EDISON

Probiodrug

Company outlook

Support for Abeta theory from Biogen/Eisai

Pharma & biotech

We believe one of the main reasons for the devaluation of Probiodrug's shares over the past year was the largely disappointing industry newsflow frustrating research on Abeta theory, even though Probiodrug's technology is differentiated from all other Abeta therapies studied in late-stage trials. The recent surprise announcement of disease-modifying effect obtained by Biogen/Eisai with their MAb BAN2401 in a Phase II trial may reignite interest in the amyloid theory and in the Alzheimer's disease (AD) field in general. While funding and lack of visibility on a partnering deal are near-term risks, we find Probiodrug's asset PQ912, a small molecule glutaminyl cyclase (QC) inhibitor, and its Phase IIa data interesting. In our view, any progress with raising new funds or finding a partnering would unlock substantial upside from the current low valuation level.

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.

Spotlight on Abeta MAbs after Biogen's Ph II results

Over the last decade there has been no lack of disappointing industry news on AD research, including multiple failures of Abeta-targeting antibodies. There have been three BACE inhibitor failures so far this year: verubecestat (Merck), atabecestat (Janssen) and lanabecestat (Eli Lilly, AstraZeneca). This negative news dampened investor confidence in Abeta-targeting strategies. However, results from Biogen and Eisai's Phase II trial with Abeta antibody BAN2401 showed a statistically significant disease modifying effect, which is a holy grail in AD research, and revived some hope for Abeta targeted therapies.

Preparing for Phase IIb initiation

As of the Q218 update, Probiodrug's next Phase IIb is in the advance set-up stage. End-H118 cash was €7.2m, in line with management expectations. Management is now focusing on strengthening the company's finances. We believe new funds will be necessary to ramp up the upcoming Phase IIb studies. Another solution could be bringing a partner on board, albeit there has been no major development on this front since the Phase IIa data released in June 2017.

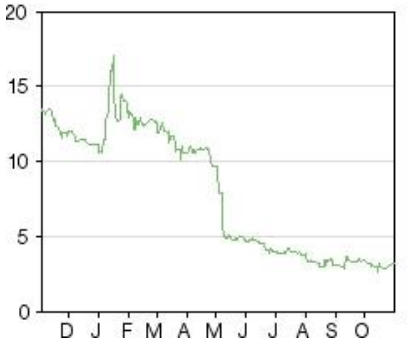
Valuation: Revised to €270m or €32.9/share

We believe Probiodrug's lack of progress in business development is underpinned by lacklustre industry newsflow, but PQ912 seems an interesting asset based on data reported so far. The new Biogen/Eisai data may renew interest in Abeta theory in general, but lack of visibility on Probiodrug deal leads us to introduce a 50% licensing risk in our model. Our updated valuation is €270m or €32.9/share, down from €513m or €62.4/share. Progress with partnering or a successful fund-raise could unlock substantial upside from the current levels, in our view.

1 November 2018

Price	**€3.15**
Market cap	**€26m**
Net cash (€m) at end-H118	7.2
Shares in issue	8.2m
Free float	90%
Code	PBD
Primary exchange	Euronext Amsterdam
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(7.4)	(16.2)	(76.5)
Rel (local)	(0.3)	(6.0)	(74.7)
52-week high/low		€17.0	€2.6

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

Q318 results	29 November 2018
Phase IIb trial start	Q418

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Investment summary

Company description: Treatments targeting toxic pGlu-Abeta

Probiodrug is a German biopharmaceutical company developing therapies for the treatment of AD. It employs an approach to targeting the toxic Abeta version of pyroglutamate-Abeta (pGlu-Abeta), which is differentiated in two ways: by preventing the formation of pGlu-Abeta or by capturing and clearing pGlu-Abeta after it has been formed. Lead product candidate, PQ912, prevents the formation of pGlu-Abeta by inhibiting QC and is due to enter Phase IIb in coming months after promising Phase IIa data. PBD-C06 is a pGlu-Abeta-specific monoclonal antibody also in preclinical stage, which directly targets pGlu-Abeta, leaving non-toxic forms of Abeta untouched (capture and clear action). Probiodrug also has PQ1565, a second small molecule QC inhibitor, in preclinical stage.

Probiodrug was founded in 1997 and has focused solely on AD since selling the diabetes franchise to OSI Pharmaceuticals for €28.7m in 2004 and the Ingenium CDK9 research programme to AstraZeneca for $1m in 2013. Probiodrug is based in Halle, Germany. Since 2007 it has raised c €114m, including gross proceeds of €23m from the IPO in October 2014, listing on Euronext Amsterdam at €15.25/share.

Exhibit 1: Product pipeline

Product	Stage	Patent expiry	Mechanism of action	Notes
PQ912	Phase IIb-ready	2030	Small molecule inhibitor of glutaminyl cyclase (QC), the enzyme catalysing the formation of pGlu-Abeta.	Phase IIb SAPHIR study (n=250 with early AD) planned to start in Q418. Key results planned Q321.
PBD-C06	Preclinical	2029	pGlu-Abeta specific monoclonal antibody. Selectively targets pGlu-Abeta.	Humanised and de-immunised. Manufacturing process optimised. Animal toxicology studies in plans.
PQ1565	Preclinical	2034	Small molecule QC inhibitor.	GMP process is being implemented.

