EDISON

Probiodrug

FY17 company update

Emerging details of PQ912 late-stage development

Pharma & biotech

The highlight of Probiodrug's FY17 results presentation was the rather detailed introduction of the Phase IIb development programme for the lead asset PQ912, a small molecule inhibitor of glutaminyl cyclase (QC) for Alzheimer's disease (AD) patients. Two Phase IIb trials (in Europe and the US) are designed to gather the amount of data that, if sufficiently positive, could allow for accelerated or conditional regulatory approval. The first Phase IIb study in Europe is expected to start by end 2018 and Probiodrug is exploring all options for funding sources. After several modest changes to our model, our updated valuation is slightly higher at €513m, €62.4/sh.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/16	0.0	(13.8)	(1.81)	0.0	N/A	N/A
12/17	0.0	(9.0)	(0.97)	0.0	N/A	N/A
12/18e	0.0	(7.8)	(0.95)	0.0	N/A	N/A
12/19e	0.0	(7.9)	(0.97)	0.0	N/A	N/A

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

European/US Phase IIb studies could lead to market

The preliminary design for the European Phase IIb trial SAPHIR 2 have been presented. The design of the Phase IIb US study should be substantially similar in regard to patent population and titration, but will likely include additional readouts and treatment period will be 18 months including an interim analysis. The primary endpoint is PQ912's effect on cognitive function measured by the neuropsychological test battery (NTB). NTB was one of the exploratory endpoints in the Phase IIa trial with PQ912 and showed initial signs of positive changes in cognitive function of AD patients after a short, three-month treatment period. AD patients will be treated for about a year on average in the upcoming European trial. If the data are sufficiently positive from both the US and European trials, Probiodrug expects to initiate a discussion with the regulatory authorities for accelerated or conditional approval (we assume in 2023).

Financials: 2018 spend expected lower than in 2017

Probiodrug reported R&D and G&A costs of €7.5m and €2.5m in 2017, close to our respective estimates of €7.7m and €3.1m. FY17 R&D spend was lower than in 2016 (€11.0m), when the Phase IIa SAPHIR trial was in full swing. Management indicated that it expects a net loss in 2018 to decrease further y-o-y mainly due to lower R&D spend as the company is preparing for the late-stage trials with PQ912. Cash at end of 2017 was €10.3m (no debt), which is sufficient for this year. Probiodrug indicated that it is focusing on strengthening its financial position.

Valuation: Marginally higher at €513m or €62.4/share

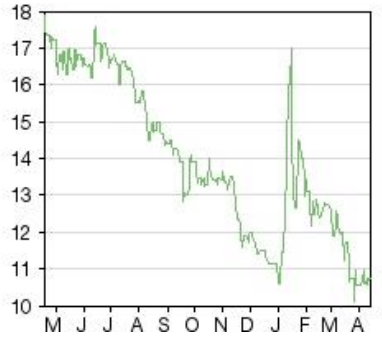
We value Probiodrug at €513m or €62.4/share, up from €496m or €60.6/share due to rolling our model forward, which offset the lower cash position of €10.3m and modest changes in our R&D assumptions (mainly timing of the licensing deal and the launch date). The initiation of the Phase IIb trial expected later this year, clarification on funding sources and any partnering deal are potential catalysts in the short term.

13 April 2018

Price	**€10.75**
Market cap	**€88m**

Net cash (€m) at end December 2017	10.3
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	(10.0)	(32.8)	(40.0)
Rel (local)	(11.6)	(31.2)	(43.3)
52-week high/low		€17.9	€10.1

Business description

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

Next events

Q118 results	15 May 2018
Phase IIb trial start	H218

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Phase IIb trial design leverages Phase IIa data

The preliminary design for the European trial (SAPHIR 2) is shown in Exhibit 1. The US study details are not yet released, but it should be similar in design to the European trial with a somewhat longer treatment period. Notably, the US study could potentially benefit from the initial titration phase in the European study. Therefore, timewise, both studies should significantly overlap. Trial design for late-stage development was inspired by the rich dataset obtained from the Phase IIa SAPHIR trial announced in June 2017. As a reminder:

