probiodrug

The 2016 financial year
Full year results

Halle (Saale), 30 March 2017

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Content

1. **Corporate introduction**
2. Results 2016
3. Outlook
4. Q & A

Longstanding track-record and renowned investor base

Brief history

- 1997: Foundation, pioneered a new class of anti-diabetics (gliptins) – partnerships with Merck & Co, Ferring and Novartis
- 2004: Sold diabetes franchise to OSI Pharmaceuticals – proceeds partially returned to shareholders and partially invested in AD
- 2007 - 2014: Series A and B financings rounds totalling appr. € 80m with top tier investors
- 2011: Progressed PQ912 in Phase 1 clinical development – first in class in clinical development
- Oct 27 2014: IPO at Euronext/ Amsterdam, raise of € 23.2m
- 2015: Initiation Phase 2 clinical development of PQ912
- Nov 2015: Private Placement of € 13.5m with top tier funds
- Oct 2016: Placement of € 14.9m with top tier funds via accelerated bookbuild offering

Major investors (> 3%)

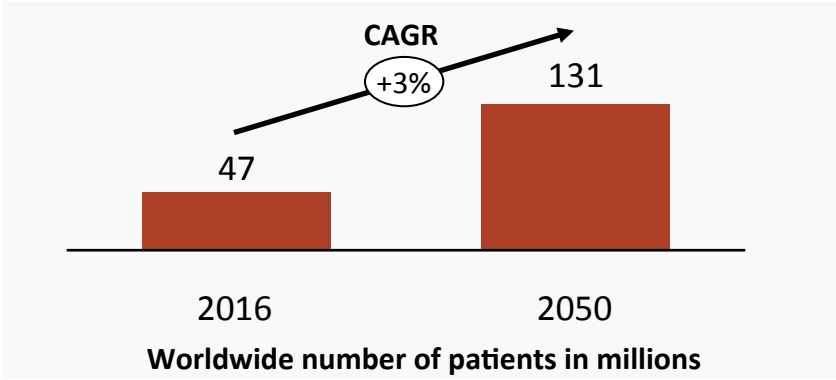
BB BIOTECH
AVIVA INVESTORS
IBG
EDMOND DE ROTHSCHILD INVESTMENT PARTNERS
TVM | Capital
HBM Healthcare Investments
LSP Life Sciences Partners
Biogen
J.P.Morgan

Alzheimer's Disease: growing burden, no cure

Alzheimer's Disease introduction

- Leading cause of dementia, ultimately leading to death
- Large burden on families
- Growing cost for society
- Available treatments marginally effective and focus on symptoms only
- Current symptomatic treatments generate ~$4bn p.a.**
- No disease modifying beneficial treatments available
- No new drugs approved since 2007***

Worldwide dementia population will triple in the next 30 years*



* WHO Alzheimer Report 2016 ** Datamonitor 2014 *** FDA Source picture: Alzheimers.org

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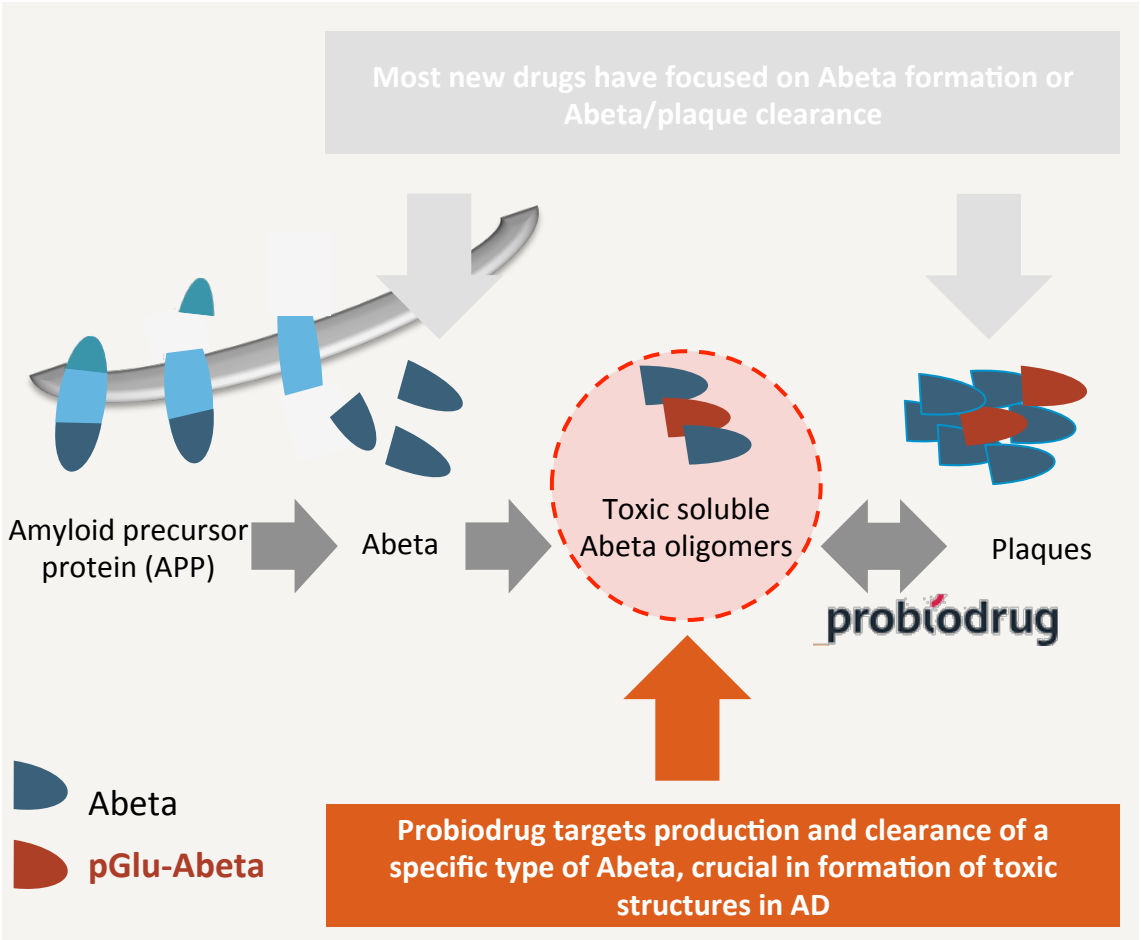
Probiodrug's **differentiated** approach