Source: Probiodrug, Edison Investment Research. Note: Patent expiries do not include potential extensions.

Valuation

Our Probiodrug valuation is now €270m or €32.9/share, based on a risk-adjusted NPV analysis using a 12.5% discount rate. This includes €7.2m net cash reported at end-H118 and PQ912 for use in early AD. We assume PQ912 could achieve peak sales of c €6bn in 2028 (around six years after our forecast 2023 launch). This is based on the assumption that PQ912 will demonstrate disease-modifying benefits, which would be likely to lead to premium pricing and would be achievable even with only modest penetration of early AD patients.

Financials

Probiodrug reported cash of €7.2m at end H118. Our model suggests this should be sufficient to fund operations to the start of 2019, but fresh funds will be needed to ramp up the Phase IIb trial. Probiodrug is now focusing on raising the funds for its R&D programme, which was presented in detail with its Q218 results. Management indicated that the European part of the Phase IIb strategy, which is the next study, could cost around €25m. The US study is planned to be longer but could be supported by the NIH grant, which will be clarified next year (see page 7).

Sensitivities

The main sensitivities are around the lead candidate, PQ912. Although it has shown efficacy in animal models and proved safe in the Phase I/IIa trials, it remains to be seen whether this will translate into a clinical benefit. The upcoming Phase IIb study will be capital intensive, therefore fresh funds or a partner will be needed. Drug development in AD is notoriously perilous, although this could be justified by the significant size of the market and potential for considerable rewards.

Biogen antibody sparked hope in AD research

On 5 July 2018, Biogen and Eisai announced initial positive results from a Phase II study with amyloid antibody BAN2401 in patients with minimal cognitive impairment (MCI) due to AD and mild AD dementia (n=856). Both companies' share prices jumped on the news (20% and 39% respectively), as well as the share price of the Swedish biotech that originated the molecule, BioArctic (334%). Following this press release, detailed data were presented a few weeks later at the Alzheimer's Association International Conference (AAIC) in Chicago on 22–26 July 2018 and a further subgroup analysis was announced at the Clinical Trials on Alzheimer's Disease (CTAD) meeting on 24–27 October 2018, Barcelona. While the reiterated top-line data were positive, the details revealed some skeletons in the closet and the share price of all three companies retracted somewhat, however, they are still higher compared to before the announcement. Given that both Biogen and Eisai are large-cap biotechs, BAN2401 data created substantial value.

Design of the trial

The BAN2401 Phase II trial enrolled **856 patients** with MCI or mild AD patients with confirmed amyloid pathology in the brain. The trial had **six arms**: 2.5mg/kg every two weeks (bi-weekly), 5mg/kg monthly, 5mg/kg bi-weekly, 10mg/kg monthly, 10mg/kg bi-weekly and placebo. Interestingly, the study had an **adaptive design** and, as it used Bayesian statistical analysis on multiple intermittent checks, more patients were directed towards the arms that showed a likelihood of better efficacy. Such trial designs tend to be complicated and are therefore used rarely, but can potentially increase the number of patients in the better-performing dose arms, which subsequently increases the statistical power. The **primary endpoints** were:

- Change from baseline in the Alzheimer's Disease Composite Score (**ADCOMS**) at 12 months. ADCOMS is a novel measure statistically derived using a combination of items (but not all of them) from classic AD tests, the:
  - Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog);
  - Clinical Dementia Rating Sum of Boxes (CDR-SB) scale; and
  - Mini-Mental State Examination (MMSE).

  This endpoint was specifically designed by the sponsoring companies of this trial, which means there is no precedent for using this endpoint, and it is therefore not clear what the regulatory authorities' conclusion would be with regard to its validity. However, all the underlying items were selected from the widely used scores (ADAS-Cog, CDR-SB, MMSE). The rationale for sponsoring companies in using this derivative score was the expected improvement in efficacy of monitoring the decline of very early AD patients, which is challenging.
- **Safety** was also listed as a primary endpoint. Notable focus was on so-called amyloid-related imaging abnormalities (**ARIAs**), which can manifest as brain swelling or microhaemorrhages and are featured side effects of the Abeta antibody class.

Results announced

Originally, the effective dose was expected to be obtained early, after 12 months of treatment (primary endpoint) using Bayesian analysis with the aim of quickly proceeding into a Phase III trial. This analysis was reported in December 2017, but no dose arms were considered as having a statistically significant chance of being effective based on a pre-specified threshold. However, statistical futility was not shown either, therefore Biogen and Eisai continued the trial and performed a conventional statistical analysis after 18 months of treatment. Detailed, but not full, results were announced on 25 July 2018 at AAIC in Chicago. These included:

- At 18 months of treatment a statistically significant slowing by 30% in cognitive decline was demonstrated using ADCOMS in the highest dose group (10mg/kg bi-weekly) compared to

placebo. Using the more conventional ADAS-Cog score (items of which are included in ADCOMS), the reduction in cognitive decline was 47%.

