Pharming Group NV

Netherlands / Biotechnology
Primary exchange: Euronext Amsterdam /
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Bloomberg: PHARM NA
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Update

RATING	**BUY**
PRICE TARGET	**€ 2.00**
Return Potential	46.2%
Risk Rating	High

STRONG CONTENDER IN HAE PROPHYLAXIS; POMPE IS PIPELINE HIGHLIGHT

Pharming's annualised revenue run-rate reached €132m in Q4 2017. Investors are now asking whether the company can push revenues further ahead in 2018 in the face of increasing competition on the hereditary angioedema (HAE) market. Another question is whether the preclinical pipeline will have any near-term impact on valuation. Our answer to both of these questions is yes. We have raised our price target slightly to €2.00 (previously: €1.90) to reflect Q4/2017 numbers which were above our forecasts. We do not yet include any of the preclinical pipeline products in our valuation but we have examined these in detail in this study and expect this to change later on this year. We are particularly optimistic about prospects in Pompe disease, for which Pharming plans to submit an investigative new drug application later this year. Our recommendation remains Buy.

Ruconest to gain further share from Firazyr and Berinert The Cinryze shortage has eased but we expect Pharming to retain most of the prophylaxis patients won from Shire during Q4/17. During most of 2018 Ruconest will be competing primarily in the acute attacks market. Ruconest's superior efficacy and safety relative to Shire's Firazyr and CSL Behring's Berinert meant that it gained share of this market in 2017. We expect this to continue in 2018.

Secure niche with severely affected HAE patients We think that bears of Pharming in prophylaxis forget that Ruconest and Lanadelumab address different market segments. The baseline average monthly attack frequency of patients in Pharming's pivotal trial of Ruconest was over 7. Around a quarter of HAE patients have more than one attack a week. Shire's trial of Lanadelumab did not produce data for this group. We maintain our forecast that Pharming will secure 25% of the HAE prophylaxis market.

Optimistic about Pompe We think Pharming's platform has great potential to circumvent the main problem with current enzyme replacement therapy in Pompe - the instability of proteins derived from Chinese hamster ovary cell-lines.

FINANCIAL HISTORY & PROJECTIONS

	2014	2015	2016	2017	2018E	2019E
Revenue (€ m)	21.19	10.83	15.87	89.62	146.00	188.66
Y-o-y growth	209.6%	-48.9%	46.6%	464.6%	62.9%	29.2%
EBIT (€ m)	2.88	-12.83	-11.54	21.91	52.33	70.58
EBIT margin	13.6%	-118.5%	-72.7%	24.4%	35.8%	37.4%
Net income (€ m)	-5.77	-9.96	-17.54	-79.96	44.39	64.75
EPS (diluted) (€)	-0.02	-0.02	-0.04	-0.16	0.07	0.11
DPS (€)	0.00	0.00	0.00	0.00	0.00	0.00
FCF (€ m)	-3.23	-18.14	-67.48	32.17	52.54	65.72
Net gearing	-109.9%	-67.0%	128.4%	116.5%	-49.0%	-72.9%
Liquid assets (€ m)	34.19	31.64	31.89	58.66	89.24	132.99

RISKS

The main risks to our price target include slower sales growth for Ruconest in the EU and the US than we currently model.

COMPANY PROFILE

Pharming develops and produces therapeutic proteins through a bioreactor recombinant technology platform. Pharming and Chinese SIPI signed a collaboration agreement in 2013, which will accelerate the addition of new projects to the firm's R&D pipeline. Lead drug Ruconest received EMA approval in 2010 and FDA approval in July 2014.

MARKET DATA

As of 07 May 2018	
Closing Price	€ 1.37
Shares outstanding	601.70m
Market Capitalisation	€ 823.13m
52-week Range	€ 0.31 / 1.56
Avg. Volume (12 Months)	21,399,674

Multiples	2017	2018E	2019E
P/E	n.a.	19.4	12.7
EV/Sales	9.4	5.8	4.5
EV/EBIT	n.a.	16.1	12.0
Div. Yield	0.0%	0.0%	0.0%

STOCK OVERVIEW

COMPANY DATA

As of 31 Dec 2017	
Liquid Assets	€ 58.66m
Current Assets	€ 88.25m
Intangible Assets	€ 56.63m
Total Assets	€ 166.19m
Current Liabilities	€ 58.53m
Shareholders' Equity	€ 18.80m

SHAREHOLDERS

FMR LLC	3.1%
Polar Capital Partners Ltd.	3.1%
Hagemann G.J.	2.4%
Flynn J.E.	1.5%
Free float and other	89.7%

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INVESTMENT CASE

We remain buyers of the Pharming share In this report we raise our price target from €1.90 to €2.00 to reflect increases to our forecasts following stronger 2017 results than we expected. Our recommendation remains Buy. However, in the weeks following the 2017 results release on 7 March bearish views on the stock began to gain greater prominence. We believe bears of the stock were encouraged by intensifying competition on the HAE market and by management's cautious outlook for 2018. Guidance is for "continued growth in sales of Ruconest". However this could be achieved with average quarterly sales in 2018 of €23m. Q4 revenue was €32.9m. The bearish case on Pharming runs like this: Pharming's sales benefited during the final quarter of 2017 from the temporary shortage of Shire's Cinryze. The return of Cinryze to the market during the first half of 2018 will bring Ruconest sales growth to a standstill or worse. In the second half of 2018, when Pharming and Ruconest are due to go head to head in the prophylaxis segment of the HAE market, Shire's big battalions will ensure that Ruconest never gets out of the starting blocks in this indication. The bear view on the product pipeline is that all the assets are preclinical and hence that revenues are too uncertain/too far in the future to positively impact the valuation in the near term.

Why we think the bear view is wrong Pharming increased the size of its US team from 11 at the end of 2016 to over 50 by the end of 2017. The Q3/17 results delivered strong evidence that Pharming has a potent sales force in the US. These numbers showed a 72% jump in revenues vs. Q2/17 to €26.1m from €15.2m. Q3/17 numbers were unaffected by the Cinryze shortage as Ruconest was distributed to Cinryze patients off-label free of charge pending their clearance for reimbursement of the Pharming product. In Q4/17 revenues jumped a further 26.1% to €32.9m. Pharming did charge former Cinryze patients for Ruconest in Q4/17 but the Cinryze shortage was largely resolved by end Q4/17. We expect Pharming to retain most of the patients won from Cinryze during Q4/17 but further gains from Cinryze during Q1/18 are likely to have been more difficult given Ruconest is still off-label in prophylaxis. Market share gains by Ruconest in Q1/18 are more likely to have come from Shire's Firazyr (acute attacks) and CSL's Berinert (acute attacks).

FDA verdict on Ruconest for prophylaxis patients by 21 September Pharming submitted an SBLA (Supplemental Biologics License Application) to the FDA late last year with a view to expanding Ruconest's indication in HAE from acute attacks to prophylaxis. The FDA has stated that it will issue a verdict on the approval of Ruconest for prophylaxis by 21 September this year. The FDA is due to take a decision on Lanadelumab, Shire's Cinryze successor-product, by 26 August.

