EDISON

Probiodrug

FY16 company results

Early PQ912 data for Huntington's; AD data soon

Pharma & biotech

Probiodrug's new preclinical data showed that PQ912 demonstrated efficacy in Huntington's disease (HD) in an animal model. Subject to further preclinical work, PQ912 could be fast-tracked to the clinic, which would diversify Probiodrug's R&D pipeline with a new indication. Much will depend on the outcome of the company's milestone clinical Phase IIa SAPHIR trial with PQ912 for Alzheimer's disease (AD) with the data readout shortly. PQ912 is a first-in-class small molecule glutaminyl cyclase (QC) inhibitor and represents a differentiated approach in the AD field. We value Probiodrug at €345m or €42.1/share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/15	0.0	(13.5)	(1.96)	0.0	N/A	N/A
12/16	0.0	(13.8)	(1.81)	0.0	N/A	N/A
12/17e	0.0	(10.5)	(1.28)	0.0	N/A	N/A
12/18e	0.0	(8.7)	(1.06)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

FY16 results in line with expectations

Probiodrug reported 2016 results in line with our estimates. R&D spend in FY16 was €11.0m, vs our expectation of €11.1m, while G&A expenditure of €2.9m was lower than our €3.3m estimate indicating good cost management. Probiodrug reported cash of €21.9m at end FY16, which included a capital raise of €14.9m in October 2016. The company guided that the net loss in 2017 could be lower than in 2016 (€13.9m) since R&D costs will decrease with the SAPHIR trial winding down.

All eyes on SAPHIR data readout

Probiodrug's Phase IIa SAPHIR is due to report results before mid-2017. The trial is investigating the effects of PQ912 in AD with safety and tolerability being the primary endpoints; however, secondary endpoints will provide insights into the effect on the pathology of the disease. Since the treatment duration in Phase IIa is a relatively short three months, the R&D strategy after the SAPHIR trial will depend on results. Presuming the safety profile is confirmed, the next goal would be to trial PQ912 for a longer treatment period in the form of a Phase IIb or Phase III study. Obtaining cognition improvement over a three-month period of treatment would be a best-case scenario, but we do not believe this is a prerequisite to establishing an attractive partnership deal before moving into late-stage development.

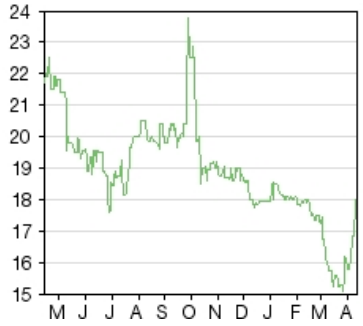
Valuation: Slightly upped to €345m

Our valuation of Probiodrug is slightly increased, from €337m or €41.2/share, to €345m or €42.1/share due to rolling our model forward, which offsets the lower cash position of €21.9m. Our model suggests cash should be sufficient to fund operations throughout 2018, which gives enough time, post-data readout, to share future development strategy and progress with potential partners depending on the results. The outcome of the Phase IIa trial is the main catalyst in the near term.

12 April 2017

Price	**€17.99**
Market cap	**€147m**
Net cash (€m) at end Q416	21.9
Shares in issue	8.2m
Free float	50%
Code	PBD
Primary exchange	Euronext Amsterdam
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	14.3	(2.0)	(20.0)
Rel (local)	12.7	(8.0)	(32.7)
52-week high/low		€23.8	€15.1

Business description

Probiodrug is a German biopharmaceutical company developing its clinical pipeline for the treatment of Alzheimer's disease. Lead product candidate PQ912 is in Phase IIa. PQ912 is a small molecule inhibitor of glutaminyl cyclase (QC), which is essential for the formation of pGlu-Abeta. Two further products are in preclinical stages.

Next events

PQ912 Phase IIa data	Q217
Q117 results	12 May 2017
Q217 results	31 August 2017

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Probiodrug is a research client of Edison Investment Research Limited

Preclinical data support new PQ912 application

Probiodrug's preclinical data revealed that PQ912 demonstrated efficacy in HD in a well characterised model. BACHD mice with human gene coding mutant protein huntingtin (mHTT), a hallmark of the disease, were used in the study. Probiodrug will present the results at the 12th Annual HD Therapeutics Conference of the CHDI Foundation on 23 April in Malta; the headline findings include:

- mHTT levels in the brain were reduced by around 30% after treating the mice for 18 weeks with PQ912.
- The mHTT reduction was associated with improvement in the pathophysiology of the disease:
  - reduction of inflammation marker the GFAP-protein;
  - normalisation of abnormal body weight gain; and
  - normalisation of several mRNA markers coding heat shock proteins, which can prevent the accumulation of misfolded mHTT and thus its toxicity.