- BAN2401 demonstrated a dose-dependent reduction in amyloid plaques, as measured by amyloid PET, and this reduction was statistically significant at all doses. In the highest dose group, amyloid plaques fell 93%, and 81% of patients in that group were considered converted from amyloid positive to negative.
- The ADCOMS endpoint did not reach significance in the lower dose arms than 10mg/kg bi-weekly, meaning that while a dose-response relationship was seen in amyloid PET imaging across all doses, this did not translate into increasing clinical efficacy in the lower dose arms.
- Unsurprisingly, the most common side effect was ARIA-E (oedema) and infusion reactions. ARIA-E incidence was not higher than 9.9% in any of the treatment arms, and was less than 14.6% in patients with APOE4 at the highest dose. This safety profile can be considered as well tolerable.

One of the key issues with the trial, which was the biggest contributor to the retraction in the sponsoring companies' share prices, was the fact that during the data presentation at the AAIC the researchers revealed that in July 2014 the regulator (European Medicines Agency) insisted on stopping recruitment of APOE4 gene carriers in the highest dose group out of fears of pronounced ARIAs. It is known that these patients are more prone to side effects from anti-amyloid antibodies. This resulted in a substantially skewed distribution of APOE4 carriers: fewer in the highest dose arm and more in lower dose arms. Because only the highest dose was effective, attention was focused on how much influence the APO4 gene had in establishing the significance of the treatment effect. While it is widely accepted that the APOE4 gene predisposes earlier onset of AD, the pace of progression of the disease is less clear and there is no broad consensus on this issue. The definitive answer to this question was supposed to be addressed by a subgroup analysis, which was presented on 25 October at CTAD. The updated findings included:

- In placebo arm APOE4, carriers and non-carriers progressed with the disease at a similar rate, which supports the opinion that APOE4 is a risk factor for age on onset of the disease, but the progression is similar to APOE4 non-carriers.

This leads to the conclusion that slowing in cognitive decline observed in the BAN2401 10mg/kg bi-weekly arm was driven by the treatment and not by the imbalance in subject allocation by APOE4 status. However, further insights were more mixed:

- APOE4 carriers (n=10) in the highest dose arm responded better than carriers in the placebo group (n=113), but the non-carrier patients treated with BAN2401 (n=69) showed little improvement when compared to placebo (n=47) (statistically significant on ADAS-Cog endpoint, but not on ADCOMS or CDR-SB).
- 14.6% APOE4 carriers in the highest dose arm experienced ARIA-E side effects, while it was seen in 8% of non-carriers.

Our take

Overall, the results support target engagement and the antibody appears to do what it was designed for – strong dose-response relationship in PET amyloid reductions across all doses, with signs of significant slowing in cognitive decline in the highest dose group. Somewhat ironically, APOE4 carriers – patients who were asked by the EU regulator to be excluded from the highest dose arm – were the same patient group that benefited most from the treatment. This resulted in a situation that the population of patients with the best response consisted of only 10 APOE4+ patients in the subgroup analysis. Biogen and Eisai have not announced further development strategy so far. One clear direction could be to focus more on APOE4 carriers as the ARIA-E side-effect prevalence of 14.6% can be considered as well-tolerable. More questions surround how to approach the APOE4 non-carrier population in future trials; however, in the AD field, even a subset

of the population would present an excellent commercial opportunity. Studies indicate that APOE4 status can vary substantially depending on geography, but nevertheless the prevalence of APOE4+ among AD patients seems to be high: around 40% in Asia and South Europe, and around 60% in North America and northern Europe. The number of people living with dementia worldwide is currently estimated at around 44 million, c 60% of whom have AD. Biogen and Eisai indicated that they are currently in discussions with the regulatory authorities on how to proceed further.

R&D strategies to tackle AD

Of the potential disease-modifying AD therapies in development, there are two main strategies: targeting either tau tangles or Abeta plaques. Tau and Abeta are proteins that exist in the brain and cerebrospinal fluid. Because of their increased presence in the AD brain as protein aggregates and significant scientific evidence that these proteins can be toxic to neurons, they are thought to be at least partially responsible for AD pathology.

The traditional amyloid hypothesis postulates that insoluble Abeta plaques are the key neurotoxic culprit in AD. In recent years a modified amyloid hypothesis has emerged, proposing that not all Abeta is toxic nor are the plaques themselves toxic. Instead, misfolded soluble **Abeta oligomers**, or 'pre-plaques', are thought to be the primary driver of the pathological pathway to AD. These toxic oligomers induce other Abeta molecules to take on the misfolded form and aggregate into plaques.

