## Probiodrug reports financial results for H1 2017 and corporate update

# PQ912 delivers positive pharmacodynamic and efficacy results in a Phase-2a study in early stage AD patients

Successful settlement of long-pending tax issue PQ912 demonstrates efficacy in a preclinical Huntington's disease model

HALLE (SAALE), Germany, 31 August 2017 - Probiodrug AG (Euronext Amsterdam: PBD), a biopharmaceutical company developing novel therapeutic solutions to treat Alzheimer's disease (AD), today announced its financial results for the first six months ending 30 June 2017, prepared in accordance with German GAAP ("HGB") and, on a voluntary basis, in accordance with IFRS as endorsed by the European Union. The reports are available on the company website (http://www.probiodrug.de/investors/reports-and-presentations/).

#### **KEY HIGHLIGHTS**

- PQ912 delivers positive pharmacodynamic and efficacy results in a Phase-2a study, the SAPHIR study, in early stage AD patients
- Successful settlement of the potential tax liability resulting from 2004
- PQ912 demonstrates efficacy in preclinical Huntington's disease model
- Publication of PQ912 pharmacology paper in a peer-reviewed journal: 'Glutaminyl Cyclase Inhibitor PQ912 improves cognition in mouse models of Alzheimer's disease - studies on relation to effective target occupancy'
- New positive results with PQ912 and PBD-C06 alone and in combination in AD animal models
  presented
- Annual Shareholders' Meeting held on 13 June 2017
- Expenditures and corresponding cash position in line with management expectations
- As of 30 June 2017, Probiodrug held EUR 14.4 million in cash and cash equivalents

#### **POST PERIOD HIGHLIGHTS**

There were no significant events subsequent to the reporting period.

#### **CONFERENCE CALL**

Probiodrug will host a conference call open to the public today at 15:000 Central European Summer Time (CEST)/ 09:00 am Eastern Daylight Time (EDT); the presentation will also be posted to the website. The conference will be held in English. To participate in the conference call, please call one of the following numbers ten minutes prior to commencement:

Please dial one of the following access numbers, then enter your PIN Code: 48432861# A Question & Answer session will follow the presentation of results.

## Dial in coordinates

Country	Toll-free	Toll/Local
Austria	0800005804	+4319286161
Belgium	080058130	+3224019516
Canada (Toronto)	18552409492	+14162164179
Finland	800778964	+358981710375
France	0805639972	+33170709502

Germany (Frankfurt)	08008050102 (DE) 08008050115 (EN)	+4969201744220 (DE) +4969201744210 (EN)
Luxemburg	080040194	+35227302111
Netherlands	08000200293	+31207168020
Sweden	0200885102	+46850644386
Switzerland	0800001875	+41445806522
United Kingdom	08002794054	+442030092470
USA		+18774230830

Commenting on the results, Dr Konrad Glund, Chief Executive Officer of Probiodrug said: "Within the first half of 2017 we have done a significant step forward in the development of our AD program. In June we announced top-line data of the Phase-2a SAPHIR trial of our lead compound PQ912.

The results show a high target occupany, a lowering of pGlu-Abeta oligomers and indicate positive effects on synaptic function, as measured by changes of biomarker, EEG and on a test of working memory. These data clearly support the hypothesis of pGlu-Abeta being synaptotoxic and the effect of Glutaminyl Cyclase (QC)-inhibitors on reversing this pathology. The data are highly valuable for guiding the further development of PQ912 as a disease-modifying drug for AD.

The beneficial effects of PQ912 in a preclinical Huntington's disease model further strengthen the case to address this devastating disease as an additional indication for our QC inhibitors. The positive results with PQ912 and PBD-C06 in AD animal models further increase the attractiveness of our data package.

Moreover, we could solve the tax topic, which was pending since 2008 and was absorbing significant resources and attention. This is a great achievement.

With its extensive data base generated, Probiodrug seems well positioned to explore partnering options."