- The Phase IIa SAPHIR study was a safety/tolerability trial, but secondary endpoints included exploratory efficacy tests, such as the NTB (Cogstate) as cognitive composite, quantitative EEG, resting state functional MRI as well as a set of molecular biomarkers in the spinal fluid.
- The highest dose of 800mg bid tested and well tolerated in the Phase I study was selected and administered for three months. Probiodrug indicated that this high dose (although not established as maximum tolerated dose over the 7-11 days of treatment in the elderly in Phase I) was strategically selected to:
  - firstly, understand the picture of safety/tolerability in AD patients treated for three months and comply with the EMA guidelines requesting that in Phase I or Phase IIa a maximum tolerated dose should be established; and
  - secondly, to get early signs of efficacy over such a short treatment period.
- The number of patients experiencing adverse events did not significantly differ between the placebo and PQ912 arms (PQ912 n=49, placebo n=45), but the total number of non-adherent to treatment patients for any reason was higher in the active arm (PQ912 n=26; placebo n=2; $p<0.01$). Skin and gastrointestinal (GI) side effects were more common in the PQ912 arm.
- Despite the short treatment period, several exploratory efficacy endpoints provided statistically significant results or trends pointing to a positive overall picture of the dataset in our view (discussed in our previous report).

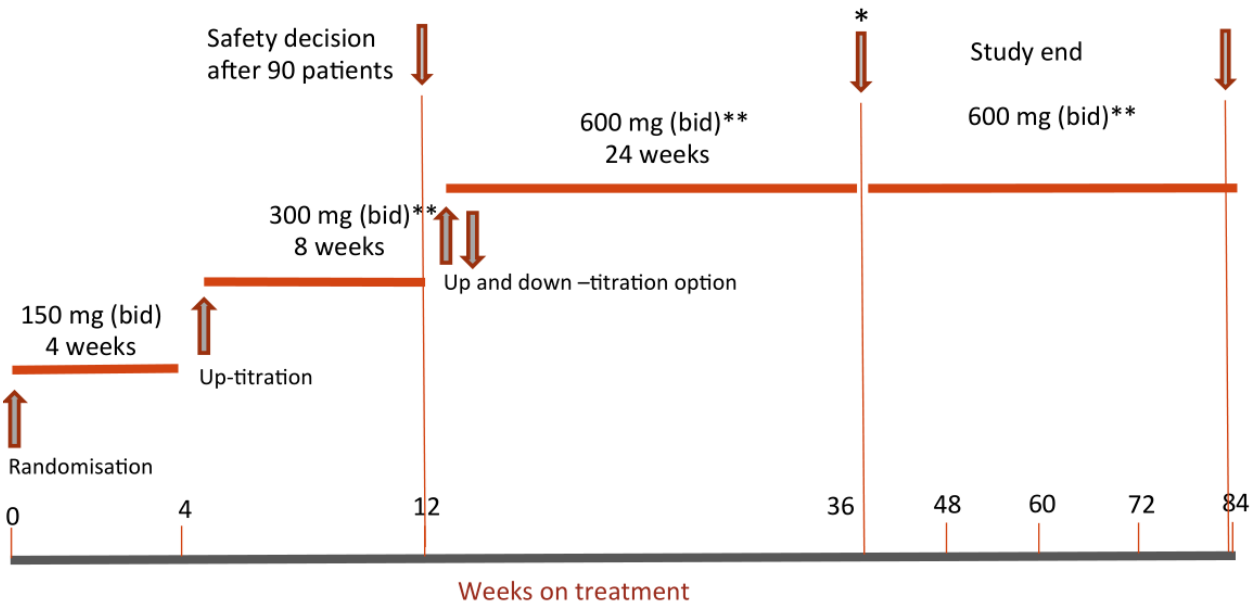
Overall, no major safety concerns associated with PQ912 were established in the Phase IIa trial. The observed skin and GI side effects were manageable, appeared early in the trial and resolved upon the discontinuation of PQ912. In upcoming Phase IIb studies to address any safety issues Probiodrug will explore lower doses and a gradual titration to maximum individually tolerable levels. Dose reduction is feasible, as in the Phase I trial, target occupancy has been shown to be 90% at a dose of 800mg bid, while a dose range of 300 to 600mg bid would still achieve target occupancy in the range of 70–80+%. Probiodrug will enrol patients into an initial 12-week treatment regimen titrating the dose of PQ912 in the range 150-300mg (Exhibit 2) over that period. Subsequently, patients will receive the maximum individually tolerable dose of 300mg or 600mg. In total, each patient is expected to be treated for between 36 and 84 weeks (on average around a year, 52 weeks).