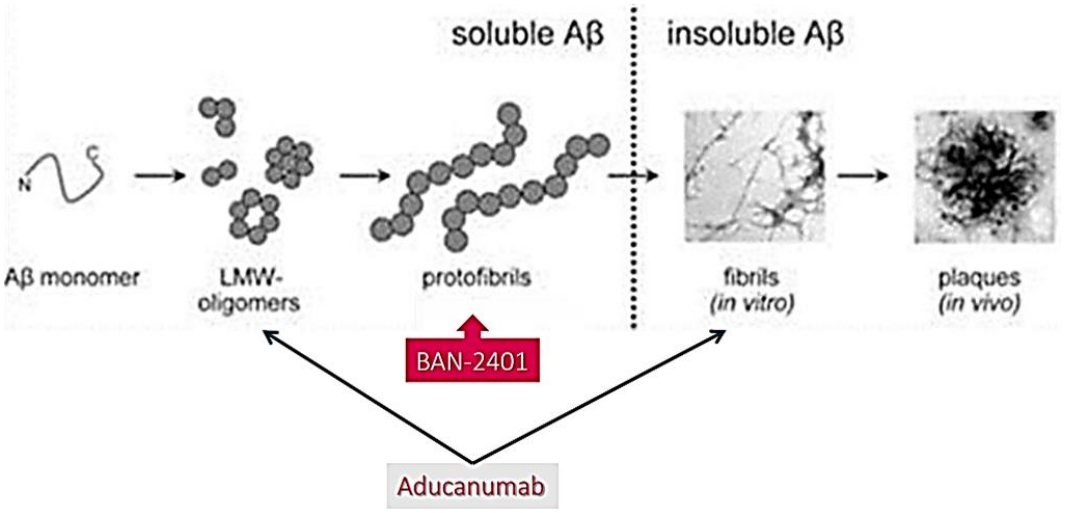
A large proportion of drugs in development are aimed at intervening in the amyloid cascade to prevent or slow these toxic effects. The original Abeta strategy was to try to capture and clear the various toxic Abeta products that have already been formed. This includes immunotherapy strategies: passive with monoclonal antibodies or more novel active with Abeta vaccines. The main passive strategies include monoclonal antibodies designed to bind different forms of Abeta through particular sections or 'domains' of the protein, and to clear or sequester the Abeta, which will prevent further damage by the toxic Abeta. Abeta vaccines have a similar approach, but induce the body's immune system to create antibodies against certain Abeta domains, thus clearing the Abeta as it is formed. Only one vaccine so far is being studied in a Phase III trial, CAD106 (Novartis).

Despite efforts over the last two decades, many traditional Abeta targeting antibody approaches have failed. Notable exceptions now are BAN2401, as described above, and aducanumab, which Biogen tested in a Phase I trial. A dose-dependent reduction of the amyloid load (measured by PET) was observed, which was associated with a significant cognitive benefit in the MMSE and CDR-SB test. Although this was an early study, the results were sufficiently impressive for Biogen to move directly into a Phase III trial in 2015. Of note is that both of these Abeta antibodies target soluble Abeta oligomers or protofibrils (Exhibit 2). Probiodrug's PQ912 targets the toxic soluble Abeta version (pGlu-Abeta).

Beta-secretase (BACE) has become a popular, more upstream target in the amyloid cascade. BACE is one of the two enzymes that catalyse the production of Abeta (Aβ1-40, Aβ1-42 and Aβ1-38) from amyloid precursor protein, the other being gamma secretase. BACE therefore acts as an upstream target in the amyloid cascade and inhibition of BACE should prevent the formation of Abeta, as well as its downstream products including Abeta oligomers, aggregates and plaques. According to amyloid hypothesis, this should prevent further AD pathology and worsening of symptoms. BACE inhibitors were viewed as having great potential and many large pharma players were heavily invested in this strategy. However, this year alone saw three BACE inhibitors failing Phase III studies: verubecestat (Merck; large reduction in CSF Abeta, but no cognitive benefit), atabecestat (Janssen; stopped because of liver toxicity) and lanabecestat (Eli Lilly, AstraZeneca; did not pass the futility test).

Failure of the Abeta targeting drugs so far is blamed on the stage of disease, with the suggestion that even if the toxic Abeta products can be cleared, it may be too late to prevent the resulting downstream toxic effects, ie activation of microglia and astrocytes, inflammation, oxidative stress and synaptic dysfunction.