Probiodrug targets toxic structures in Alzheimer's Disease



Considerations*

- Probiodrug and others have progressed insights on Abeta and its role in AD
- Abeta has a physiological function
- Plaques are not the primary toxic culprit
- In fact, an oligomer structure is most toxic and relevant from a clinical perspective
- Probiodrug targets a specific type of Abeta, **pGlu-Abeta**, which is crucial in the formation of these toxic oligomers

* Company analysis, Mullard A Nat Rev Drug Discov 2012

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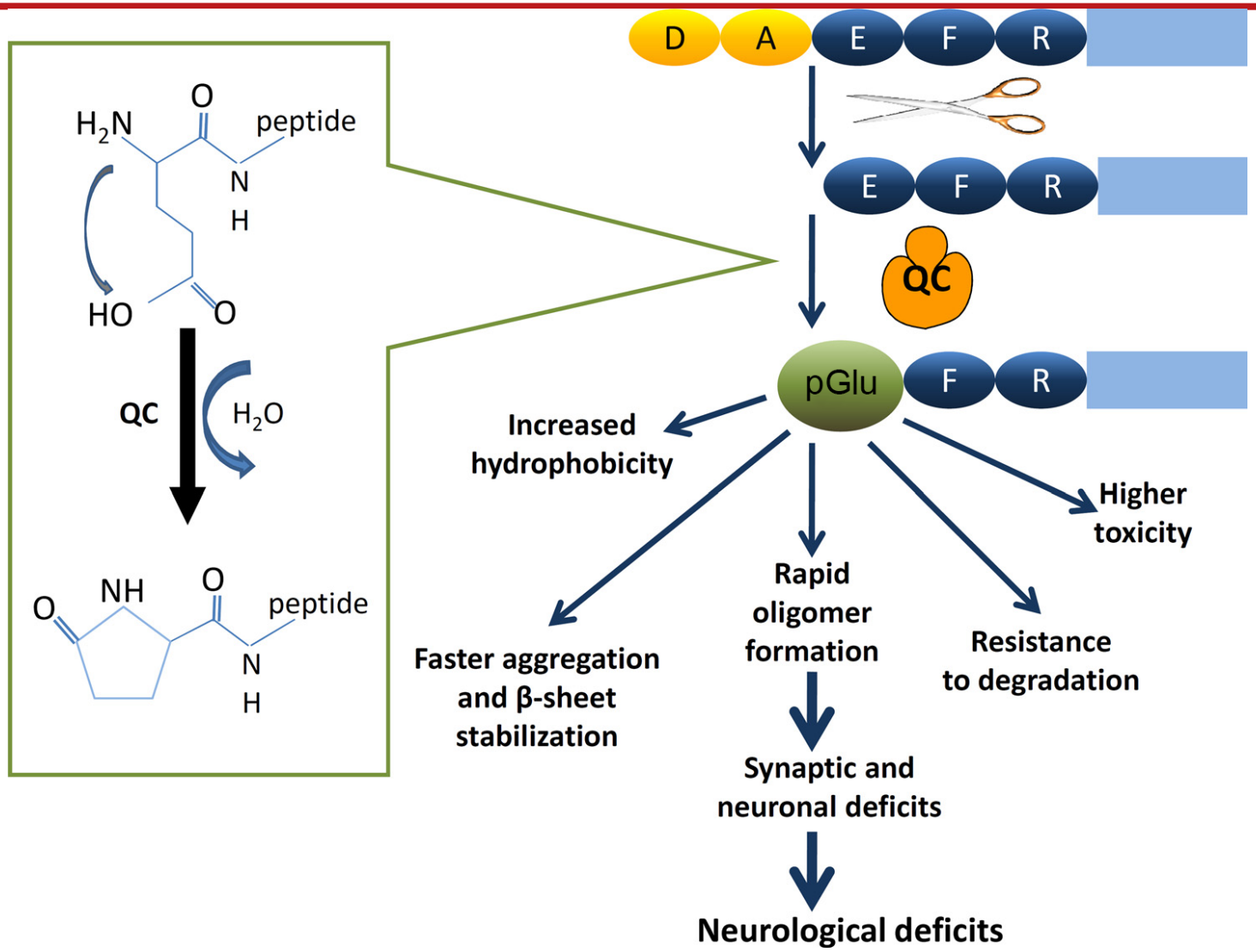
pGlu-Abeta - N-modified Abeta



