Probiodrug reports full year 2017 financial results

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* *PQ912 delivers positive pharmacodynamic and efficacy results in a Phase 2a study in early stage AD patients - data presented at CTAD, Boston, November 2017*
* *PQ912 Phase 2b core program initiated*
* *PQ912 demonstrates efficacy in a preclinical Huntington's disease model*
* *Unique binding mode of PBD-C06 to pGlu-Abeta peptides identified*
* *Successful settlement of pending tax issue*

**HALLE (SAALE), Germany, 03 April 2018** Probiodrug AG (Euronext Amsterdam: PBD), a clinical stage biopharmaceutical company developing novel therapeutic solutions to treat Alzheimer's disease (AD), today announced its financial results for the twelve-month period ending 31 December 2017 prepared in accordance with German GAAP ("HGB") and, on a voluntary basis, in accordance with IFRS as endorsed by the European Union. The Financial Statements 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
* Phase 2a SAPHIR study results presented in November 2017 at Clinical Trials on Alzheimer's Disease (CTAD), Boston, USA
* Initiation of PQ912 Phase 2b core program - trial design based on new FDA draft guidelines and the new guideline version of the EMA for early AD
* PQ912 demonstrates efficacy in preclinical Huntington's disease model
* Publication of new results of PQ912 pharmacology in peer reviewed journal
* Positive results with PQ912 and PBD-C06 alone and in combination in AD animal models presented
* Unique binding mode of Probiodrug's anti-pGlu-Abeta antibody PBD-C06 published in a peer reviewed journal
* Successful settlement of pending tax liability
* Annual Shareholders' Meeting held on 13 June 2017
* Expenditures and corresponding cash position in line with management expectations
* Cash and cash equivalents of EUR 10.3 million as of 31 December 2017, providing according to present projections a cash reach through 2018

**POST PERIOD HIGHLIGHTS**
Probiodrug made a presentation entitled *"Inhibition of glutaminyl cyclase as a new concept for the treatment of Alzheimer's disease: PQ912, the first-in-class QC-inhibitor in clinical development for AD"* at the **255th National Meeting & Exposition of the American Chemical Society (ACS), New Orleans, USA**in March 2018.

**CONFERENCE CALL**
Probiodrug will host a conference call open to the public today, 03 April 2018, at 15:00 Central European Summer Time (CEST) / 09:00 Eastern Daylight Times (EDT); the presentation will also be available on the company website. The conference will be held in English. A Question & Answer session will follow the presentation of results.

To participate in the conference call, please call one of the following numbers 10 minutes prior to commencement.

Please dial one of the following access numbers, then enter the PIN Code: **09533722#**

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**Commenting on the 2017 results, Dr Konrad Glund, Chief Executive Officer of Probiodrug, said:**
"2017 has been a milestone year for Probiodrug. The positive results of the PQ912 Phase 2a SAPHIR trial have ensured a big leap forward in adding further validation and value to the program. The strong efficacy signals obtained after only three months of treatment support our concept of pGlu-Abeta being central for the synaptic impairment and over-inflammatory status within the continuum of the pathological process of AD.

"We are now in planning/ set-up phase for a robust proof of concept Phase 2b program for PQ912 consisting of an EU and an US trial. The studies are designed in accordance with the newest regulatory guidelines, also with a view on the optionality of a conditional approval with convincing positive Phase 2b data, and state of the art scientific concepts. We are convinced that our stepwise rational development strategy with clear objectives and hard state of the art cognition and functional endpoints increases likelihood of success. We believe the Phase 2a data and the next steps create interest and will convince third parties to support the development of PQ912. The implementation of the basis and securing the resources for the execution of the programs are a key strategic goal for 2018."

