# First Quarter 2018 Business Update

**HALLE (SAALE), Germany, 15 May 2018** – Probiodrug AG (Euronext Amsterdam: PBD), a clinical stage biopharmaceutical company developing novel therapeutic solutions to treat Alzheimer's disease (AD), today announces its first quarter business update for the period ending 31 March 2018, in the form of an interim management report.

## OPERATIONAL HIGHLIGHTS

- Presentation of inhibition of Glutaminyl Cyclase as a new treatment concept for Alzheimer's Disease at the 255th ACS National Meeting & Exposition in New Orleans, USA
- Expenditures and corresponding liquidity position (31 March 2018, EUR 9.3 million) in line with management expectations
- On 3 April 2018 (post period end) detailed study design of PQ912 Phase 2b core program outlined during full year 2017 financial results presentation
- On 23 April 2018 (post period end) Probiodrug announced the appointment of Dr Ulrich Dauer as Chief Executive Officer effective 1 May 2018; Dr Konrad Glund and Dr Hendrik Liebers left the executive team effective 30 April 2018 and continue to support in advisory roles

**Commenting on the results, Dr Ulrich Dauer, Chief Executive Officer of Probiodrug, said:**
"This is an exciting time ahead for Probiodrug. We are very pleased by the promising results of our Phase 2a SAPHIR trial and focused on taking our lead drug candidate PQ912, towards Phase 2b, i.e. clinical proof of concept.

"We are also encouraged by the newest FDA and EMA draft guidance for early AD trials as published in February 2018. The development strategy of the Phase 2b core program has built in this draft guidance for which our European study is in the setup phase, and the US study is in an advanced stage of planning. We firmly believe that our novel therapeutic approach to a disease modifying treatment for AD bears the potential to make a true difference for patients suffering from this devastating disease."

## 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.


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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**

***Encouraging Phase 2a data***

In June 2017 Probiodrug communicated positive pharmacodynamic and efficacy results of PQ912 in the Phase 2a SAPHIR Study. 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.

The SAPHIR study was the first clinical trial to investigate PQ912 in patients with early AD over a treatment period of 12 weeks. 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 highest dose of 800mg bid PQ912 used in the Phase 1 multiple dose study was applied and showed a high level of 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 subjects with 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.

***Detailed design of Phase 2b core program presented (post period)***

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. In April 2018 Probiodrug presented the detailed study design of the Phase 2b core program**.**

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


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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 serve 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/PD™ 2017), Vienna, Austria.

***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. 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.

PBD-C06 revealed a unique binding mode, published 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.

**Operational Update**

Probiodrug 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***


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***AD"*** at the 255th National Meeting & Exposition of the American Chemical Society (ACS), New Orleans, USA in March 2018.

The presentation highlighted Probiodrug's first-in-class small molecule QC-Inhibitor PQ912, selected for development due to a good drug-like profile and a comprehensive preclinical proof of concept data package showed an excellent dose-dependent brain penetration and target engagement in man and an attractive therapeutic window. The first 3-month trial in early AD patients provided a set of positive pharmacodynamic and efficacy results which all support the underlying concept of QC-Inhibition reducing the seeding of highly synaptotoxic oligomers and providing guidance for the outline of the next Phase 2b study (see Pipeline Update above).

## CORPORATE REVIEW

### Financials

The first quarter of 2018 was characterized by EUR 1,026k research and development expenses, significantly lower than in the first quarter of 2017 (EUR 2,268k). The higher costs in the first quarter 2017 resulted from the Phase 2a study (SAPHIR) of PQ912, which was completed in the second quarter 2017. General and administrative expenses amounted to EUR 513k and were at the same level as in the first quarter of 2017 (EUR 507k). In the first quarter 2018 the Company has not generated any revenues, also in line with the corporate planning. Correspondingly, the comprehensive loss of the reporting period was EUR 1,511k, compared to EUR 2,798k in the first quarter of 2017.

All results are in line with management expectations.

Probiodrug held EUR 9.3 million in cash and cash equivalents as of 31 March 2018.

## POST PERIOD UPDATE

### Probiodrug Appoints Dr Ulrich Dauer as Chief Executive Officer

On 23 April 2018, Probiodrug announced the appointment of Dr Ulrich Dauer to the position of Chief Executive Officer effective 1 May 2018. He teams up with long-serving Chief Development Officer Dr Inge Lues who has borne key responsibility for development of Probiodrug's pipeline. Dr Konrad Glund, CEO and co-founder of the company, retired effective 30 April 2018. CFO Dr Hendrik Liebers, by mutual agreement, resigned from the Management Board effective 30 April 2018. Dr Glund and Dr Liebers continue to support Probiodrug in advisory roles.

### Detailed study design of Phase 2b core program of PQ912 presented on 3 April 2018, during full year 2017 financial results

The overarching Phase 2b development program will comprise two trials, one in Europe and one in the USA. The trials will be complementary having a set of key elements of the design in common (such as patient population, inclusion criteria etc.) but will include several differences such as treatment duration, additional endpoints and difference in futility/interim analyses.


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The clinical efficacy endpoints will be sensitive measures of cognition and of activities of daily living. Both studies will include dose titration and/or several doses for efficacy and safety and are suitable to provide Proof of Concept. The trials are designed according to the latest regulatory guidelines by the FDA (draft) and the European EMA (both February 2018). Probiodrug is pursuing a step-wise clinical development approach with a current focus on clinical Proof of Concept, which contrasts with a frequently used strategy for other programs, jumping from Phase 1b/ to Phase 3 based only on biomarkers effects - to increase time to market but accepting a risk of late stage failure.

The European study is in the setup phase whereas the US study is in advanced planning status.

The key design of the Phase 2b core EU study SAPHIR 2 is built on the outcome of the Phase 2a SAPHIR 1 study. Objectives are safety and efficacy evaluated in two stages: stage one (3 months) will focus on safety followed by stage 2 with efficacy as primary endpoint for a total treatment duration of at least 9 months.

- The target population are patients with early AD as in SAPHIR 1; eligibility is defined by Abeta/p-Tau biomarker cut-offs.
- The Neuro-Psychological Test Battery (NTB) to be used is identical to the one applied in the Phase 2a study. The sample size of 250 patients to be randomized into the study was calculated based on an extrapolated effect size for those tests of the NTB, which were positively affected by PQ912 in the Saphir trial. The progression of the extrapolated placebo group from SAPHIR 1 was very much in line with the slope of control groups from 4 different historical data sets provided by Cogstate obtained from more than 300 patients.
- The secondary endpoints will be the full NTB and the Amsterdam Instrumental Activity of Daily Living Questionnaire, the EEG and the synaptic marker neurogranin as well as the inflammatory marker YLK-40, which were both reduced by PQ912 in the SAPHIR 1 study.
- The investigator trial network and the CRO core team will be identical to the Phase 2a study, additional countries and sites will be added.

In summary, the innovative design of the EU study has a long enough treatment duration to enable predictive cognitive read-outs and to inform about an optimal dose.

**Invitation to Probiodrug's Ordinary General Meeting of Shareholders on 21 June 2018**
On 09 May 2018 Probiodrug invited its shareholders to its ordinary general meeting of shareholders to be held on Tuesday, 21 June 2018 at 11:00 am (CEST), at the das Leonardo Royal Hotel Berlin Alexanderplatz, Otto-Braun-Straße 90, 10249 Berlin, Germany. The relevant documents can be found at http://www.probiodrug.de/investors/annual-shareholders-meeting-2018/.

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**Halle (Saale), 15 May 2018**
**Management Probiodrug**


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