Ruconest better suited to severely affected prophylaxis patients than Lanadelumab During the first two thirds of this year Ruconest will be competing in the market for treatment of acute attacks. In the U.S. the overall HAE market was worth USD1.7-1.8bn in 2017 with the acute segment of the market accounting for 50-55% of the total and prophylaxis for the remainder. Ruconest's superior efficacy and safety relative to Firazyr (2017 U.S. sales of USD581m) and Berinert meant that it gained share of the acute market in 2017 and we expect this to continue in 2018. With respect to prophylaxis, we believe that bears of Pharming are overlooking the fact that Ruconest and Lanadelumab address different segments of this market. The baseline average monthly attack frequency of patients in Pharming's pivotal trial of Ruconest was over 7. Around a quarter of HAE patients have more than one attack a week. Shire's trial of Lanadelumab did not produce data for this group.

The design and results of the Ruconest and Lanadelumab trials in prophylaxis patients suggest that Ruconest is better suited to severely affected patients and Lanadelumab to mild and moderate HAE sufferers. We thus maintain our forecast that Ruconest will secure 25% of the HAE prophylaxis market.

Greater resources for pipeline development following 2017 revenue breakthrough Pharming acquired full commercial rights to Ruconest in the U.S. at the end of 2016 and in 2017 group revenues jumped 465% from €15.9m to €89.6m. Following this breakthrough, Pharming has greater financial and management resources to devote to R&D in indications for Ruconest other than HAE and also to the development of other products based on its transgenic platform. The company devoted substantial space in the 2017 results presentation and annual report to discussion of its product pipeline.

The new indications which Pharming is exploring for Ruconest include Ischaemic Reperfusion Injury and Delayed Graft Function. The company is also looking to develop recombinant proteins as therapies for lysomal storage disorders, Pompe disease and Fabry‘s disease. Meanwhile development of human recombinant factor VIII for the treatment of Hemophilia A continues at Pharming’s Chinese partner China State Institute of Pharmaceutical Industry (CSIPI).

Pharming has great potential to improve safety and efficacy of Pompe therapy We find the plans in Pompe disease the most interesting of the R&D projects mentioned above. Sanofi’s Myozyme/Lumizyme (2017 sales of €789m) is currently the only product approved for Pompe. Myozyme/Lumizyme is a protein produced from chinese hamster ovary (CHO) cell lines. CHO-derived proteins are unstable in the bloodstream which increases the dosage required to achieve efficacy and exacerbates immunogenicity. With Myozyme/Lumizyme immunogenicity is serious enough to warrant a black box warning on the FDA label. The three clinical phase products under development for the disease are also based on CHO cell lines but with various add-ons to raise the amount of the drug which reaches the target cells, thereby raising efficacy, lowering the required dosage and hence immunogenicity. We believe that the protein under development by Pharming using its transgenic platform has the potential to greatly improve efficacy and safety of therapy for Pompe by circumventing the underlying problem of the instability of proteins derived from CHO cell lines. Pharming has stated that it is currently upscaling production of recombinant alpha-glucosidase for Pompe to produce supplies for clinical testing. We expect the filing of an investigative new drug (IND) application in Pompe by the end of this year.

Strategy of prioritising Pompe over Fabry looks sound Sanofi’s Fabrazyme is the only drug currently approved for Fabry’s disease in both the U.S. and EU markets. Replagal (Shire) and Migalastat (Amicus) are approved in the EU. Worldwide sales of these three products were over USD1.3bn in 2017. The efficacy of current therapies shows clear deficiencies. Tissue penetration of the infused protein is incomplete and efficacy is also compromised by the body’s formation of antibodies. However, we think the need for a new pipeline drug candidate for Fabry‘s disease is a not as urgent as with Pompe’s disease. This is because immunogenicity is not as pressing an issue with current therapies for Fabry as for Pompe and the existing pipeline in Fabry also looks more promising than in Pompe. We therefore think Pharming’s strategy of prioritising Pompe over Fabry is sound.

Ischaemic reperfusion injury (IRI) is the tissue damage caused when blood supply returns to tissue after a period of ischaemia or lack of oxygen. C1 inhibitors, such as Pharming’s Ruconest but also Shire’s Cinryze and CSL Behring’s Berinert have been shown to be useful in moderating the inflammatory response which is partially responsible for the damage of IRI. Delayed Graft Function (DGF) is a form of IRI and is a serious and costly complication in clinical transplantation.

Both IRI and DGF represent large unmet medical needs. In 2013 Pharming reported that Ruconest had been shown to have a beneficial effect as a donor pre-treatment therapy in an animal model of kidney transplantation. Financial constraints prevented Pharming from carrying out any further trials of Ruconest in the indications IRI/DGF during the period 2013-2017.

Pharming preparing clinical trial of Ruconest with DGF patients However, competitors CSL Behring and Shire have been active in conducting trials with their respective products Berinert and Cinryze. Pharming is currently preparing a clinical trial of Ruconest with DGF patients but we think it likely that both Shire and CSL are ahead of Pharming in developing products for DGF/IRI. CSL has completed a phase I/II study of C1-inhibitor in DGF & IRI while Shire has completed a phase I study of C1-inhibitor in DGF.

Hemophilia is the largest rare disease market worth around USD10bn and growing at 7% per year. For many years the market was relatively stable with the largest players such as Shire, Novo Nordisk and Bayer supplying factor VIII replacement requiring dosage 3-4 times weekly. But, the market now looks to be changing rapidly. Roche's Hemlibra was approved by the FDA in late 2017 for the one third of hemophilia A patients who have inhibitors to standard factor VIII replacement therapies. However, the approval came with a black box warning that severe blood clots have been discovered in patients who were additionally given a rescue treatment (activated prothrombin complex concentrate) against breakthrough bleeds. Dosing frequency for Hemlibra is only once a week. The FDA also recently granted a breakthrough therapy designation to Hemlibra for patients without factor VIII inhibitors on the basis of data from an ongoing phase II trial. Dosage frequency in this trial is once a week or every two weeks.

Most interestingly in our view, in December 2017, the New England Journal of Medicine (NEJM) published an independent, peer-reviewed article on the BioMarin phase 1/2 study of Valoctocogene Roxaparvovec in hemophilia patients assessing its safety and efficacy at the 6e13 vg/kg dose after 52 weeks. The NEJM article reported "sustained normalisation" of Factor VIII activity over the 52-week period for six of seven study participants. In addition, all seven participants demonstrated stabilisation of hemostasis and a "profound" reduction in Factor VIII use. Safety findings were limited to elevations in liver function tests. While noting the relatively small sample size, NEJM gave its article the title "A Cure for Hemophilia within Reach".

Development of innovative hemophilia therapy a challenge for Pharming/CSIPI Pharming is working on the development of human recombinant factor VIII for the treatment of hemophilia A through its Chinese partner China State Institute of Pharmaceutical Industry (CSIPI). The challenge for Pharming/CSIPI will be to produce a product able to compete with the latest developments in the indication.