**KEY FIGURES (ACCORDING TO IFRS)**

|  |  |  |
| --- | --- | --- |
| in EUR k, unless otherwise stated | **2017** | **2016** |
| **Earnings, Financial and Net Assets Position** |   |   |
| Operating loss | -9,961 | -13,777 |
| Finance income/loss | 850 | -114 |
| Income tax gain | 1,102 | 0 |
| Net loss for the period | -8,009 | -13,891 |
| Equity (end of the year) | 8,923 | 16,376 |
| Equity ratio (end of the year) (in %) | 82.9 % | 73.2 % |
| Balance sheet total (end of the year) | 10,762 | 22,366 |
| Cash flows used in operating activities (year) | -12,117 | -13,255 |
| Cash flows used in operating activities (monthly average) | -1,010 | -1,105 |
| Cash flows used in investing activities (year) | 459 | -124 |
| Cash flows provided by financing activities (net) | 127 | 13,915 |
| Cash and cash equivalents at the end of period | 10,291 | 21,897 |
|   |   |   |
| **Personnel** |   |   |
| Total number of employees (incl. Board of management) (end of the year) | 14 | 13 |
| Average number of employees  (incl. Board of management) | 13.3 | 14.5 |
|   |   |   |
| **Probiodrug-Share** |   |   |
| Loss per share (basic and diluted) (in EUR) | -0.98 | -1.82 |
| Number of shares issued (end of the year) | 8,208 | 8,187 |

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

*Net loss*
The net loss amounts to EUR 8,009k (2016: EUR 13,891k), thereof EUR 9,961k (2016: EUR 13,777k) operating loss, which is partly offset by EUR 850k (2016: EUR -114k) financial income and EUR 1,102k (2016: EUR 0k) income from tax gain. The majority of the operating loss is due to the research and development expenses amounting to EUR 7,454k (2016: EUR 10,951k), whereas the general and administrative expenses of EUR 2,511k (2016: EUR 2,909k) represent the smaller fraction thereof. The financial income amounting to EUR 850k and the income taxes gain amounting to EUR 1,102k result from the successful settlement of the potential tax liability from the financial year 2004. All expenditures are in line with the projections of Probiodrug.

*Equity*
The equity amounts to EUR 8,923k (2016: EUR 16,376k), leading to an equity ratio of 82.9%. In 2017, the share capital increased by 21,274 shares from the conditional capital 2010 via the exercise of outstanding stock options. By this the share capital increased from EUR 8,186,735 to EUR 8,208,009.

*Cash*
The cash flow used in investing activities shows proceeds from the expiration of a pension liabilities insurance in the amount of EUR 467k (2016: EUR 0k) and costs in intangible assets and equipment in the amount of EUR 8k (2016: EUR 124k). Cash and cash equivalents at year end 2017 were EUR 10,291k (2016: EUR 21,897k).

*Noncurrent/ current liabilities*
The noncurrent liabilities with EUR 1,171k (2016: EUR 850k) represent the net commitment (defined benefit liability) of the pension commitments (defined benefit obligations) of EUR 1,619k (2016: EUR 1,644k). The current liabilities decreased significantly and amounted to EUR 668k (2016: EUR 5,140k) as at 31 December 2017. The decrease in the current liabilities is mainly driven by the successful settlement of the potential tax liability and the decrease of the trade payables. According to the settlement, Probiodrug paid in total (taxes including accrued interest) an amount of EUR 775k and released the remaining provision of EUR 1,964k. The trade payables amounting to EUR 344k (2016: EUR 1,893k) result from of the ordinary course of business. They have a remaining term of up to one year.

**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 formation 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**
***Phase I***
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.

***Phase 2a***
PQ912 is the first QC-inhibitor being tested in patients. In January 2017 Probiodrug announced the completion of the recruitment for the SAPHIR Phase 2a study of PQ912 in early Alzheimer's disease patients. The randomized, double-blind multi-center study enrolled 120 patients with early stage Alzheimer's disease, surpassing the 110 patients planned in the study protocol. 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, NL being the lead center. In April 2017 Probiodrug announced the Last Patient Last Visit (LPLV) reached in the SAPHIR Study.

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.

In June 2017 Probiodrug communicated positive pharmacodynamic and efficacy results of PQ912 in the Phase 2a SAPHIR Study. The SAPHIR study was the first clinical trial to investigate PQ912 in patients with early AD over a treatment period of 12 weeks. The highest dose of 800mg bid PQ912 used in the Phase 1 multiple dose study was applied and 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. Regarding safety overall no major safety concern associated with PQ912 was raised. There were no significant differences in the number of AE or SAE between active and control arm. A significantly higher number of patients discontinuing within first weeks of treatment with PQ912 compared to placebo was observed; there were clinically relevant differences in the number of patients with skin and GI effects. These events appeared early in the study and were fully reversible. Safety and tolerability are likely to be improved by lower dose, still showing a high enzyme inhibition, and a slower titration regime. In summary 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.