Probiodrug hypothesised that these effects may result from an inhibition of similar molecular mechanisms that were already well explored in AD. While encouraging, this is still the first preclinical data set released, so it is not clear whether this would translate to clinical efficacy. The company has not revealed further development strategy yet; in our view, much will depend on the outcome of the SAPHIR trial due shortly. Since PQ912 has already established safety data (short term in humans and long-term toxicity data in animals), we believe that the drug candidate could be fast-tracked to studies with HD patients. This means that Probiodrug would not be a single indication company anymore, which we believe would be a welcome diversification. The company also communicated that it is exploring PQ912's potential in other conditions, such as Down's syndrome.

HD market potential

HD is an incurable, inherited disorder associated with a loss of neurons in specific locations, resulting in symptoms such as involuntary movements (chorea), dementia and behavioural changes. Estimated prevalence is 4.1-8.4 per 100,000 people, translating to a patient population in the range of 13-27k (source: Huntington Disease, Medscape). HD is a progressive disease with onset in 30-40-year-olds and patients surviving 10-25 years on average. There is currently no disease modifying therapy for this condition, only various treatment options to alleviate symptoms such as chorea or improve patients' quality of life. Therefore, the progress of the disease cannot be stopped.

According to EvaluatePharma, tetrabenazine (Xenazine) is notable among the branded drugs used to alleviate chorea in HD. Xenazine is a monoamine inhibitor, which depletes neurotransmitters dopamine, noradrenaline and serotonin, altering transmission of electric signals from the brain that control movement. Marketed by Lundbeck in the US, Xenazine had $317m in peak sales in 2015, which then fell to $233m in 2016 after the introduction of the first generic versions. Notably, such sales were achieved with only a symptomatic drug, while a disease modifying drug would very likely achieve much higher levels, in our view.

Financials

R&D spend in FY16 was €11.0m, in line with our €11.1m. G&A expenditure of €2.9m was lower than our €3.3m estimate for FY16, indicating good cost management. We keep our FY17 R&D cost

estimate of €7.7m unchanged in line with Probiodrug's guidance that 2017 net loss may be lower than in 2016, as the SAPHIR trial is winding down. We slightly lower our FY17 G&A costs expectations to €3.1m from €3.4m and subsequently expect the 2017 EPS loss at €1.30, an improvement from our previous loss of €1.35 (Exhibit 1).

Probiodrug reported cash of €21.9m at end FY16, which included a capital raise of €14.9m in October 2016. Our post-FY16 model suggests that this should be sufficient to fund operations into 2019. If the company is required to repay tax provisions of €2.6m (originating from 2002-2005 and with no court decision yet), then the cash reach could be to Q418.

We continue to project that if the Phase IIa trial results are positive, a licensing deal in 2017 is likely given the high profile of Probiodrug's R&D programme among the larger players in the AD field. Although our valuation includes a risk-adjusted milestone (€25m) from a partner for PQ912 that could be triggered by licensing (more details in our initiation report) our financial forecasts do not include any such income.

Exhibit 1: Summary of the main changes to our Probiodrug financial forecasts

€m	2016			2017e			2018e
	Estimate	Actual	% change	Old	New	% change	New
Revenues	**0.000**	**0.000**	**N/A**	**0.000**	**0.000**	**N/A**	**0.000**
Gross profit	**0.000**	**0.000**	**N/A**	**0.000**	**0.000**	**N/A**	**0.000**
Research and development costs	(11.105)	(10.951)	-1%	(7.669)	(7.669)	+0%	(5.669)
Selling, general and administration costs	(3.279)	(2.909)	-11%	(3.443)	(3.054)	-11%	(3.207)
EBITDA	**(14.285)**	**(13.680)**	**-4%**	**(11.018)**	**(10.508)**	**-5%**	**(8.632)**
Operating profit (reported)	**(14.342)**	**(13.777)**	**-4%**	**(11.070)**	**(10.640)**	**-4%**	**(8.793)**
Profit before tax (rep)	(14.220)	(13.891)	-2%	(11.053)	(10.623)	-4%	(8.793)
Profit after tax (rep)	**(14.220)**	**(13.891)**	**-2%**	**(11.053)**	**(10.623)**	**-4%**	**(8.793)**
EPS (€, rep)	**(1.82)**	**(1.82)**	**+0%**	**(1.35)**	**(1.30)**	**-4%**	**(1.07)**