NTB will be used to assess PQ912's efficacy on the cognitive function of AD patients (primary endpoint). NTB was one of the exploratory endpoints in the Phase IIa trial with PQ912 and two out of seven cognitive assessments (that constitute the NTB) showed significant or trending positive changes in cognitive function of AD patients after the short, three-month treatment period. Secondary endpoints (changes in daily activities measured by the Amsterdam Instrumental Activity of Daily Living Questionnaire, effect on EEG and synaptic brain connectivity) and exploratory endpoints (CSF biomarkers, MRI imaging of brain) also build on the insights from the Phase IIa trial, where several of the tests showed statistically significant or trending changes.

Exhibit 1: Preliminary Phase IIb SAPHIR 2 trial (Europe) details	
Aim	Clinical proof of concept in cognition.
Summary design	Prospective, multi-centre, randomised controlled trial.
Design details	250 early-stage AD patients. 12 weeks of treatment with 150–300mg (bid) for initial safety readout. Patients then receive individually highest tolerated doses (300 or 600mg bid). Each patient will be treated for 36 to 84 weeks.
Patients	Male or female; MMSE 21-30, CSF amyloid & tau positive; on standard of care or treatment naïve.
Endpoints	Primary: efficacy of PQ912 on cognitive function in early AD (NTB). Secondary: efficacy on activities of daily living, effect on qEEG on synaptic function and brain connectivity. Exploratory readouts: CSF-based biomarker and MRI imaging of brain and hippocampal volume.
Timelines	Start Q418; interim safety/futility analysis Q419; key results Q321.

Source: Probiodrug, Note: MMSE = mini mental state examination.

Exhibit 2: SAPHIR 2 trial time schedule



* All patients will have a study duration of at least 36 weeks on treatment. The earlier randomised patients will continue after week 36 until the last patient in the study reached week 36. Depending on timing for each individual patient this means treatment up to week 36, week 48, week 60, week 72 **or** week 84

** Subjects who experience AEs compromising the tolerance of the treatment or the safety and wellbeing of the subjects can reduce the dose anytime back from 300 mg (bid) to 150 mg (bid) during weeks 5-12 and from 600 mg (bid) to 300 mg (bid) during weeks 13 to 84.

Source: Probiodrug

The preliminary timelines indicate that the European Phase IIb trial could start in Q418. Interim safety analysis is planned by end 2019 and final data are expected in Q321. Details for the US study are yet to be finalised, but potentially both trials should run at least partially in parallel. If sufficiently positive data are obtained, Probiodrug expects to discuss accelerated or conditional approval with the regulatory authorities. Alternatively, a pivotal Phase III programme will be initiated. With regards to funding sources, the company indicated that it is working on strengthening its financial position.

Valuation

We value Probiodrug at €513m or €62.4/share, up from €496m or €60.6/share previously due to rolling our model forward, which offsets the lower cash position of €10.3m at the end of 2017. We have made some modest changes to our model. Our key assumption was that Probiodrug will out-license the project to a partner for a pivotal study in 2017 and, if successful, the drug will be

launched in 2022. From the timeline perspective we view the conditional approval scenario as consistent with our model since the timelines for the European Phase IIb trial are in line with our assumptions. Given that the timelines for the US study are not fully defined, we leave some room by postponing the launch date in our model from 2022 to 2023. Another change in our NPV model was the timing of the licensing deal.