VALUATION

Our valuation €2.00 per share (previously: €1.90). Buy recommendation maintained. 2017 revenues exceeded our forecasts while EBIT was below our projection due mainly to higher Q4/17 marketing expenses than we had modelled. Based on stronger than expected 2017 revenue numbers and also on market data showing that the U.S. HAE prophylaxis market was worth over USD800m in 2017 (our previous projections were based on a market size of USD700m), we have raised our forecasts and valuation as shown in figures 2-4 below. We have revised up our PV after costs estimate by 12.4% to €1.36bn (previously: €1.21bn). Our price target rises by only 5.2% to €2.00 (previously: (€1.90) for two reasons. First, the end 2017 contingent consideration was higher than we modelled. This number relates to the agreement Pharming made with Valeant when it acquired the outstanding 70% of the commercialisation rights for Ruconest in the U.S. in 2016. The consideration is contingent on the achievement of sales milestones by Pharming. Pharming's strong sales performance in 2017 means that the contingent consideration is now valued at €28.3m (previously: €4.7m). Second, warrants and options were converted in Q1/18 more quickly than we had anticipated. This raises the proforma share count. We now see fair value for the share at €2.00 (previously: €1.90). We maintain our Buy recommendation.

Figure 1: 2017 results versus our forecasts

All figures in €m	2017A	2017E	Delta	2016A	Delta
Sales	89.62	86.72	3.3%	15.87	464.7%
EBIT	21.91	22.31	-1.8%	-11.54	n.m
margin	*24.4%*	*25.7%*	-	*neg.*	-
Net income	-79.96	-30.12	-	-17.54	n.m.
margin	*neg.*	*neg.*	-	*neg.*	-
EPS (in €)	-0.16	-0.06	-	-0.04	n.m.

Source: Pharming, First Berlin Equity Research estimates

Figure 2: Changes to our forecasts

	2018E			2019E		
All figures in €m	Old	New	Delta	Old	New	Delta
Sales	142.27	146.00	2.6%	179.74	188.66	5.0%
EBIT	50.11	52.33	4.4%	64.49	70.58	9.4%
margin	*35.2%*	*35.8%*	-	*35.9%*	*37.4%*	-
Net income	42.17	44.39	5.3%	56.32	64.75	15.0%
margin	*29.6%*	*30.4%*	-	*31.3%*	*34.3%*	-
EPS (in €)	0.07	0.07	5.3%	0.09	0.11	15.0%

Source: First Berlin Equity Research estimates

Figure 3: Valuation model

Compound	Project[1)]	Present Value	Patient Pop	Treatment Cost	Market Size	Market Share	Peak Sales	Gross margin	Discount Factor	Patent Life2[)]	Time to Market
Ruconest (EU)	HAE-AA	€105.5M	4K	€ 41,667	€167M	20%	€39M	60%	10%	16	-
Ruconest (US)	HAE-AA	€1,404.7M	4K	€ 197,368	€789M	25%	€306M	90%	10%	12	-
Ruconest (EU)	HAE-PR	€30.8M	1K	€ 83,333	€83M	20%	€20M	60%	12%	6	2 Years
Ruconest (US)	HAE-PR	€848.0M	2K	€ 444,444	€693M	25%	€271M	90%	12%	8	1 Years
PV of gross profits		€2,389.0M			€1,733M		€636M				
Costs PV		€1,030.8M									
PV after costs		€1,358.1M									
Contingent consideration		€28.3M									
Net Debt (pro-forma)		€33.0M									
Fair Value		€1,296.9M									
Share Count (fully diluted, PV)		649,017K									
Fair value per share		€ 2.00									

1) A project typically refers to a specific indication or, where necessary or relevant, a combination between indication and geographic market

2) Remaining patent life after the point of approval

Source: First Berlin Equity Research estimates

Figure 4: Changes to our valuation model

	Old	New	Delta
PV of gross profits	**€2,214.6M**	**€2,389.0M**	**7.9%**
Costs PV	€1,006.7M	€1,030.8M	2.4%
PV after costs	**€1,207.9M**	**€1,358.1M**	**12.4%**
Contingent consideration	€4.7M	€28.3M	502.1%
Proforma net debt	€27.8M	€33.0M	18.7%
Fair Value	€1,175.4M	€1,296.9M	10.3%
Share Count (fully diluted, PV)	606,482K	649,017K	7.0%
Fair value per share	**€ 1.90**	**€ 2.00**	**5.2%**

Source: First Berlin Equity Research estimates

PIPELINE

POMPE DISEASE

Pompe disease is caused by dysfunction of the acid alpha-glucosidase gene containing the information for production and function of the protein acid alpha-glucosidase (GAA). Because of the shortage of this protein (an enzyme) a complex sugar named glycogen cannot be degraded to a simple sugar such as glucose and accumulates within the lysosomes. Lysosomes are small compartments inside the cells wherein various substances are digested. The accumulation of glycogen within the lysosomes leads sequentially to cellular malfunction, cellular damage, tissue damage, and ultimately organ dysfunction. Pompe disease occurs in various populations and ethnic groups around the world. Estimates vary, but its incidence is generally placed at approximately 1 in 40,000 births in the United States. Males and females are affected in equal numbers.

First symptoms of Pompe disease can occur at any age from birth to late adulthood. Earlier onset compared to later onset is usually associated with more rapid progression and greater disease severity. At all ages the disease is characterised by skeletal muscle weakness and wasting which cause mobility problems and also affect respiratory function. The most severely affected infants usually show symptoms of the disease within the first 3 months after birth. They have cardiac problems (dysfunction due to cardiac enlargement) in addition to generalised skeletal muscle weakness and a life expectancy of less than 2 years, if untreated. Less severe forms of Pompe disease with onset during childhood, adolescence, or adulthood rarely manifest cardiac problems, but gradually lead to walking disability and reduced respiratory function.

Only drug approved so far is an enzyme replacement therapy from Sanofi Pompe is treated through enzyme replacement therapy (ERT). The only drug to have been approved so far (in both the U.S. and the EU) is Sanofi's Myozyme/Lumizyme which is recombinant human GAA produced from Chinese hamster ovary cells. In 2017 Myozyme/Lumizyme generated sales of €789m. However, Myozyme/Lumizyme has an unfavourable side-effect profile. The FDA label carries a black box warning of side effects including life-threatening anaphylactic reactions, severe hypersensitivity reactions, immune-mediated reactions presenting as nephrotic syndrome and necrotising skin lesions, as well as risk of cardiorespiratory failure.

Figure 5: Myozyme/Lumizyme monopolises ERT of Pompe's disease

Company	Product	Date of first U.S. approval	Date of first EU approval	Production method/ mode of action	Administration route	Dosage/frequency
Sanofi	Myozyme/ Lumizyme	2010	2006	recombinant DNA in CHO cell line	intraveneous infusion	20mg/kg every 2 weeks

Source: company documents

Proteins produced from CHO cell lines tend to be unstable The reason for Myozyme/Lumizyme's unfavourable side effect profile is that recombinant proteins produced from animal cell culture are not stable and their glycosylation is not reliable. Proteins are synthesised in the body and then undergo enzymatic modifications. One of the most important of these modifications is glycosylation. This is a process by which carbohydrate molecules are attached to proteins. Glycosylation promotes folding thereby improving stability. Myozyme/Lumizyme unfolds in the bloodstream. This limits its effectiveness by restricting the ability of the protein to reach and bind to specific receptors on target cells. It can also elicit an immune response, further limiting the ability of the drug to compensate for the missing GAA enzyme.