#### **KEY FIGURES (ACCORDING TO IFRS)**

	Jan - June 2017	Jan - June 2016	Jan - Dec 2016
In EUR k, unless otherwise stated			
<b>Earnings, Financial and Net Assets Position</b>	·		
Operating loss	-6,262	-5,987	-13,777
Income from release of tax provision	1,956	0	0
Net loss for the period	-4,306	-6,044	-13,891
Equity (end of the reporting period)	12,211	10,465	16,376
Equity ratio (end of the reporting period) (in %)	81.6%	66.6%	73.2 %
Balance sheet total (end of the reporting period)	14,971	15,740	22,366
Cash flows from operating activities (cum.)	-7,508	-7,000	-13,255
Cash flows from operating activities (monthly average)	-1,251	-1,167	-1,105

Cash flows from financing activities (net)	0	0	13,915
Cash and cash equivalents at the end of the reporting period	14,385	14,245	21,897

Personnel			
Total number of employees(incl. Board of management) (end of the reporting period)	14	16	13
Probiodrug-Share			
Loss per share (basic/diluted) (in EUR)	-0,53	-0,81	-1,82
Number of shares issued (end of the reporting period)	8,187	7,442	8,187

#### DETAILS OF THE FINANCIAL RESULTS (ACCORDING TO IFRS)

The comparison figures for the first six months 2017 shown below refer to the corresponding 2016 numbers.

#### **Net loss**

The net loss amounts to EUR 4,306k (Jan - June 2016: EUR 6,044k). EUR 6,262k (Jan - June 2016: EUR 5,987k) are to be attributed to the operating loss, EUR 856k to the financial income (Jan - June 2016: EUR 57k financial loss) and EUR 1,100k (Jan - June 2016: EUR 0k) to the gain from income taxes. The financial income and the gain from income taxes result from the successful settlement of the potential tax liability from the financial year 2004 (see Corporate Review). The operating loss is primarily driven by research and development expenses amounting to EUR 4,937k (Jan - June 2016: EUR 4,711k) and to a lesser degree by the general and administrative expenses of EUR 1,329k (Jan - June 2016: EUR 1,325k). The slight increase in research and development expenses reflects primarily the development activities of PQ912. These expenditures are in line with the expectations of Probiodrug.

#### **Equity**

As of 30 June 2017, the equity amounts to EUR 12,211k (as of 31 December 2016: EUR 16,376k), corresponding to an equity ratio of 81,6% (as of 31 December 2016: 73.2%).

#### Cash

Cash and cash equivalents were EUR 14,385k compared with EUR 21,897k as of 31 December 2016.

#### Noncurrent/ current liabilities

The noncurrent liabilities amount to EUR 859k (as of 31 December 2016: EUR 850k), consisting completely of the net commitment (defined benefit liability) of the pension commitments. The current liabilities amount to EUR 1,901k (as of 31 December 2016: EUR 5,140k), consisting mainly of trade payables in amounts of EUR 1,655k (as of 31 December 2016: EUR 1,893k), resulting from of the ordinary course of business. They have a remaining term of up to one year.

The decrease of the current liabilities is mainly driven by successful settlement of the potential tax liability. According to this settlement, Probiodrug paid in total (taxes including accrued interest) in an amount of EUR 775k, thereof EUR 9k paid in July 2017, and could release the remaining provision of EUR 1,964k.

#### **OPERATIONAL REVIEW**

## Pipeline update

Probiodrug's therapeutic approach targets pyroglutamate-Abeta (pGlu-Abeta, also called N3pG Abeta) as a therapeutic strategy to fight Alzheimer's disease (AD). This modified Abeta is considered to be linked with disease initiation and progression by seeding the formation of soluble neurotoxic amyloid oligomers. Probiodrug is developing proprietary product candidates to target toxic pGlu-Abeta via two modes of action: by (i) inhibiting the production of pGlu-Abeta; and (ii) clearing existing pGlu-Abeta from the brain.

Probiodrug's innovative approach is based on the development of specific inhibitors for the enzyme Glutaminyl Cyclase (QC), which is instrumental in the creation of pGlu-Abeta. In addition, the company is developing a monoclonal antibody targeting pGlu-Abeta to enhance its clearance.