Exhibit 2: Both aducanumab and BAN-2401 target soluble Abeta components

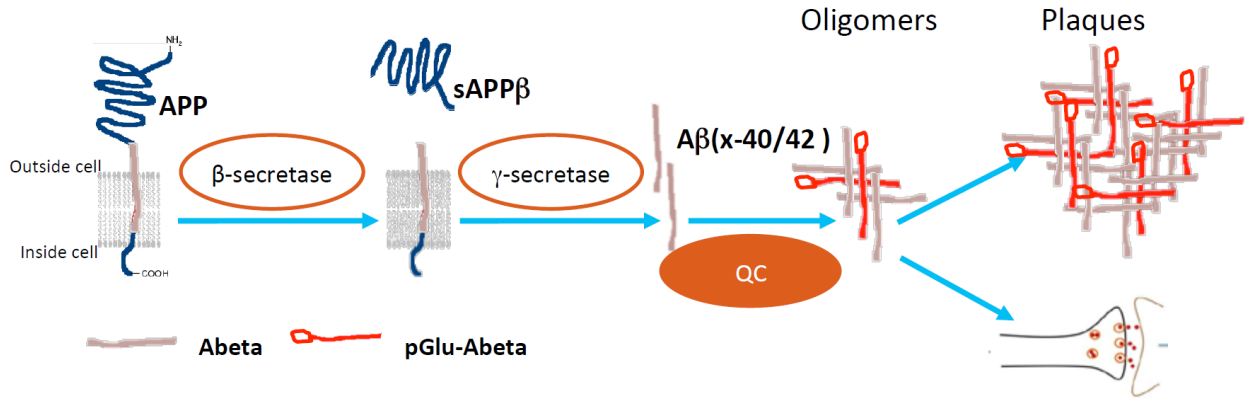


Source: Biogen, Eisai

Two-pronged approach from Probiodrug

A specific, post-translationally modified variant of Abeta, **pGlu-Abeta** has been shown to trigger the formation of hypertoxic Abeta oligomers, propagating in a chain reaction-like mechanism.[1] This initiates a pathological cascade, with loss of connection between neurons (synaptic dysfunction), tau pathology, neuroinflammation and eventual neuronal death (neurodegeneration) with resultant cognitive decline. Unlike Abeta plaques, which are also seen in cognitively normal individuals, pGlu-Abeta is specific to AD and correlates with the progression of AD pathology.

Exhibit 3: Amyloid cascade and pGlu-Abeta



Source: Probiodrug

In 2004 Probiodrug's scientists discovered the key enzyme that is essential for the formation of pGlu-Abeta from Abeta peptides, **QC**. QC expression has been found to be upregulated in the brains of people with AD correlating with the appearance of pGlu-Abeta and the decline in MMSE.

[1] Morawski M, et al. Glutaminyl cyclase in human cortex: correlation with (pGlu)-Amyloid- βload and cognitive decline in Alzheimer's disease. Journal of Alzheimer's Disease **39**, 385-400 (2014).

Inhibition of QC in animal AD models effectively blocked the production of pGlu-Abeta, prevented the aggregation of all types of Abeta in the brain and demonstrated that QC inhibitors can reduce neurotoxicity, neuroinflammation and restore cognitive function.[2]

After this fundamental discovery, Probiodrug now has a pipeline of drug candidates that can either inhibit QC or capture and clear pGlu-Abeta. Lead product candidate PQ912 (Phase IIb ready) is a first-in-class, small molecule QC inhibitor discovered by Probiodrug, with the aim of preventing formation of pGlu-Abeta and resulting toxic oligomers. To our knowledge, no other company is developing a drug to prevent formation of pGlu-Abeta. The company's second lead product is pGlu-Abeta specific monoclonal antibody PBD-C06 in preclinical development. Preclinical AD animal studies have demonstrated PBD-C06's ability to reduce pGlu-Abeta and total Abeta, with a consequent rescue of short-term memory deficits and significant improvement in learning and memory after chronic treatment. PBD-C06 has been successfully humanised and de-immunised with the manufacturing process optimised in 2015. Probiodrug is investigating its potential as a combination therapy with PQ912 as well.

Eli Lilly also developing a pGlu-Abeta MAb

Eli Lilly is also developing a pGlu-Abeta antibody, **LY3002813** (Lilly's internal name is anti-N3pG monoclonal antibody), which has been studied as monotherapy in a Phase I trial (n=100). At the 2016 AAIC conference in Toronto, Lilly presented results from 49 patients. The patients had MCI due to AD or mild to moderate AD, and received single ascending and multiple ascending (MAD, monthly) doses. Key findings include:

- Patients who received the highest dose (10mg intravenously) in the MAD part showed a significant reduction in Abeta plaques of about 40% measured by PET scans. This made LY3002813 one of very few antibodies shown to actually reduce brain amyloid. However, there were only six patients in this arm.
- The effective dose of 10mg did not induce ARIA-E and only two asymptomatic microhaemorrhages (ARIA-H) were reported.

Eli Lilly commented that the half-life of antibodies was unexpectedly short, with four days using the 3mg dose and 10 days with the 10mg dose, whereas antibodies usually have a half-life of at least 20 days. Another surprising issue was the high levels of anti-drug antibodies (patient's own immune system neutralising the drug).

Given the amyloid clearing effect and good safety profile, Lilly initiated another Phase I trial (n=150) with higher doses. Initial findings from 58 patients were presented at the AAIC conference in August 2018. In the highest dose group of 20mg/kg monthly for six months, all six patients responded to treatment and three out of those six have become amyloid negative. While this effect appears to be significantly larger numerically, the patients in higher dose arms also reported ARIAs. At the time of the presentation, Lilly mentioned that the treatment of 12 patients (of the 58 evaluated) was discontinued because of ARIAs. The company is monitoring all patients for 18 months. While this study is ongoing, Lilly has advanced LY3002813 to Phase II (study completion estimated in 2021), where it is being explored in combination with its BACE inhibitor LY3202626.