In October 2017 Probiodrug announced the initiation of the Phase 2b core program for PQ912 and detailed the strategy. The Phase 2b core program is planned to comprise of two complementary clinical Proof of Concept studies in Europe and the USA. The development strategy has built in the newest FDA and EMA draft guidance for early AD trials as published in February 2018.

The Phase 2b core program will consist of two clinical trials, to be executed in the European Union (EU) and the USA, respectively. The first Phase 2b study is intended to investigate the safety and efficacy of the optimal dose range of PQ912 in early AD patients. This trial will build on the excellent and efficient infrastructure which was established for the Phase 2a SAPHIR study. Moreover, it is based on the valuable results of the SAPHIR study and has been designed with the guidance of international KOLs in the Alzheimer's field. Prof Philip Scheltens, MD PhD, Director of the Alzheimer Center VU University Medical Center Amsterdam, NL will once again serves as Principal Investigator and Chairperson for this study, which is to be conducted in the EU. A second complementary study is currently in the planning phase and is intended to be carried out in the USA and will also be chaired by a highly renowned Principal Investigator.

***Combination therapies***
Probiodrug is also working on potential combination therapies. Here, 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 March 2017.

***Huntington's disease***
Probiodrug is exploring potential second indications for its QC inhibitors. PQ912 demonstrated beneficial effects in a preclinical Huntington's disease (HD) model; the data of this study have been presented at the 12th Annual HD Therapeutics Conference of the CHDI Foundation, Malta, in April 2017. 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 changes, metabolic and neuropathological signs of the disease become visible. 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, the energy metabolism as well as 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. PBDC06 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 PBDC06.

PBD-C06 revealed a unique binding mode, published in August 2017 in the Journal of Biological Chemistry (*Piechotta et al.,  J. Biol. Chem. 2017 292:12713*).

**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.

**Publications**

***13th International Conference on Alzheimer's and Parkinson's Diseases (AD/PDTM 2017), Vienna, Austria:*** In March 2017 Probiodrug presented an oral presentation entitled: *"Selective targeting of pGlu-Abeta with an IgG2a in tg mice is effective in lowering plaque pathology and improving cognition, a combination of a QC-inhibitor and a pGlu-Abeta specific antibody showed superior efficacy*". The data resulted from a collaboration between Probiodrug and Harvard, BWH, Boston, USA. Additionally, two posters were presented:

* *"In CSF from AD patients high correlation of QC activity with AD related biomarkers and inflammatory molecules were found"* in cooperation with the VUmed Center Amsterdam, The Netherlands and
* *"Based on PKPD analysis in animal studies, a 50% inhibition of QC activity in the brain leads to a robust effect - an important translational guidance for therapeutic dosing in clinical studies"* in cooperation with Fraunhofer Institute, Halle (Saale), Germany.

***Journal of Pharmacology and Experimental Therapeutics:***In May 2017 Probiodrug announced the publication of a PQ912 pharmacology paper entitled *"Glutaminyl Cyclase Inhibitor PQ912 improves cognition in mouse models of Alzheimer's disease - studies on relation to effective target occupancy"*in a peer-reviewed journal (T. Hofmann et al. Journal of Pharmacology and Experimental Therapeutics April 26, 2017, jpet.117.240614; DOI: <https://doi.org/10.1124/jpet.117.240614>))..

***Journal of Biological Chemistry:*** In August 2017 the unique binding mode of PBD-C06 to pGlu-Abeta peptides was published ("*Structural and functional analyses of pyroglutamate-amyloid-ß-specific antibodies as a basis for Alzheimer immunotherapy*"; Piechotta et al. J. Biol. Chem. 2017 292:12713). In these studies, the binding characteristics of a murine version of Probiodrug's lead therapeutic antibody (PBD-C06) against its designated target pGlu-Abeta was analyzed at the molecular level applying co-crystallization and X-ray structure analysis. The studies revealed a unique binding mode of PBD-C06 to pGlu-Abeta peptides, which are believed to catalyze the seeding of synapto/neurotoxic Abeta oligomers, a key culprit in the pathology of AD. Furthermore, the data provide a rationale for the high target specificity of PBD-C06 and suggest low binding to off-targets, such as unmodified, less toxic Abeta peptides.