To date, Probiodrug's pipeline consists of two small molecule inhibitors of the QC-enzyme, PQ912 and PQ1565, and a monoclonal antibody, PBD-C06, targeting pGlu-Abeta.

#### PQ912

Probiodrug's lead product candidate, PQ912, is a highly specific and potent inhibitor of QC, which has shown therapeutic effects in AD-animal models. In a Phase-1 study with healthy young and elderly volunteers, PQ912 was shown to be safe and well-tolerated and also revealed a dose dependent QC-inhibition in the CSF, reaching 90 % at the highest dose used.

PQ912 is the first QC-inhibitor being tested in patients. The Phase-2a study, the SAPHIR trial, was a randomized, double-blind multi-center study which enrolled a total of 120 patients with early stage Alzheimer's disease. The study was led by internationally renowned experts in AD in seven European countries at 21 sites, with the Alzheimer Center, VU Medical Center (VUmc), Amsterdam being the lead center. The primary endpoint of the trial was the safety and tolerability of PQ912 compared with placebo over a three-month treatment period. Additionally, a set of exploratory read-outs comprising cognitive tests, functional assessments by EEG and functional MRI and new molecular biomarkers in CSF were used to evaluate the compound's effect on the pathology of AD, in particular the effect on synaptic impairment, an early pathological change in the early stages of AD.

The SAPHIR trial used a high dose of PQ912 (which showed 90% QC-enzyme inhibition in CSF in Phase-1) in order to find both

- early-on tolerability signs and
- first signals on various sensitive secondary exploratory outcome measures in a relatively short time frame.

With respect to the primary endpoints there were no statistically significant differences of PQ912 vs placebo between the number of patients experiencing an adverse event or a serious adverse event. Patients in the treatment arm did show a significantly higher discontinuation rate due to SAE or grade 3 adverse events compared to patients in the placebo arm and the total number of patients non-adherent to randomised treatment for any reason was higher in the treatment arm. Skin and gastrointestinal organ system related adverse events were observed in a higher frequency in the PQ912 arm compared to placebo and occurred in the majority in the first half of the treatment period. Dose reductions prescribed by the investigator were identical in the treatment and the placebo arm. With a view on the high dose applied, Probiodrug is confident that with lower doses showing still quite high levels QC-inhibition and a slower titration scheme the drug will be safe and well-tolerated in AD patients

With respect to the secondary exploratory endpoints PQ912 showed a very strong target engagement (QC inhibition), confirming the finding in Phase-1 in elderly healthy volunteers of more than 90%, significant improvements of one test of working memory (one back test ) and a clear trend in detection test (attention domain). At the functional level a very significant positive effect was found on the EEG theta power. Regarding exploratory biomarkers in the spinal fluid, encouraging results in the right direction on synaptic and inflammatory CSF markers were obtained.

In summary, the positive effects on secondary exploratory efficacy markers are strongly supporting of (a) the hypothesis of pGlu-Abeta being synaptotoxic and (b) the therapeutic concept pursued by Probiodrug.

The study revealed a positive benefit risk ratio of PQ912 and provides important guidance how to move forward in the development pf PQ912 as a disease-modifying drug for AD. Altogether, the results make the program highly attractive for further development.

New positive results with PQ912 and PBD-C06 alone and in combination in AD animal models have been presented at the 13th International Conference on Alzheimer's and Parkinson's Diseases (AD/PDTM 2017), Vienna, Austria. In addition an evaluation of exploratory biomarkers in cerebrospinal fluid (CSF) from AD patients has also been presented.