Phase IIb SAPHIR 2 strategy involves two studies

The protocol for the Phase IIb SAPHIR 2 European trial has been completed, whereas the design of the US trial is the preliminary stage (both shown in Exhibit 4). Time wise, the studies should significantly overlap. The US study will have a longer treatment period and could potentially benefit

[2] Schilling S, et al. Glutaminyl Cyclase inhibition attenuates pyroglutamate Abeta and Alzheimer's disease-like pathology. Nature Medicine **14**(10):1106-11 (2008).

from an initial titration phase of the European study. The focus of the European trial will be on PQ912's synaptic effects with tools investigated in the Phase IIa trial. Classic Cogstate (working memory/ attention composite) will be used as a primary endpoint to assess PQ912's efficacy in the European study, while secondary and exploratory endpoints will build on those used in the Phase IIa trial, where several of the tests showed statistically significant or trending changes. In the US trial patients will be treated for longer, so the focus will be on the cognitive effects across domains and daily function measured by the classic CDR-SB.

In forthcoming Phase IIb studies to address any safety issues (see SAPHIR Phase IIa data summary, below), Probiodrug will explore lower doses and a gradual titration to the maximum individually tolerable levels. Dose reduction is feasible because the Phase I trial target showed occupancy was 90% at a dose of 800mg bid, while a dose range of 300-600mg bid would still achieve target occupancy in the range of 70-80% plus. In the European study, Probiodrug will enrol patients into an initial 12-week treatment regimen titrating the dose of PQ912 in the range 150-300mg 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 52 weeks). The US trial should be similar in design, but will treat the patients longer for 18 months on average.

Management indicated that the European Phase IIb trial could start in Q418 and final data are expected in Q321. Details of the US study are yet to be finalised, but potentially could recruit the first patient in Q219 with data readout in Q322, so both trials should run substantially in parallel. The rational for this Phase IIb strategy is based on stepwise risk reduction and value creation, the ability to engage with the regulatory authorities to discuss the Phase IIb data sooner and understand in a timely manner whether the data are supportive of early NDA filing with the expectation of conditional approval or whether a Phase III trial will be needed. When it comes to funding, Probiodrug indicated the total cost of the European trial is estimated at €25m and >€60m for the US study. The company could potentially receive funding of up to $15m from the NIH, which would substantially alleviate the burden. There are several options when it comes to funding the trials, including a fund-raise or a partnership.

Exhibit 4: Phase IIb strategy (SAPHIR 2) in Europe and US

European study	**Focus on synaptic effects with tools investigated in Phase IIa**
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 Each patient will be treated for 36 to 84 weeks (mean 12 months)
Patients	Male or female; MMSE 21-30, CSF amyloid & tau positive; on standard of care or treatment naïve
Endpoints	Primary: working memory/attention composite (Cogstate) Secondary: effect on qEEG on synaptic function and brain connectivity, total Cogstate and Instrumental Activities of Daily Living (IADL) Exploratory readouts: CSF-based biomarker and MRI imaging of brain and hippocampal volume
Timelines	Trial start in coming months, depending on funding; recruitment duration 16 months;
US study	**Focus on cognitive effects across domains and daily function**
Summary design	Prospective, multi-centre, randomised controlled trial
Design details	460 early-stage AD patients At least 8 weeks of treatment with 150–300mg (bid) for initial safety readout in first 180 patients Patients then receive individually highest tolerated doses Long-term drug exposure, 18 months on average
Patients	Male or female; FDA stage 3+4 (MMSE: 21-30 inclusive, CSF AD pathophysiology amyloid + and pTau & tau/A-beta ratio + Patients on SoC or treatment naïve)
Endpoints	Primary: CDR-SB Secondary: efficacy on composite measure of cognition and function (CFC2) Exploratory readouts: CSF and plasma based biomarkers, MRI imaging, EEG network connectivity
Timelines	Trial start in 2019, depending on funding

Source: Probiodrug, Note: MMSE = Mini-Mental State Examination.

SAPHIR Phase IIa data summary

In December 2015, Probiodrug announced the publication of the full Phase I results in a peer-reviewed journal describing first-in-man PQ912 safety and PK/PD, which we reviewed in our previous outlook report. The first data from the Phase IIa SAPHIR trial were 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 neuropsychological test battery (CogState) as cognitive composite, quantitative EEG, resting state functional MRI and 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 obtain 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 patients who were non-adherent to treatment 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 on discontinuation of PQ912.

Long quest for AD medicine

Multiple failures of late stage clinical trials with antibodies targeting Abeta over the last decade have dampened the enthusiasm of investors. The most recent additions to this trend have been BACE inhibitors, with three key late-stage failures in 2018 alone. In February, Merck announced that it was terminating its BACE inhibitor verubecestat Phase III APECS study in prodromal AD. This decision was based on the recommendation from an independent data monitoring committee that if the study continued it would be unlikely that a positive benefit/risk ratio would be established. The results were later published, which showed that despite a large reduction in CSF Abeta, patients in the treatment group declined at a similar rate to the placebo group.