Figure 6: Competitors' pipeline products for Pompe disease

Company	Product	Technology/ mode of action	Phase	No. participants	Study start date	Estimated primary completion date
Sanofi	GZ/402666	recombinant DNA in CHO cell line/ enhanced affinity for M6P receptors	III	96	October 2016	November 2021
Amicus	ATB200/AT2221	recombinant DNA in CHO cell line/ pharmacological chaperone	I/II	32	January 2016	September 2019
Valerion	VAL-1221	recombinant DNA in CHO cell line/ proprietary antibody delivery	I/II	12	June 2017	December 2018
Audentes	AT982	gene therapy	file IND mid-2018 phase I/II from Q4/18	-	-	-

Source: company documents

The race to develop improved therapies for Pompe Several companies are currently developing drugs with a view to supplanting Myozyme/Lumizyme (see figure 6). In 2016 Sanofi itself completed a phase I/II trial with 24 patients of GZ402666, a prospective successor to Myozyme/Lumizyme. Overall, 8 of 10 patients (80.0%) in the treatment-naive group and 12 of 14 patients (85.7%) in the treatment-experienced group had at least one treatment-emergent adverse event (AE) during the study. The majority of treatment-emergent AEs were non-serious, mild to moderate in intensity and assessed as unrelated to study drug. The most frequently reported treatment-emergent AEs considered related to the study drug were myalgia or muscle pain (7 events in 2 patients), headache (3 events in 2 patients) and fatigue (3 events in 3 patients). Sanofi states that in preclinical studies, GZ402666 showed approximately five-fold greater potency than Myozyme/Lumizyme in terms of tissue glycogen reduction. According to the company, the improvement in efficacy is due to the design of GZ402666 for enhanced receptor targeting and enzyme uptake through greater affinity for the M6P (mannose-6 phosphate) receptors on muscle cells. The addition of M6P residues is another of the enzymatic modifications mentioned above. The M6P-enzyme complex binds to the M6P receptor and is transported to the lysosomes. Because GZ402666 has a greater affinity for the M6P receptors than Myozyme/Lumizyme, more of it reaches the lysosomes thereby enhancing glycogen clearance.

In October 2016, Sanofi started a phase III trial with 96 participants comparing the efficacy and safety of GZ402666 with Myozyme/Lumizyme in patients with late onset Pompe disease who have not previously been treated for the condition. The estimated primary completion date is November 2021.

Amicus Therapeutics' ATB200 drug candidate is also produced from Chinese hamster ovary (CHO) cells. However, Amicus Therapeutics (Amicus) attempts to circumvent the problem of enzyme instability associated with this production method through the use of a specially developed pharmacological chaperone – AT2221. AT2221 is a companion drug designed to stabilise ATB200. Data from studies undertaken so far suggest that co-administration of the two drugs results in enhanced uptake and activity of the replacement enzyme in muscle tissue. In January 2016, Amicus started a phase I/II trial with 32 participants to evaluate the safety, tolerability, and phamacodynamics of ATB200 alone and when co-administered with AT2221. The estimated primary completion date is September 2019.

Valerion Therapeutics' VAL-1221 is a recombinant human GAA (produced in CHO cells) combined with a proprietary antibody delivery technology to improve the delivery of the drug to affected tissues. Pompe disease is characterised by accumulation of glycogen in both the lysosomes and the cytoplasm (the material within a living cell, excluding the cell nucleus). A February 2017 study published by Sun et al, Duke University, Division of Medical Genetics suggests that VAL-1221 has potential benefit over current ERT by clearing both lysosomal and cytoplasmic glycogen. Valerion is currently carrying out a phaseI/II study of VAL-1121 in late onset Pompe patients.

Audentes' AT982 gene therapy candidate for Pompe consists of an adeno-associated virus (AAV) 8 vector that delivers a GAA gene expression cassette containing a novel hybrid promoter designed to increase GAA activity in targeted tissues, including skeletal and cardiac muscle, the nervous system and the liver.

A 2011 study by Byrne et al demonstrated that systemic administration of AAV to deliver acid alpha-glucosidase in GAA-deficient mice significantly increased GAA activity in cardiac and skeletal muscle. This led to improved diaphragm contractile strength, reduced cardiac glycogen, reduced left ventricular mass, and improved ejection fraction. A more recent study (2015) by Falk et al of a mouse model of Pompe disease compared the effects of a single systemic injection of AT982 (AAV-GAA) to bi-monthly injections of recombinant human GAA (ERT) over a three-month period. Improvements in diaphragmatic contractile and cardiac function were observed in both treatment groups at three months post-injection compared with untreated animals, while breathing frequency and expiratory time were significantly improved in AAV-GAA treated animals but not in ERT treated animals. In addition, glycogen deposition was significantly elevated in untreated and ERT animals, but not in AAV-GAA treated animals at three months post treatment. Audentes plans to file an IND for AT982 in mid-2018 and to initiate a Phase 1/2 clinical study in the fourth quarter of 2018.

Pharming has great potential to improve safety and efficacy of Pompe therapy We believe that the protein under development by Pharming using its transgenic platform has the potential to greatly improve efficacy and safety of therapy for Pompe by circumventing the underlying problem of the instability of proteins derived from CHO cell lines. Pharming has stated that it is currently upscaling production of recombinant alpha-glucosidase for Pompe to produce supplies for clinical testing. We expect the filing of an investigative new drug (IND) application in Pompe by the end of this year.

FABRY'S DISEASE

Fabry's disease also caused by dysfunctional gene and resulting enzyme deficiency
Like Pompe Disease, Fabry Disease belongs to the group of diseases known as lysosomal storage disorders. It is caused by mutations (or alterations) in the a-Gal A gene (GLA) that instructs cells to make the a-Gal A enzyme. a-Gal A functions within lysosomes to break down specific complex sugar-lipid molecules called glycolipids. The enzyme deficiency causes a continuous build-up of glycolipids in the body's cells, resulting in cell abnormalities and organ dysfunction that particularly affect the heart and kidneys.

Males are typically more severely affected than females. The disease takes a more variable course in females, who may be asymptomatic or as severely affected as males. There are two major disease phenotypes: the type 1 "classic" and type 2 "later-onset"subtypes. Both lead to renal failure, and/or cardiac disease, and early death. Type 1 males have little or no functional a-Gal A enzymatic activity and marked accumulation of glycolipids in capillaries and small blood vessels which cause the major symptoms in childhood or adolescence. These include acroparesthesia (excruciating pain in the hands and feet which occur with exercise, fevers, stress, etc.); angiokeratomas (clusters of red to blue rash-like discolorations on the skin); anhidrosis or hypohidrosis (absent or markedly decreased sweating); gastrointestinal symptoms including abdominal pain and cramping, and frequent bowel movements; and a characteristic corneal dystrophy (star-burst pattern of the cornea seen by slit-lamp ophthalmologic examination) that does not affect vision. With increasing age, the systemic glycolipid deposition, especially in the heart leads to arrhythmias, left ventricular hypertrophy and then hypertrophic cardiomyopathy, and in the kidneys to progressive insufficiency thento renal failure, and/or to cerebrovascular disease including transient ischemic attacksand strokes.