***CTAD 2017, Boston, USA:*** In November 2017 Prof Philip Scheltens, MD, PhD, Principal Investigator of the SAPHIR study, presented the data from this trial during the Late Breaking Oral Communications session at the CTAD 2017. The presentation was entitled *"Phase 2a study results with the glutaminylcyclase inhibitor PQ912 in early Alzheimer's Disease".*

**Partnerships**
In December 2017 Probiodrug and dutch company Crossbeta Biosciences B.V. extended their strategic partnership in the field of Alzheimer's disease biomarkers in order to utilize Crossbeta's proprietary technology to support of Probiodrug's biomarker development activities.

**CORPORATE REVIEW**

**General Meeting of Shareholders of Probiodrug AG on 13 June 2017**
All resolutions proposed by the Company's Management and Supervisory Board were approved at the meeting with a large majority:

* 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
* Election of the 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**
The general shareholder meeting on 13 June 2017 re-elected Dr Erich Platzer, Dr Dinnies von der Osten and Dr Jörg Neermann. The Supervisory Board then re-elected Dr Erich Platzer as chairman and Dr Dinnies von der Osten as vice chairman.

Mr Kees Been resigned from his board position in November 2017 for personal reasons.

**POST PERIOD HIGHLIGHTS**
**255th National Meeting & Exposition of the American Chemical Society (ACS), New Orleans, USA:** Dr Ulrich Heiser, Director Medicinal Chemistry/CMC gave a presentation entitled *"Inhibition of glutaminyl cyclase as a new concept for the treatment of Alzheimer's disease: PQ912, the first-in-class QC-inhibitor in clinical development for AD"* in March 2018.

**OUTLOOK**

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

* Execution of the Phase 2b clinical study program for PQ912
* Continuing the development of PBD-C06
* Conclusion of one or more industrial partnerships
* Further scientific analysis of potential second indications for the use of QC-inhibitors
* Further strengthening Probiodrug's financial resources.

Probiodrug projects a net loss for the financial year 2018 which, based on the current budget, is expected to be lower than that of 2017.

**ANNUAL FINANCIAL REPORT 2017**

Probiodrug has finalized its financial statements for the year ended 31 December 2017 according to German GAAP ("HGB") and IFRS. The auditor KPMG has issued an unqualified auditors report for both statements. The reports are available on the company website (<http://www.probiodrug.de/investors/reports-and-presentations/>).

**FINANCIAL CALENDAR**

|  |  |
| --- | --- |
| 15 May 2018 | Interim Management Statement Q1 2018 |
| 21 June 2018 | Annual General Meeting 2018 |
| 30 August 2018 | Interim Report, Half Year Results 2018 |
| 29 November 2018 | Interim Management Statement Q3 2018 |

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**Notes to Editors:**
**About Probiodrug AG**
Headquartered in Halle (Saale), Germany, Probiodrug AG (Euronext Amsterdam: PBD) is a clinical stage 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) as a therapeutic strategy. Its lead product, PQ912, has successfully completed a Phase 2a (SAPHIR) study. The company's pipeline also includes PBD-C06, an anti-pGlu-Abeta-specific monoclonal antibody, in preclinical development. Probiodrug 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.

**About PQ912**
PQ912, is a first in class, highly specific and potent inhibitor of Glutaminyl Cyclase (QC), the enzyme catalyzing the formation of synaptotoxic pGlu-Abeta. PQ912 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  with >90% target occupancy in the spinal fluid. In June 2017, Probiodrug announced top-line data of the Phase-2a SAPHIR trial of PQ912 and presented the study results at CTAD 2017. Results strongly support (a) the hypothesis of pGlu-Abeta being synaptotoxic and (b) the therapeutic concept pursued by Probiodrug. The study 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; the company has initiated the preparation of a Phase 2b core program.

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. 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](http://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. Today, 47 million people live with dementia worldwide, and this number is projected to treble to more than 131 million by 2050, as the global population ages. 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.*