Probiodrug AG Announces Acceptance of PQ912 Pharmacology Paper by Peer Reviewed Journal

HALLE (SAALE), Germany, 16 May 2017 - Probiodrug AG (Euronext Amsterdam: PBD), a biopharmaceutical company developing novel therapeutic solutions to treat Alzheimer's disease (AD), today announces that a paper concerning the pharmacological profile of its lead product candidate, the QC inhibitor PQ912, has been accepted by the peer-reviewed Journal of Pharmacology and Experimental Therapeutics. The paper is entitled:

'Glutaminyl Cyclase Inhibitor PQ912 improves cognition in mouse models of Alzheimer's disease - studies on relation to effective target occupancy'

Authored by 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

Inge Lues, Chief Development Officer at Probiodrug commented: These animal data are an important component of target validation and translation into the clinic. Together with the pharmacokinetic/pharmacodynamic data obtained in the MAD Phase 1 study with PQ912 they have been very important in guiding our decision for dose selection in the Phase 2 SAPHIR study. Due to the good safety and tolerability profile of PQ912 demonstrated in Phase 1 we selected a dose which would result, on average, in a target occupancy of about 90%. SAPHIR Phase 2 results are expected to be available in Q2 this year.

Context: The majority of Abeta peptides deposited in Alzheimer's Disease (AD) are truncated and post-translationally modified at the N-terminus. Among these, pyroglutamyl-Abeta (pE-Abeta or N3pE-Abeta) has been identified as particularly neurotoxic. N-terminal pE modification increases the peptide's hydrophobicity, reduces susceptibility to degradation by peptidases and strongly accelerates formation of neurotoxic amyloid beta oligomers, which have been shown to impair synaptic integrity and brain connectivity, physiological substrates for cognitive functions. It has been shown that the formation of pE-Abeta is strictly dependent on glutaminyl cyclase activity (QC). Thus, inhibiting QC activity is an attractive option to treat AD pursued by Probiodrug.

Results and conclusions:

- In this paper, we present data about the pharmacological *in vitro* and *in vivo* efficacy of the QC-inhibitor PQ912, the first-in-class compound that is in clinical development.
- PQ912 QC-activity of various species with K_i-values in the range between 20 and 65 nM.
- Chronic oral treatment of $hAPP_{SL}$xhQC double transgenic mice applying PQ912 via chow *(200 mg/kg/day)* demonstrates a significant reduction of brain-pE-Abeta levels and concomitant improvement of spatial learning in a Morris water maze test paradigm.
- The dose used resulted in a brain and CSF (cerebrospinal fluid) concentration of PQ912 which relates to a QC target occupancy of on average about 60 %.

Thus, we conclude that > 50 % inhibition of QC activity in the brain leads to robust treatment effects. Secondary pharmacology experiments in mice indicate a fairly large potency difference for glutamate cyclisation of Abeta compared to glutamine cyclisation of physiological substrates, suggesting a robust therapeutic window in humans. These results constituted an important translational guidance for predicting the therapeutic dose range in clinical studies with PQ912.

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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.

Founded in 1997, 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's aim is to become a leading company in the development of Alzheimer's disease treatments and to thereby provide a better life for Alzheimer's disease patients. It has identified a new therapeutic concept linked to disease initiation and progression. The development approaches are targeting pyroglutamate-Abeta (pGlu-Abeta) as a therapeutic strategy to fight Alzheimer's disease. The Company has medical use and composition of matter patents related to the inhibition of Glutaminyl Cyclase (QC) and anti-pGlu-Abeta- specific monoclonal antibodies, providing it, in the Company's view, with a leading position in this field of research.

Probiodrug's lead product candidate, PQ912, is a highly specific and potent inhibitor of Glutaminyl Cyclase (QC), which has shown therapeutic effects in Alzheimer's animal models. PQ912 is currently in a Phase 2a study, the SAPHIR trial. In a preceding Phase 1 study with healthy young and elderly volunteers, PQ912 has shown to be safe and well tolerated and also revealed high QC-inhibition.

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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.