Prior to renal replacement therapy (i.e., dialysis and transplantation) and enzyme replacement therapy (ERT), the average age of death of affected males with the type 1 classic phenotype was ~40 years. The incidence of males with the type 1 classic phenotype is about 1 in 40,000 males, but varies with demography and race, ranging from about ~1 in 18,000 to 1 in 95,000 based on newborn screening studies.

In contrast, males with the type 2 "later-onset" phenotype (previously called cardiac or renal variants) have residual a-Gal A activity, lack glycolipid accumulation in capillaries and small blood vessels, and do not manifest the early manifestations of type 1 males (i.e., the acroparesthesias, hypohidrosis, angiokeratomas, corneal dystrophy, etc). They experience an essentially normal childhood and adolescence. They typically present with renal and/or cardiac disease in the third to seventh decades of life. Most type 2 later-onset patients have been identified by enzyme screening of patients in cardiac, hemodialysis, renal transplant, and stroke clinics and recently by newborn screening. Based on these screening studies the incidence of type 2 later-onset males varies by demography, ethnicity, and race, but is at least 10 times more frequent than that of the type 1 males from the same region, ethnic group, or race.

Figure 7: Current therapies for ERT of Fabry's disease

Company	Product	Date of first U.S. approval	Date of first EU approval	Technology/ mode of action	Administration route	Dosage/frequency
Sanofi	Fabrazyme	2003	2001	recombinant DNA in CHO cell line	intraveneous infusion	1mg/kg every 2 weeks
Shire	Replagal	-	2001	recombinant DNA in human cell line	intraveneous infusion	0.2mg/kg every 2 weeks
Amicus	Migalastat	-	2016	small molecule pharmacological chaperone	oral	123mg (1 capsule) every 2 days

* not approved in the U.S. Approved in the EU in 2001
** not approved in the U.S. Approved in the EU in 2016

Source: company documents

Sanofi's Fabrazyme only therapy approved in both U.S. and EU As figure 7 shows, Sanofi's Fabrazyme is currently approved for treatment of Fabry disease in both the U.S. and the EU while Shire's Replagal and Amicus' Miglastat are approved in the EU only.

In the U.S. Transkaryotic Therapies (acquired by Shire in 2006) submitted its biologics license application (BLA) for Replagal in June 2000 one week ahead of Genzyme's (acquired by Sanofi in 2011) BLA submission for Fabrazyme.

The FDA approved Fabrazyme despite noting that while Genzyme's pivotal phase III study "…did assess clinically meaningful endpoints, no effect on these were demonstrated" and also that "The study was relatively short for a disorder where progression to renal failure may take many years".

The primary efficacy endpoint of the study was the morphologic assessment of globotriaosylceramide (GL-3) inclusions in the capillary endothelium (vasculature) of the kidney at 20 weeks. The study did succeed in demonstrating that Fabrazyme altered the capillary endothelium to achieve a near-normal appearance with regard to accumulationof GL-3. The FDA determined this to be a "surrogate endpoint reasonably likely to predict a clinical benefit". On this basis and on the understanding that Genzyme would complete further studies to verify the Fabrazyme's clinical benefit, the FDA approved Fabrazyme.

FDA's reservations about Fabrazyme Genzyme completed a further three studies in adults of the efficacy of Fabrazyme all of which demonstrated sisgnificant reductions in GL-3. However the FDA label still contains the wording: "The reduction of GL-3 inclusions suggests that Fabrazyme may ameliorate disease expression; however, the relationship of GL-3 inclusion reduction to specific clinical manifestations of Fabry disease has not been established."

The FDA panel concluded that the data from TKT was not good enough to back approval. The FDA required TKT to conduct a new study providing a head-to-head comparison of Replagal with Fabrazyme. TKT decided that meeting the FDA's requirements would cost too much time and money and halted its efforts to gain approval for Replagal on the U.S. market.

Shire abandoned attempts to have Replagal approved in the US in 2009 Having acquired TKT in 2006, Shire filed a BLA with the FDA for Replagal in late 2009 after a shortage of Fabrazyme had arisen. But it ended its attempts to enter the U.S. market with the drug in early 2012 after the FDA indicated that further trials would be required for approval.

Amicus' Migalastat targets 30-50% of patient population with amenable mutations Amicus' Migalastat is not an enzyme replacement therapy but binds and stabilises endogenous alpha-Gal A in order to transport it to the lysosomes. Migalastat targets the estimated 30-50% of the Fabry disease population aged 16 and older which have amenable mutations and may benefit from the drug.

Figure 8: Competitors' pipeline products for Fabry's disease

Company	Product	Technology/ mode of action	Phase	No. participants	Study start date	Estimated primary completion date
Sanofi	GZ/SAR402671	glucosylceramide synthase inhibitor	II	8	July 2015	November 2018
Protalix	Pegunigalsidase alfa	plant-cell based expression system	III	30	September 2017	August 2019
AVROBIO	AVR-RD-01	lentiviral gene therapy	I/II	12	February 2018	June 2020

Source: company documents

Among the drug candidates Sanofi's GZ/SAR402671 is designed to be taken orally and works by blocking the formation of glucosylceramide (GL-1), a key intermediate in the synthesis of GL-3.

Protalix Biotherapeutics' pegunigalsidase alfa is a chemically modified plant cell derived PEGylated covalently bound homodimer designed to achieve higher uptake and prolonged uptake in target organs. Protalix claims that its half life is 490 times greatet than Fabrazyme.

AVROBIO presented initial six-month clinical data from the first patient with Fabry disease treated with AVR-RD-01 In October 2017 at the Annual Meeting of the Japanese Society for Inherited Metabolic Diseases in Kawagoe, Japan. At the initiation of the study, the patient with Fabry disease had plasma a-Gal A activity near zero. Within 45 days of receiving AVR-RD-01, the patient's plasma a-Gal A activity increased into the normal range for individuals without Fabry. The six-month assessment demonstrated continued plasma a-Gal A activity within the normal range for individuals without Fabry.

Pharming's strategy of prioritising Pompe over Fabry looks sound As we have seen above, the efficacy of current therapies for Fabry shows clear deficiencies. Tissue penetration of the infused protein is incomplete and efficacy is also compromised by the body's formation of antibodies. However, we think the need for a new pipeline drug candidate for Fabry's disease is a not as urgent as with Pompe's disease. This is because immunogenicity is not as pressing an issue with current therapies for Fabry as for Pompe and the existing pipeline in Fabry also looks more promising than in Pompe. We therefore think Pharming's strategy of prioritising Pompe over Fabry is sound.

ISCHAEMIC REPERFUSION INJURY/DELAYED GRAFT FUNCTION

C1-inhibitor plays an important role in the regulation of vascular permeability and in the suppression of inflammation. Dysfunctional regulation of vascular permeability due to a deficiency of C1 inhibitor is the cause of HAE. C1-inhibitor also exerts anti-inflammatory effects. Ischaemic reperfusion injury (IRI) is the tissue damage caused when blood supply returns to tissue after a period of ischaemia or lack of oxygen. The absence of oxygen and nutrients from blood during the ischaemic period creates a condition in which the restoration of circulation results in inflammation and oxidative damage through the induction of oxidative stress. The inflammatory response is partially responsible for the damage of reperfusion injury. C1 inhibitor has been shown to be therapeutically useful in a variety of animal models of inflammatory diseases, including a variety of ischemic reperfusion injuries (heart, intestine, skeletal muscle, liver, brain). These indications are all large unmet medical needs but are very difficult to study in a clinical setting. Pharming is currently working with partners to explore the use of Ruconest in these indications. One of these partners is the U.S. Army Institute of Surgical Research.