In May, Janssen (part of Johnson & Johnson) announced that it was stopping its Phase IIb/III study in late-onset, preclinical-stage AD and Phase II long-term safety study due to liver toxicity. Also, in June, Eli Lilly and AstraZeneca announced that they were terminating the Phase III AMARANTH and DAYBREAK-ALZ trials for lanabecestat in MCI due to AD or early AD and mild AD dementia. This decision was based on the recommendation from an independent data monitoring committee that if the study continued it would likely not meet the efficacy endpoint.

Current consensus is that therapies should target the earliest stages of the Abeta pathogenic sequence – in pathological terms, ideally before plaques are established, and in clinical terms when

there remains potential for a sufficient cognitive reserve.[3] This is also reflected in the recently updated EMA and FDA 2018 clinical trial guidelines, which now recommend that clinical trials study an earlier AD population including 'preclinical' or non-symptomatic.

One of the likely reasons for lack of efficacy in the previous AD trials is that the stage of AD studied is still too late to slow or stop Abeta formation and toxicity. This means that even if these drugs have prevented further formation of Abeta products, it might still be too late to prevent Abeta toxicity caused by Abeta products that have already formed. An interesting approach was taken by Novartis, which is conducting late-stage prevention trials in asymptomatic patients for its BACE inhibitor CNP520 and its Abeta vaccine CAD106 (Exhibit 5). Patients are selected for these trials based on their ApoE4 genotype. According to clinicaltrials.gov, these trials are due to read out in 2024.

Abeta monoclonal antibodies currently in Phase III trials include aducanumab (Biogen, Eisai) and gantenerumab (Roche), which both have high affinity for aggregated Abeta, and crenezumab (Roche), which has high affinity for oligomeric and fibrillary Abeta and amyloid plaques. These drugs are all targeting early AD. Aducanumab Phase III data are expected in 2020, while multiple studies with gantenerumab and crenezumab should report data over 2020-23 and 2021-23 respectively.

Exhibit 5: Ongoing Abeta Phase III trials

Pharmacological class	Drug	Target/mechanism of action	Company	Ongoing Phase III trials	Stage of AD	Estimated trial completion
Abeta MAbs	Aducanumab	Aggregated Abeta	Biogen, Eisai	NCT02477800	MCI/mild AD	2020
				NCT02484547	MCI/mild AD	2020
	Gantenerumab	Aggregated Abeta	Roche	NCT02051608	Mild AD	2020
				NCT03444870	Prodromal/mild AD	2022
				NCT03443973	Prodromal/mild AD	2022
	Crenezumab	Oligomeric and fibrillary Abeta and amyloid plaques	Roche	NCT02670083 (CREAD Study)	Prodromal/mild AD	2020
				NCT03114657 (CREAD 2)	Prodromal/mild AD	2021
				NCT03491150 (CREAD OLE open label extension study)	Prodromal/mild AD	2023
Abeta vaccine	CAD106	Vaccine induces Abeta antibodies which target Abeta N-terminus 1-6	Novartis	NCT02565511	At risk of AD*	2024
Small molecule BACE inhibitor	CNP520	BACE1	Novartis, Amgen	NCT03131453	At risk of AD*	2024
				NCT02565511 (CNP520 and CAD106 combination study)	At risk of AD*	2024
	Elenbecestat	BACE1	Biogen, Eisai	NCT02956486 (MissionAD1)	MCI/mild AD	2020
				NCT03036280 (MissionAD2)	MCI/mild AD	2020

Source: clinicaltrials.gov, Global Data, Evaluate Pharma. Note: *Based on age, APOE genotype and elevated amyloid. BACE = Beta-secretase, Abeta = amyloid beta, MAb = monoclonal antibody.

Alzheimer's disease and the vast target population

The number of people living with dementia worldwide is currently estimated at around 44 million, c 60% of whom have AD. Given the lack of a preventative or curative treatment, this number is set to almost double by 2030 and more than triple by 2050 (World Alzheimer Report 2014). In 2015, the direct costs to American society of caring for those with AD totalled an estimated $226bn, which is expected to increase to c $1.1trn by 2050 (2015 Alzheimer's Disease Facts and Figures). Despite having no disease-modifying ability and limited symptomatic efficacy, the four FDA-approved AD treatments had combined 2015 sales of c $3.8bn globally (source: EvaluatePharma). Notably, generic donepezil commanded $780m of these sales (21% market share). The Namenda franchise

[3] Lemere, C. Immunotherapy for Alzheimer's disease: hoops and hurdles. Mol Neurodegener. 8:36 (2013).