PQ912 demonstrates beneficial effects in a preclinical Huntington's disease model, which have have been presented at the 12<sup>th</sup> Annual HD Therapeutics Conference of the CHDI Foundation on 23<sup>rd</sup> of April in St. Julian's, Malta. HD is the most common inherited neurodegenerative disorder where, due to a mutation, the poly-glutamine amino acid sequence is expanded in a protein called huntingtin (HTT). There is currently no disease modifying therapy for this condition. PQ912 clearly improved several signs of the disease in a well characterized BACHD mouse model of HD. BACHD mice carry the human gene for mutant HTT (mHTT). At six weeks old, parallel to the onset of first behavioral, metabolic and neuropathological signs of the disease, the BACHD mice were treated for 18 weeks with food pellets containing PQ912. PQ912 treatment for 18 weeks caused a significant reduction (approximately 30%) in brain mHTT levels. These lowered mHTT levels were associated with reduced levels of the inflammation/gliosis marker GFAP-protein, a striking normalization of the abnormal body weight gain and energy metabolism as well as a normalization of several mRNA levels coding for HSPs in BACHD mice at 24 weeks of age.

#### PBD-C06

PBD-C06 is a monoclonal antibody, currently in preclinical stage. PBD-C06 targets pGlu-Abeta, aiming to selectively clear the brain of pGlu-Abeta while leaving non-toxic forms of Abeta untouched. PBD-C06 has been successfully humanized and also de-immunized to avoid detection by the patient's endogenous immune system. For the first time for an anti-pGlu-Abeta approach PBD-C06 has not only shown the ability to reduce Abeta/plaques but also to significantly improve cognitive deficits in aged Alzheimer's mice. Moreover, no evidence was found of increased microhemorrhages after treatment with PBD-C06.

The development of the manufacturing process of this molecule is running.

#### **PQ1565**

PQ1565 is a QC-inhibitor, currently in preclinical stage. The product candidate has shown attractive drug-like properties in preclinical studies. The compound is ready for regulatory toxicology studies.

#### **CORPORATE REVIEW**

### Settlement of the potential tax liability resulting from the financial year 2004

In the reporting period the company could successfully reach an agreement with the relevant authorities of Saxony-Anhalt about the corporate income and trade tax claim for the assessment period 2004.

Following a tax audit in 2008, the tax authorities retroactively increased the taxable profits for 2004 by approximately EUR 10 million, resulting in a potential tax liability including accrued interest payment of a total of approx. EUR 2.7 million as of the end of 2016. Probiodrug believed that the better arguments spoke against the tax authorities' view and had contested the claims of the tax authorities. The matter was pending with the competent tax court. While still being convinced, that the better arguments were on its side, Probiodrug was seeking a solution with the relevant tax authorities of Saxony-Anhalt, which ultimately was reached in the first half of 2017. According to this settlement, Probiodrug paid in total (taxes including accrued interest) an amount of EUR 775k.

With this step Probiodrug brought this long-pending topic to its conclusion and could thereby prevent a further distraction of its attention and resources.

# **Annual Shareholders' Meeting 2017**

On 13 June 2017, Probiodrug held its 2017 Annual Shareholders' Meeting. All resolutions proposed by the Company's Management and Supervisory Board were approved at the meeting, including:

- Adoption of a resolution on the approval of the actions of the management board members for the financial year 2016
- Adoption of a resolution on the approval of the actions of the supervisory board members for the financial year 2016
- Appointment of the statutory financial statements auditor for the financial year 2017
- Elections to the supervisory board
- Resolution on the creation of the Authorized Capital 2017 concurrently cancelling the Authorized Capital 2014 as well as the corresponding amendments to the Articles of Association
- Resolution on the specification of the number of the Supervisory Board members as well as the corresponding amendment to the Articles of Association

#### **Supervisory Board**

Dr Erich Platzer, Dr Dinnies von der Osten and Dr Jörg Neermann were re-elected as members of the Supervisory Board, with Dr Platzer being appointed as chairman and Dr von der Osten being appointed as vice-chairman and Chairman of the Audit Committee.

#### OUTLOOK

The mid-term focus of Probiodrug's business activities can be summarised as follows:

- Continuing the clinical development of PQ912 with a focus on dose dependency and a longer treatment period,
- Exploring partnering options,
- Continuing the development of PBD-C06,
- Further scientific analysis of potential additional indications for the use of QC inhibitors,
- Further increasing visibility and acceptance as an important prerequisite for obtaining additional capital as well as for an industrial transaction.
- Further strengthening Probiodrug's financial resources.