Delayed Graft Function (DGF) is a serious and costly complication in clinical transplantation. It is a form of IRI resulting in acute renal failure, low urine output post-transplantation, increased allograft immunogenicity, risk of acute rejection episodes, and decreased long-term survival. Conventional practice focuses on cold storage or machine perfusion of the organ after it is harvested from the donor.

In 2013 Pharming reported that Ruconest had been shown to have a beneficial effect as a donor pre-treatment therapy in an animal model of kidney transplantation. In the study, Dr. Luis Fernandez of the University of Wisconsin used a non-human primate model to evaluate the outcomes of kidney transplantation from brain-dead donors. Kidneys that were treated with Ruconest prior to transplantation had a significantly lower incidence of DGF when transplanted to the recipient animals. Dr. Fernandez and colleagues were also able to demonstrate how Ruconest inhibited the complement system to confer this benefit.

Pharming preparing clinical trial of Ruconest with DGF patients Financial constraints prevented Pharming from carrying out any further trials of Ruconest in the indications IRI/DGF during the period 2013-2017. However, as figures 9 and 10 below show, competitors CSL Behring and Shire have been active in conducting trials with their respective products Berinert and Cinryze in DGF and antibody mediated rejection (AMR). Pharming is currently preparing a clinical trial of Ruconest with DGF patients.

Figure 9: Shire clinical trials in DGF and AMR

Study title	Phase	No. participants	Study start date	Estimated primary completion date	Results available
Pilot study of C1-inhibitor in patients with acute AMR	II	18	June 2010	August 2015	Yes
Efficacy and safety of C1-Inhibitor for acute AMR in renal transplant patients	III	112	October 2015	February 2022	No
C1-inhibitor as a donor pre-treatment strategy in kidney recipients of KDPI>85% organs	I	72	May 2018	May 2019	No

Source: ClinicalTrials.gov

Figure 10: CSL Behring clinical trials in DGF and AMR

Study title	Phase	No. participants	Study start date	Estimated primary completion date	Results available
C1-Inhibitor preoperative and post-kidney transplant to prevent DGF & IRI	I/II	70	September 2014	March 2017	No
C1-Inhibitor for renal allograft salvage in refractory AMR in renal transplants	II	5	October 2016	October 2021	No
C1-Inhibitor as add-on to standard of care for treatment of refractory AMR in renal transplant recipients	III	90	November 2017	October 2023	No

Source: ClinicalTrials.gov

HEMOPHILIA A

Pharming cooperating with Chinese partner on development of factor VIII Pharming is working on the development of human recombinant factor VIII for the treatment of Hemophilia A through its Chinese partner, China State Institute of Pharmaceutical Industry (CSIPI). Founded in 1957 and based in Shanghai, CSIPI is a susbsidiary of the China National Pharmaceutical Group Corporation (Sinopharm). Together these two entities comprise the largest medical and healthcare group in China. A strategic collaboration concluded with Pharming in 2013 entails the development, manufacture and commercialisation by CSIPI/Sinopharm of new products based on the Pharming technology platform. Pharming also granted CSIPI an exclusive license to commercialise Ruconest in China.

Hemophilia is the largest rare disease market generating annual revenues of around USD10bn and growing at 7% per year. Hemophilia is a mostly inherited genetic disorder which impairs blood clotting thereby leading to recurrent and extended bleeding episodes. These may cause pain, irreversible joint damage and life-threatening hemorrhages. There are two main types of hemophilia - hemophilia A and hemophilia B. Hemophilia A results from a deficiency of the protein known as factor VIII and hemophilia B from not enough factor IX protein.

In its 2016 Annual Global Survey, the World Federation of Hemophilia estimated that nearly 150,000 people worldwide were living with hemophilia A while nearly 30,000 people were diagnosed with hemophilia B. However, it is thought that the true prevalence of the disease is probably double these numbers.

The leading cause of morbidity for people with hemophilia is joint disease. This is caused by frequent bleeds into joints over time, often resulting in chronic pain and disability. Long term minimisation of joint damage is a critical unmet need in hemophilia therapy. The disease is treated by injecting clotting factor into the patient's bloodstream. Therapy is administered either according to a schedule to help prevent or reduce bleeding episodes (prophylaxis) or to control bleeding when it occurs (on-demand). Therapy is moving from on-demand treatment to prophylaxis due to observed improvements in long-term clinical outcomes, such as joint damage. In the U.S., the February 2016 guidelines of the Medical and Scientific Advisory Council of the National Hemophilia Foundation recommended routine prophylaxis as optimal for the treatment of people with severe hemophilia.

Hemophilia therapy historically used factors derived from human blood plasma. Recombinant products based on recombinant DNA technology became available in the early 1990s and by 2016 accounted for over 75% of sales globally. Hemophilia A accounts for around 80% of identified patients and a similar proportion of market value.

Figure 11: Severity of hemophilia A

Level	Percentage of normal factor activity in bleed	Number of international units (IU) per millilitre (ml) of whole blood
normal range	50%-150%	0.50-1.5 IU
mild hemophilia	5%-40%	0.05-0.40 IU
moderate hemophilia	1%-5%	0.01-0.05 IU
severe hemophilia	less than 1%	less than 0.01 IU

Source: World Federation of Hemophilia

Figure 11 relates severity of hemophilia A to percentage of normal factor activity in bleed. Patients on prophylactic therapy are largely drawn from the severely and moderately affected parts of the patient population. Market growth is being driven by the trend towards prophylaxis which in turn is supported by the introduction of longer half life products.

Figure 12: Leading companies' 2017 hemophilia sales

	2017 hemophilia therapy sales (USDm)	% total
Shire	2,957	30.5%
Octapharma	1,944	20.0%
Novo Nordisk	1,591	16.4%
Bayer	1,093	11.3%
Sanofi	1,090	11.2%
CSL Behring*	1,023	10.5%
Total	9,697	100.0%

* June year-end

Source: Company data

Figure 13 shows the 2017 sales of the leading companies in hemophilia market. The numbers include sales in both hemophilia A and B as some of the companies shown below do not break out sales by indication.

