.4	-18.4
Other operating expenses/income (net)	-1.8	-25.6	-24.7
EBITDA	**25.3**	**47.9**	**81.1**
Depreciation and amortization	-0.6	-0.7	-0.9
EBIT	**21.9**	**45.7**	**78.4**
Interest expense	-111.3	-10.3	-7.9
Taxes	9.4	0.0	-1.5
Other financial items	--	--	--
Net profit	**-80.0**	**35.4**	**69.0**

Balance Sheet (FY 31-Dec, EUR m)	2017A	2018E	2019E
Cash and cash equivalents	60.0	55.2	90.7
Receivables	11.3	18.6	22.7
Inventories	18.3	30.3	36.9
Deferred tax assets	9.4	7.4	1.8
Financial assets and other current assets	2.3	1.9	1.5
Tangible fixed assets	8.2	10.5	12.3
Intangible fixed assets	56.6	56.6	56.6
Goodwill	--	--	--
Other non-current assets	--	--	--
Total assets	**166.2**	**180.5**	**222.5**
Payables	27.2	32.5	39.5
Deferred revenue (milestones / pre-payments)	2.3	0.0	0.0
Other current liabilities	28.3	28.4	24.7
Provisions	--	--	--
Long-term liabilities	89.6	65.4	35.0
Total liabilities	**147.4**	**126.3**	**99.2**
Total liabilities and shareholder's equity	**166.2**	**180.5**	**222.5**

Cash Flow Statement (FY 31-Dec, EUR m)	2017A	2018E	2019E
EBITDA	25.3	47.9	81.1
Cash interest income/expenses	-111.3	-10.3	-7.9
Cash taxes	9.4	0.0	-1.5
Changes in provisions	--	--	--
Changes in working capital	13.9	-14.0	-3.6
Changes in deferred revenue (milestones)	-0.9	-2.3	0.0
Other cash adjustments	12.3	-6.8	1.9
Cash flow from operating activities	**-51.3**	**14.5**	**70.0**
Cash flow from investments	**-3.5**	**-1.1**	**-1.4**
Dividends paid	--	--	--
Proceeds from equity issues	71.3	0.0	0.0
Debt drawdowns/(repayments)	14.1	-15.2	-30.4
Cash flow from financing activities	**85.4**	**-15.2**	**-30.4**

Ratios	2017A	2018E	2019E
EV/revenues	3.8x	5.4x	4.0x
EV/EBITDA	13.5x	16.6x	9.0x
P/E	nm	22.1x	11.4x
Net debt / EBITDA (x)	0.8x	0.2x	-0.7x

Metrics	2017A	2018E	2019E
Total revenue growth	nm	nm	nm
COGS as % of revenue	13.9%	10.0%	10.0%
SG&A as % of revenue	-35.1%	-27.9%	-21.1%
R&D as % of revenue	-20.8%	-12.5%	-10.2%
EBITDA margin (%)	28.3%	32.4%	45.0%
EBIT margin (%)	24.4%	30.9%	43.5%
Net profit margin (%)	-89.2%	23.9%	38.3%
Cash as % of market cap	18.7%	7.0%	11.6%
YE number of FTE	--	--	--

Source: Kempen estimates

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Total	165 (100%)	100%

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Source: Kempen estimates
* Price: Previous day closing price

Buy (B); Neutral (N); Sell (S); Not rated (NR); Restricted (R)

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