(formerly of Forest Laboratories, now Actavis) had combined revenues of $1.8bn in 2015 (48% market share). Thus, AD not only represents a significant unmet clinical need, it also represents a substantial market opportunity for disease-modifying therapies. As a result, drug development for AD has become a major political, academic and industrial effort, as evidenced by initiatives such as the Global Dementia Discovery Fund and the big pharma collaborations between Biogen and Eisai, AstraZeneca and Eli Lilly. This illustrates the scope and willingness of the industry to support development of novel treatments in AD.

Sensitivities

Probiodrug is subject to the usual risks associated with drug development, including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks, and financing and commercial risks. The biggest near-term sensitivity for Probiodrug is the success or failure of lead asset PQ912 for AD. PQ912 has already demonstrated in Phase I and IIa trials that it can successfully inhibit QC. However, whether this has any cognitive benefits, as suggested by preclinical models, is yet to be established in humans.

Funding is a near-term risk for Probiodrug. The company currently has €7.2m in cash ahead of the Phase IIb trial initiation for lead asset PQ912, as announced in the Q218 company update. Management indicated in the Q218 results that it is focusing on strengthening the company's financial position with all options on the table. We have said in previous reports that we believe positive Phase IIa data should help secure a partner. However, a deal has not been achieved.

Our peak sales forecast assumes PQ912 can offer disease-modifying benefit. AD is a substantial market with a large unmet medical need, hence any disease-modifying therapy is likely to generate significant sales. However, development risk is high, with multiple failures in the past, and late-stage trials will be costly. Future pricing and market dynamics are hard to predict, especially if competitors are successful, biomarkers lead to improved diagnosis, and combination therapy emerges as the main focus of development.

Financials and valuation

Probiodrug reported R&D and G&A costs of €2.6m and €1.6m in H118, largely in line with our expectations. We expect total operating 2018 costs of €7.8m to be lower than the €10.0m in 2017, when the SAPHIR study ended. The next Phase IIb studies are planned to start this year, depending on available funding, which implies R&D costs ramp up in 2019. Cash at the end of H118 was €7.2m (no debt), which is sufficient for this year.

Probiodrug indicated that it is focusing on strengthening its financial position. We have assumed a licensing deal in 2018 following positive Phase IIa results in June 2017. We believe that lack of progress in business development for Probiodrug was mainly underpinned by lacklustre newsflow from the industry, but PQ912 seems to be an interesting asset based on the data reported so far. The new Biogen/Eisai data may renew interest in Abeta theory in general, but lack of Probiodrug deal visibility leads us to introduce a 50% licensing risk in our model. Our updated valuation is therefore €270m or €32.9/share, down from €513m or €62.4/share. Any progress with partnering or a successful fund-raise could unlock substantial upside from the current levels, in our view. For the time being, we make no other changes to our R&D assumptions, but once there are more details on funding sources for the Phase IIb trials, we will revise our model accordingly.

Exhibit 6: Probiodrug rNPV valuation

Product	Indication	Launch	Peak sales (€m)	Value (€m)	Tech. prob.	Deal prob.	rNPV (€m)	NPV/share (€/share)
PQ912	Alzheimer's disease	2023	6,200	1,445.9	35%	50%	263.1	32.0
Net cash				7.2	100%		7.2	0.9
Valuation				**1,453.1**			**270.3**	**32.9**

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

Exhibit 7: Financial summary

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

Source: Probiodrug accounts, Edison Investment Research

Contact details	Revenue by geography
Probiodrug AG Weinbergweg 22 06120 Halle/Saale Germany +49 345 555 9900 www.probiodrug.de/	N/A

Management team

CEO: Dr Ulrich Dauer	CDO: Dr Inge Lues
Dr Ulrich Dauer joined Probiodrug as CEO on the 1st May 2018. He was one of the co-founders of Probiodrug and has a career spanning more than 20 years in the biopharmaceutical industry, in both public and private companies. He previously worked for 14 years as CEO of 4SC, attracting multiple private and public investors after the IPO. In subsequent leadership he executed the €130m sale of Activaero in 2014 and later acted as the CEO of two privately held biotech companies. Dr Dauer holds a PhD in Chemistry from the Julius-Maximilians University of Würzburg.	Inge Lues joined Probiodrug as R&D adviser in 2008 and has been CDO since 2013. From 2007 to 2013 she was also an adviser to other biotech companies and public research institutions. Before this, Dr Lues was head of global drug discovery and non-clinical development pharma at Merck KGaA (2002-07). Between 1998 and 2002 she headed Merck's Business Area CNS, achieving the strategic goal of out-licensing the CNS assets under development. Dr Lues received holds a PhD in Physiology and has completed post-doctoral training in pharmacology.

Principal shareholders	(%)
IBG Beteiligungsgesellschaft Sachsen-Anhalt	10.88
Aviva Investors Global Services	9.88
Edmond de Rothschild Asset Management	8.60
Life Sciences Partners	7.80
TVM Capital	6.80
HBM Healthcare Investments	4.94
Biogen	3.39

Companies named in this report

Biogen (BIIB.US), AstraZeneca (AZN.LN), Eli Lilly (LLY.US), Roche (ROG.SWX), Novartis (NOVN.SWX)

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