Figure 13: Therapies currently approved for hemophilia A

Company	Product	Date of first US approval	Administration route	Dosage frequency for prophylaxis
Shire	Advate	2003	intraveneous	3-4 times weekly
Shire	Adynovate	2015	intraveneous	2 times weekly
Octapharma	NUWIQ	2015	intraveneous	every other day
Novo Nordisk	Novoeight	2013	intraveneous	dependent on type of bleeding
Bayer	Kogenate	1993	intraveneous	3 times weekly
Bayer	Kovaltry	2016	intraveneous	2-3 times weekly
Sanofi	ELOCTATE	2014	intraveneous	Every 4 days
CSL Behring	AFSTYLA	2016	intraveneous	2-3 times weekly
Roche	HEMLIBRA*	2017	subcutaneous	once weekly

*black box warning

Source: Company data

Trend in hemophilia therapy is towards reduced dosage frequency Factor VIII brings together the clotting factors IXa and X. This is a key step in blood clot formation to stop bleeding. However nearly one in three people with hemophilia A develop inhibitors to standard factor VIII replacement therapies. In November 2017 the FDA approved Roche's Hemlibra for treatment of hemophilia A patients with factor VIII inhibitors. Hemlibra is the first new drug in nearly twenty years to serve this segment of the market. Hemlibra (emicizumab) is a bispecific monoclonal antibody which brings together factors IXa and X independently of factor VIII. However its U.S. label contains a black box warning that severe blood clots have been discovered in patients who were additionally given a rescue treatment (activated prothrombin complex concentrate) against breakthrough bleeds. FDA approval of Hemlibra for hemophilia A factor VIII inhibitor patients was based on Roche's HAVEN 1 study.

HAVEN 2 studied children below 12 years of age with hemophilia A with inhibitors. HAVEN 3 is evaluating Hemlibra prophylaxis dosed once weekly or once every other week in people 12 years of age or older with haemophilia A without inhibitors to factor VIII. HAVEN 4 is evaluating Hemlibra prophylaxis dosed every four weeks in people 12 years of age or older with haemophilia A with or without inhibitors.

On 17 April the FDA granted a breakthrough therapy designation to Hemlibra in patients without inhibitors on the basis of the HAVEN 3 study. Breakthrough Therapy Designation is designed to accelerate the development and review of medicines intended to treat a serious condition with preliminary evidence that indicates they may demonstrate a substantial improvement over existing therapies.

Figure 14: Pipeline for hemophilia A

Company	Product	Technology	Phase
Shire	SHP654	gene therapy	I
Novo Nordisk	N8-GP	long-acting recombinant factor VIII	IIIa
Novo Nordisk	Subcutaneous N8-GP	long-acting recombinant factor VIII	I
Bayer	Damactocog alpha pegol	long-acting recombinant factor VIII	Submitted for approval
Bayer	BAY1093884	anti-TFPI inhibitor antibody	I
Sanofi	BIVV001	combination of recombinant factor VIII-Fc fusion protein with part of Von Wildebrand factor	I/IIa
Sanofi	gene therapy	gene therapy	preclinical
Sanofi	Bispecific antibody programme	Bispecific antibody programme	preclinical
CSL Behring	CSL689	recombinant factor VIII fusion protein	III
CSL Behring	CSL626 rD'D3-FP	long-acting recombinant factor VIII fusion protein	III
Roche	HEMLIBRA	Bispecific antibody dosed once a week or every two weeks	III
Roche	HEMLIBRA	Bispecific antibody dosed every four weeks	III
Biomarin	Valoctocogene Roxaparvovec	gene therapy	III

Source: company data

Extremely interesting clinical results from BioMarin On 9 December last year, the U.S. company BioMarin published 1.5 years of clinical data from the phase I/II study of its gene therapy drug candidate, Valoctocogene Roxaparvovec.

Figure 15: Factor VIII level in Valoctocogene Roxaparvovec patients

Week	20	24	28	32	36	40	44	48	52	65	78
No. patients	7	7	7	7	7	7	7	7	7	7	7
Median Factor VIII level (%)	97	101	122	99	99	111	105	105	89	98	90
Mean Factor VIII level (%)	118	129	123	122	116	124	122	106	104	93	89
Range (low, high)	(12,254)	(12,227)	(15,257)	(26,316)	(31,273)	(17,264)	(20,242)	(23,195)	(20,218)	(16,145)	(11,179)

Source: company data

Figure 15 above shows the development of mean and median Factor VIII level between weeks 20 and 78 in the seven patients who had an infusion of 6e13 vg/kg Valoctocogene Roxaparvovec at the start of the trial. All patients had severe hemophilia A at baseline, defined as less than or equal to 1% of Factor VIII activity levels, expressed as a percentage of normal factor activity in blood (see figure 11 for World Federation of Hemophilia definitions of the severity of the disease). Figure 15 below shows that Factor VIII levels returned to normal for all patients while median annualised bleeding episodes and Factor VIII infusions both fell to 0. BioMarin also reported that Valoctocogene Roxaparvovec was overall well-tolerated, that no patients developed inhibitors to Factor VIII and no patients withdrew from the study.

Figure 16: Bleeding and factor VIII infusions for Valoctocogene Roxaparvovec patients

	Before valoctocogene roxaparvovec infusion	After valoctocogene roxaparvovec infusion
	Median (mean, SD)	Median (mean, SD)
Annualised Bleeding Rate (bleeding episodes per year per subject	16.5 (16.3,15.7)	0.0 (0.5,1.2)
Annualised FVIII infusions (infusions per year per subject)	138.5 (136.7, 22.4)	0.0 (6.1, 14.9)

Source: company data

Also on 9 December 2017, the New England Journal of Medicine (NEJM) published an independent, peer-reviewed article on the BioMarin Phase 1/2 study of Valoctocogene Roxaparvovec assessing its safety and efficacy at the 6e13 vg/kg dose after 52 weeks. The NEJM article reported "sustained normalisation" of Factor VIII activity over the 52-week period for six of seven study participants.

In addition, all seven participants demonstrated stabilisation of hemostasis and a "profound" reduction in Factor VIII use. Safety findings were limited to elevations in liver function tests. While noting the relatively small sample size, NEJM gave its article the title “A Cure for Hemophilia within Reach”.

On 19 December 2017, BioMarin announced the start of a phase III trial with 40 severe hemophilia A patients to confirm the safety and effectiveness of the 6e13 vg/kg dose of Valoctocogene Roxaparvovec.

INCOME STATEMENT

All figures in EUR '000	2014A	2015A	2016A	2017A	2018E	2019E
Revenues	**21,186**	**10,828**	**15,873**	**89,620**	**146,000**	**188,660**
Costs of sales	-3,427	-4,800	-4,683	-12,445	-18,870	-23,748
Gross profit	**17,759**	**6,028**	**11,190**	**77,175**	**127,130**	**164,912**
Other income	105	147	335	790	0	0
Research and development	-11,663	-14,180	-15,388	-18,657	-22,000	-30,186
General and administrative	-3,324	-3,744	-4,642	-5,974	-6,800	-9,433
Marketing and sales	0	-1,085	-3,035	-31,422	-46,000	-54,711
Operating income (EBIT)	**2,877**	**-12,834**	**-11,540**	**21,912**	**52,330**	**70,582**
Net financial income	-8,644	2,877	-5,996	-111,311	-7,940	-5,833
Pre-tax income (EBT)	**-5,767**	**-9,957**	**-17,536**	**-89,399**	**44,390**	**64,749**
Income taxes	0	0	0	9,442	0	0
Minority interests	0	0	0	0	0	0
Net income / loss	**-5,767**	**-9,957**	**-17,536**	**-79,957**	**44,390**	**64,749**
Diluted EPS	**-0.02**	**-0.02**	**-0.04**	**-0.16**	**0.07**	**0.11**
EBITDA	**3,915**	**-11,871**	**-10,784**	**25,327**	**54,865**	**72,890**
Ratios						
Gross margin on revenues	83.8%	55.7%	70.5%	86.1%	87.1%	87.4%
EBITDA margin on revenues	18.5%	n.m.	n.m.	28.3%	37.6%	38.6%
EBIT margin on revenues	13.6%	n.m.	n.m.	24.4%	35.8%	37.4%
Net margin on revenues	n.m.	n.m.	n.m.	n.m.	30.4%	34.3%
Expenses as % of revenues						
Cost of sales	16.2%	44.3%	29.5%	13.9%	12.9%	12.6%
Research and development	55.1%	131.0%	96.9%	20.8%	15.1%	16.0%
General and administrative	15.7%	34.6%	29.2%	6.7%	4.7%	5.0%
Marketing and sales	n.m.	10.0%	19.1%	35.1%	31.5%	29.0%
Y-Y Growth						
Revenues	209.6%	-48.9%	46.6%	464.6%	62.9%	29.2%
Operating income	n.m.	n.m.	n.m.	n.m.	138.8%	34.9%
Net income/ loss	n.m.	n.m.	n.m.	n.m.	n.m.	45.9%