Source: Edison Investment Research, Probiodrug accounts

Operational update: SAPHIR trial in focus

Probiodrug's Phase IIa SAPHIR trial is primarily a safety and tolerability study, but a set of exploratory readouts will assess PQ912's effect on the pathology of the disease. Secondary endpoints include:

- assessment of short-term memory and verbal function (neuropsychological test battery);
- functional assessments by EEG and functional MRI, which will be indicative of changes in synaptic plasticity and neuronal connectivity respectively; and
- molecular biomarkers in cerebrospinal fluid (CSF), such as pGlu-Abeta, Abeta oligomers, neurogranin and inflammatory markers.

More details about the trial design are provided in Exhibit 2.

Exhibit 2: SAPHIR clinical study design

Aim	To determine the safety, tolerability and preliminary efficacy of PQ912 in patients with early/mild AD. Exploratory readouts will be used to look for an efficacy signal to justify advancing to pivotal study.
Summary design	Multicentre (21 sites, seven EU countries), randomised, double-blind, placebo-controlled, parallel-group study.
Design details	n=110 planned, 120 enrolled. Treatment-naïve patients (no concomitant symptomatic AD medication) with mild cognitive impairment due to AD or mild dementia due to AD. MMSE score of 21-30 inclusive, CSF Abeta concentration of < 638 ng/L AND total tau >375 ng/L OR p-tau > 52 ng/L; Tau/Abeta ratio in CSF >0.52; positive amyloid PET if available. Half will receive PQ912, 800mg, twice a day (with an option to decrease the dose if necessary), the other half will receive placebo.
Primary endpoints	Frequency of adverse events and serious adverse events (timeframe: 12 weeks, four weeks follow-up).
Exploratory readouts	Assessments of cognitive function and change from baseline in brain functional assessments as brain functional connectivity and synaptic plasticity and molecular biomarker levels in CSF.
Start date	March 2015
Completion dates	Full results in Q217.

Source: Probiodrug, Edison Investment Research; clinicaltrials.gov. Note: MMSE = mini mental state examination.

Probiodrug's strategy is to establish a partnership to develop PQ912 through late-stage studies. In our view, if the Phase IIa trial shows cognition improvements with a treatment time of just three months, the company would be in an excellent position to negotiate an attractive partnership deal. Nevertheless, we believe that cognition improvement is not a prerequisite for a partnership and that a partnership will depend on the data readout. As far as we are aware, Probiodrug is the only company developing a QC inhibitor, so we expect a number of players will pay close attention to the outcome of the SAPHIR trial.

Envisaging PQ912's further development, the strategy after Phase IIa will depend on the results of the trial. A base case scenario could be a Phase IIb study to evaluate the efficacy over a longer treatment period based on encouraging signals in exploratory readouts. In the case of very strong signals in several readout categories, this would allow going directly into a pivotal longer treatment study.

Valuation

We value Probiodrug at €345m or €42.1/share, up from €337m or €41.2/share previously, due to rolling our model forward, which offsets the lower cash position of €21.9m. We are interested to see progress with PQ912 for HD, which we would add to our valuation upon entering clinical development. The breakdown of our rNPV valuation, which uses a discount rate of 12.5%, is shown in Exhibit 3. Our valuation only includes PQ912, with no value assigned to the preclinical pipeline given its earlier stage of development. Full details are discussed in our last outlook report.

Exhibit 3: Probiodrug rNPV valuation

Product	Indication	Launch	Peak sales (€m)	Value (€m)	Probability	rNPV (€m)	NPV/share (€/share)
PQ912	Alzheimer's disease	2022	6,200	1,240.8	25%	323.1	39.5
Net cash				21.9	100%	21.9	2.7
Valuation				**1,262.7**		**345.0**	**42.1**

Source: Edison Investment Research. Note: peak sales are rounded to the nearest €100m.