# FINANCIAL STATEMENTS January to June 2017

Probiodrug has finalized its financial statements for the first six months 2017 according to German GAAP ("HGB") and IFRS. The auditor KPMG has reviewed the IFRS statements. The reports are available on the company website (http://www.probiodrug.de/investors/reports-and-presentations/).

#### Financial calendar 2017

30 November 2017

Interim Management Statement Q3 2017

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#### **Notes to Editors:**

#### **About Probiodrug AG**

Headquartered in Halle (Saale), Germany, Probiodrug AG (Euronext Amsterdam: PBD) is a biopharmaceutical company focused on the development of new therapeutic products for the treatment of Alzheimer's disease (AD). Probiodrug has identified a new therapeutic concept linked to disease initiation and progression. The development approaches are targeting a key neuro/synaptotoxic component of the pathology, pyroglutamate-Abeta (pGlu-Abeta, N3pG) as a therapeutic strategy.

Probiodrug's lead product candidate, PQ912, is a highly specific and potent inhibitor of Glutaminyl Cyclase (QC), which has shown therapeutic effects in AD animal models. A Phase-1 study in healthy young and elderly volunteers revealed a dose dependent exposure and showed good safety and tolerability up to the highest dose showing >90% target occupancy in the spinal fluid. In June 2017 Probiodrug announced top-line data of the Phase-2a SAPHIR trial of its lead candidate (<a href="Probiodrug announces encouraging results">Probiodrug announces encouraging results of the Phase 2a SAPHIR Study</a>). The positive effects seen on secondary exploratory efficacy markers are strongly supporting (a) the hypothesis of pGlu-Abeta being synaptotoxic and (b) the therapeutic concept pursued by Probiodrug. The study revealed a positive benefit risk ratio of PQ912 and provides important guidance how to move forward in the development of PQ912 as a disease-modifying drug for AD. Altogether, the results make the program highly attractive for further development.

Complementary to the small molecule PQ912 inhibiting the formation of the synaptotoxic agent pGlu-Abeta, the company is developing PBD-C06, an anti-pGlu-Abeta-specific monoclonal antibody. The Company has medical use and composition of matter patents related to the inhibition of QC and anti-pGlu-Abeta-specific monoclonal antibodies, and has, in the Company's view, a leading position in this field of research.

Founded in 1997 by Hans-Ulrich Demuth and Konrad Glund, the company successfully developed a novel therapeutic concept for diabetes - the DP4 inhibitors - which provided the basis for a novel class of antidiabetics - the gliptins. Its core capabilities are based on its long-standing expertise in the elucidation of the structure and function of enzymes involved in the modification of proteins and peptides, which play a central role in pathological conditions.

Today, Probiodrug aims to become a leading company in the development of AD treatments and to thereby provide a better life for Alzheimer's disease patients.

# www.probiodrug.de

#### **About Alzheimer's disease**

Alzheimer's disease is a neurological disorder, which is the most common form of dementia, and ultimately leads to death. Because Alzheimer's disease cannot be cured and is degenerative, the affected patients must increasingly rely on others for assistance. Today, 47 million people live with dementia worldwide, and this number is projected to treble to more than 131 million by 2050, as populations age. Dementia also has a huge economic impact. Alzheimer's has an estimated, global societal cost of US\$ 818 billion, and it will become a trillion dollar disease by 2018. (World Alzheimer Report 2016).

## Forward Looking Statements

Information set forth in this press release contains forward-looking statements, which involve a number of risks and uncertainties. The forward-looking statements contained herein represent the judgment of Probiodrug AG as of the date of this press release. Such forward-looking statements are neither promises nor guarantees, but are subject to a variety of risks and uncertainties, many of which are beyond our control, and which could cause actual results to differ materially from those contemplated in these forward-looking statements. We expressly disclaim any obligation or undertaking to release publicly any updates or revisions to any such statements to reflect any change in our expectations or any change in events, conditions or circumstances on which any such statement is based.