BALANCE SHEET

All figures in EUR '000	2014A	2015A	2016A	2017A	2018E	2019E
Assets						
Current assets, total	**49,143**	**51,092**	**62,190**	**88,251**	**133,477**	**189,916**
Cash and cash equivalents	34,185	31,643	31,889	58,657	89,239	132,995
Receivables	1,554	3,220	12,360	11,260	20,440	26,300
Inventories	13,404	16,229	17,941	18,334	23,798	30,621
Other current assets	0	0	0	0	0	0
Non-current assets, total	**6,575**	**6,585**	**64,593**	**77,339**	**76,976**	**77,975**
Property, plant & equipment	5,598	5,661	6,043	8,234	10,220	11,272
Long term prepayments	0	0	1,622	2,296	0	0
Deferrred tax assets	0	0	0	9,442	9,442	9,442
Goodwill & other intangibles	777	724	56,680	56,631	56,578	56,525
Restricted cash	200	200	248	736	736	736
Total assets	**55,718**	**57,677**	**126,783**	**165,590**	**210,453**	**267,891**
Shareholders' equity & debt						
Current liabilities, total	**14,873**	**13,475**	**51,378**	**57,928**	**67,902**	**73,496**
Debt	0	3,047	26,136	21,962	21,962	21,962
Deferred license fee income	2,200	2,207	943	204	204	204
Derivative financial liabilities	4,266	953	9,982	8,301	8,973	4,102
Trade and other payables	7,781	7,005	14,054	27,198	36,500	46,965
Finance lease liabilities	626	263	263	263	263	263
Longterm liabilities, total	**11,002**	**20,363**	**47,938**	**88,860**	**80,031**	**62,255**
Debt	0	11,757	40,395	58,684	36,722	14,760
Deferred license fee income	10,022	7,808	2,270	1,467	14,600	18,786
Finance lease liabilities	965	798	599	390	390	390
Other liabilities	15	0	4,674	28,319	28,319	28,319
Minority interests	**0**	**0**	**0**	**0**	**0**	**0**
Shareholders equity	**29,843**	**23,839**	**27,467**	**18,802**	**62,520**	**132,141**
Total consolidated equity and debt	**55,718**	**57,677**	**126,783**	**165,590**	**210,453**	**267,891**

Ratios						
Current ratio (x)	3.30	3.79	1.21	1.52	1.97	2.58
Quick ratio (x)	2.40	2.59	0.86	1.21	1.62	2.17
Net gearing	-109.9%	-67.0%	128.4%	116.5%	-49.0%	-72.9%
Book value per share (€)	0.07	0.06	0.06	0.03	0.10	0.22
Net debt	-32,794	-15,978	35,256	21,906	-30,638	-96,356
Return on equity (ROE)	-33.1%	-37.1%	-68.4%	-345.6%	109.2%	66.5%

CASH FLOW STATEMENT

All figures in EUR '000	2014A	2015A	2016A	2017A	2018E	2019E
EBIT	**2,877**	**-12,834**	**-11,540**	**21,912**	**52,330**	**70,582**
Depreciation and amortization	1,038	963	756	3,415	2,535	2,307
EBITDA	**3,915**	**-11,871**	**-10,784**	**25,327**	**54,865**	**72,890**
Changes in working capital	-7,474	-5,267	642	11,099	10,087	1,967
Other adjustments	986	-103	138	1,787	-7,940	-5,833
Operating cash flow	**-2,573**	**-17,241**	**-10,004**	**38,213**	**57,012**	**69,024**
CAPEX	-654	-898	-57,474	-6,045	-4,468	-3,306
Free cash flow	**-3,227**	**-18,139**	**-67,478**	**32,168**	**52,544**	**65,718**
Debt financing, net	**-682**	**15,524**	**63,635**	**-10,088**	**-21,962**	**-21,962**
Equity financing, net	**19,375**	**483**	**8,825**	**6,833**	**0**	**0**
Other changes in cash	**-1,249**	**-210**	**-4,688**	**-1,057**	**-1,336**	**0**
Net cash flows	**14,217**	**-2,342**	**294**	**27,856**	**29,246**	**43,756**
Cash, start of the year	19,968	34,185	31,843	32,137	59,993	89,239
Cash, end of the year	**34,185**	**31,843**	**32,137**	**59,993**	**89,239**	**132,995**
EBITDA/share	**0.01**	**-0.03**	**-0.03**	**0.05**	**0.09**	**0.12**
Y-Y Growth						
Operating cash flow	n.m.	n.m.	n.m.	n.m.	49.2%	21.1%
Free cash flow	n.m.	n.m.	n.m.	n.m.	63.3%	25.1%
EBITDA/share	n.m.	n.m.	n.m.	n.m.	81.5%	32.9%

FIRST BERLIN RECOMMENDATION & PRICE TARGET HISTORY

Report No.:	Date of publication	Previous day closing price	Recommendation	Price target
Initial Report	10 November 2009	€ 0.52	Buy	€ 0.70
2...36	↓	↓	↓	↓
37	14 September 2017	€ 0.47	Buy	€ 1.50
38	7 December 2017	€ 1.19	Buy	€ 1.70
39	18 January 2017	€ 1.30	Buy	€ 1.90
40	Today	€ 1.37	Buy	€ 2.00

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INFORMATION PURSUANT TO SECTION 34B OF THE GERMAN SECURITIES TRADING ACT [WPHG], TO REGULATION (EU) NO 596/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF APRIL 16, 2014, ON MARKET ABUSE (MARKET ABUSE REGULATION) AND TO THE GERMAN ORDINANCE ON THE ANALYSIS OF FINANCIAL INSTRUMENTS [FINANV]

First Berlin Equity Research GmbH (hereinafter referred to as: "First Berlin") prepares financial analyses while taking the relevant regulatory provisions, in particular the German Securities Trading Act [WpHG], Regulation (EU) No 596/2014 of the European Parliament and of the Council of April 16, 2014, on market abuse (market abuse regulation) and the German Ordinance on the Analysis of Financial Instruments [FinAnV] into consideration. In the following First Berlin provides investors with information about the statutory provisions that are to be observed in the preparation of financial analyses.

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