The key near-term sensitivity is obtaining the required funds for the Phase IIb trials. Probiodrug's current cash reach is until early 2019, according to our model. For comparison, the Phase IIa study ran from Q115 to Q317 and Probiodrug's total R&D spend for 2015–2017 was €28.6m. Part of that was spent on preclinical development, but the bulk of it likely accounted for the costs related to the Phase IIa trial. As the next studies will be larger, the R&D costs will be substantially higher. As before, Probiodrug indicated that all financing options for the late-stage development are on the table, that is, share issue, non-dilutive funding options or a partnership deal. For the time being we maintain our out-licensing approach (the partner will take over the development) in our model with same terms as before, but move the deal to 2018. We include €35m in income from the partner in 2018 in our risk-adjusted NPV, but do not show it in our financial summary table as the deal is not certain. The breakdown of our rNPV valuation, which uses a discount rate of 12.5%, is shown in Exhibit 3. 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	2023	6,200	1,380.2	35%	502.2	61.2
Net cash				10.3	100%	10.3	1.3
Valuation				**1,390.5**		**512.5**	**62.4**

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

Exhibit 4: Financial summary

€000s	2015	2016	2017	2018e	2019e
December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	0	0	0	0	0
Cost of Sales	0	0	0	0	0
Gross Profit	0	0	0	0	0
Research and development	(10,158)	(10,951)	(7,454)	(5,169)	(5,169)
EBITDA	(13,337)	(13,680)	(9,855)	(7,763)	(7,905)
Operating Profit (before amort. and except.)	(13,363)	(13,700)	(9,876)	(7,790)	(7,932)
Intangible Amortisation	(30)	(77)	(85)	(11)	(1)
Exceptionals	0	0	0	0	0
Other	0	0	0	0	0
Operating Profit	(13,393)	(13,777)	(9,961)	(7,801)	(7,933)
Net Interest	(112)	(114)	850	0	0
Profit Before Tax (norm)	(13,475)	(13,814)	(9,026)	(7,790)	(7,932)
Profit Before Tax (FRS 3)	(13,505)	(13,891)	(9,111)	(7,801)	(7,933)
Tax	0	0	1,102	0	0
Profit After Tax (norm)	(13,475)	(13,814)	(7,924)	(7,790)	(7,932)
Profit After Tax (FRS 3)	(13,505)	(13,891)	(8,009)	(7,801)	(7,933)
Average Number of Shares Outstanding (m)	6.9	7.6	8.2	8.2	8.2
EPS - normalised (€)	(1.96)	(1.81)	(0.97)	(0.95)	(0.97)
EPS - normalised and fully diluted (€)	(1.96)	(1.81)	(0.97)	(0.95)	(0.97)
EPS - (IFRS) (€)	(1.97)	(1.82)	(0.98)	(0.95)	(0.97)
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	n/a	n/a	n/a	n/a	n/a
EBITDA Margin (%)	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
BALANCE SHEET					
Fixed Assets	140	167	69	41	23
Intangible Assets	56	96	11	1	0
Tangible Assets	81	68	55	37	20
Investments	3	3	3	3	3
Current Assets	21,726	22,199	10,693	3,206	402
Stocks	0	0	0	0	0
Debtors	0	0	0	0	0
Cash	21,361	21,897	10,291	2,804	0
Other	365	302	402	402	402
Current Liabilities	(4,911)	(5,140)	(668)	(668)	(668)
Creditors	(4,911)	(5,140)	(668)	(668)	(668)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	(822)	(850)	(1,171)	(1,171)	(5,996)
Long term borrowings	0	0	0	0	(4,825)
Other long term liabilities	(822)	(850)	(1,171)	(1,171)	(1,171)
Net Assets	16,133	16,376	8,923	1,408	(6,239)
CASH FLOW					
Operating Cash Flow	(12,149)	(13,255)	(12,117)	(7,477)	(7,619)
Net Interest	0	0	0	0	0
Tax	2	0	0	0	0
Capex	(6)	(7)	(7)	(10)	(10)
Acquisitions/disposals	0	0	0	0	0
Financing	12,594	13,798	518	0	0
Dividends	0	0	0	0	0
Net Cash Flow	441	536	(11,606)	(7,487)	(7,629)
Opening net debt/(cash)	(20,920)	(21,361)	(21,897)	(10,291)	(2,804)
HP finance leases initiated	0	0	0	0	0
Other	(0)	0	0	0	0
Closing net debt/(cash)	(21,361)	(21,897)	(10,291)	(2,804)	4,825

Source: Probiodrug accounts, Edison Investment Research

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