Exhibit 4: Financial summary

€'000s	2012	2013	2014	2015	2016	2017e	2018e
Year end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS							
Revenue	6	0	0	0	0	0	0
Cost of Sales	0	0	0	0	0	0	0
Gross Profit	6	0	0	0	0	0	0
Research and development	(9,255)	(8,004)	(8,008)	(10,158)	(10,951)	(7,669)	(5,669)
EBITDA	(10,206)	(9,387)	(11,173)	(13,337)	(13,680)	(10,508)	(8,632)
Operating Profit (before amort. and except.)	(10,521)	(9,675)	(11,241)	(13,363)	(13,700)	(10,534)	(8,658)
Intangible Amortisation	(37)	(26)	(26)	(30)	(77)	(106)	(134)
Exceptionals	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0
Operating Profit	(10,558)	(9,701)	(11,267)	(13,393)	(13,777)	(10,640)	(8,793)
Net Interest	(314)	(106)	(170)	(112)	(114)	17	0
Profit Before Tax (norm)	(10,835)	(9,781)	(11,411)	(13,475)	(13,814)	(10,518)	(8,658)
Profit Before Tax (FRS 3)	(10,872)	(9,807)	(11,437)	(13,505)	(13,891)	(10,623)	(8,793)
Tax	(656)	0	0	0	0	0	0
Profit After Tax (norm)	(11,491)	(9,781)	(11,411)	(13,475)	(13,814)	(10,518)	(8,658)
Profit After Tax (FRS 3)	(11,528)	(9,807)	(11,437)	(13,505)	(13,891)	(10,623)	(8,793)
Average Number of Shares Outstanding (m)	4.1	4.3	4.9	6.9	7.6	8.2	8.2
EPS - normalised (€)	(2.84)	(2.30)	(2.35)	(1.96)	(1.81)	(1.28)	(1.06)
EPS - normalised and fully diluted (€)	(2.84)	(2.30)	(2.35)	(1.96)	(1.81)	(1.28)	(1.06)
EPS - (IFRS) (€)	(2.85)	(2.30)	(2.35)	(1.97)	(1.82)	(1.30)	(1.07)
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	n/a	n/a	n/a	n/a	n/a	n/a
EBITDA Margin (%)	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Operating Margin (before GW and except.) (%)	n/a	n/a	n/a	n/a	n/a	n/a	n/a
BALANCE SHEET							
Fixed Assets	996	425	186	140	167	152	109
Intangible Assets	67	101	82	56	96	107	90
Tangible Assets	926	321	101	81	68	42	16
Investments	3	3	3	3	3	3	3
Current Assets	9,009	5,856	21,294	21,726	22,199	10,963	2,284
Stocks	18	0	0	0	0	0	0
Debtors	5	0	0	0	0	0	0
Cash	7,726	4,421	20,920	21,361	21,897	10,661	1,982
Other	1,260	1,435	374	365	302	302	302
Current Liabilities	(3,570)	(9,320)	(4,580)	(4,911)	(5,140)	(4,263)	(4,083)
Creditors	(3,570)	(3,974)	(4,580)	(4,911)	(5,140)	(4,263)	(4,083)
Short term borrowings	0	(5,346)	0	0	0	0	0
Long Term Liabilities	(1,070)	(1,265)	(929)	(822)	(850)	(850)	(850)
Long term borrowings	0	0	0	0	0	0	0
Other long term liabilities	(1,070)	(1,265)	(929)	(822)	(850)	(850)	(850)
Net Assets	5,365	(4,304)	15,971	16,133	16,376	6,003	(2,540)
CASH FLOW							
Operating Cash Flow	(12,090)	(8,477)	(10,540)	(12,149)	(13,255)	(11,136)	(8,562)
Net Interest	22	9	(54)	0	0	17	0
Tax	28	9	5	2	0	0	0
Capex	(64)	(4)	(2)	(6)	(7)	0	0
Acquisitions/disposals	0	0	0	0	0	0	0
Financing	9,516	(188)	32,436	12,594	13,798	(117)	(117)
Dividends	0	0	0	0	0	0	0
Net Cash Flow	(2,588)	(8,651)	21,845	441	536	(11,236)	(8,679)
Opening net debt/(cash)	(10,314)	(7,726)	925	(20,920)	(21,361)	(21,897)	(10,661)
HP finance leases initiated	0	0	0	0	0	0	0
Other	0	0	0	(0)	0	0	0
Closing net debt/(cash)	(7,726)	925	(20,920)	(21,361)	(21,897)	(10,661)	(1,982)

Source: Probiodrug accounts, Edison Investment Research

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