Jawhar, S., Wirths, O., Bayer, T.A. JBC 286, 45, 2011

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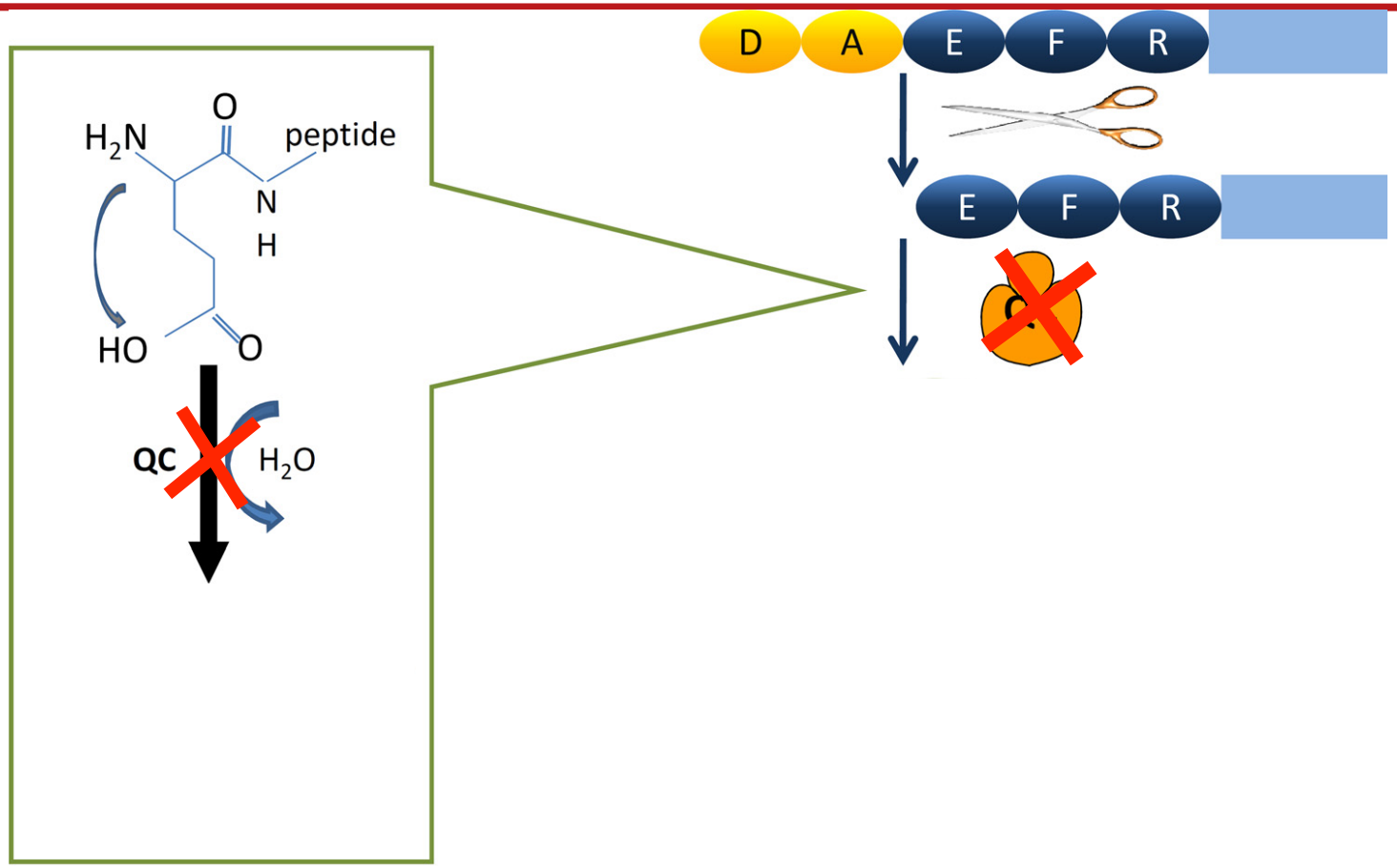
Target pGlu-Abeta: small molecule approach (QC inhibitor)



Probiodrug was first to discover the role of QC and has full ownership of broad target IP

Jawhar, S., Wirths, O., Bayer, T.A. JBC 286, 45, 2011; modified

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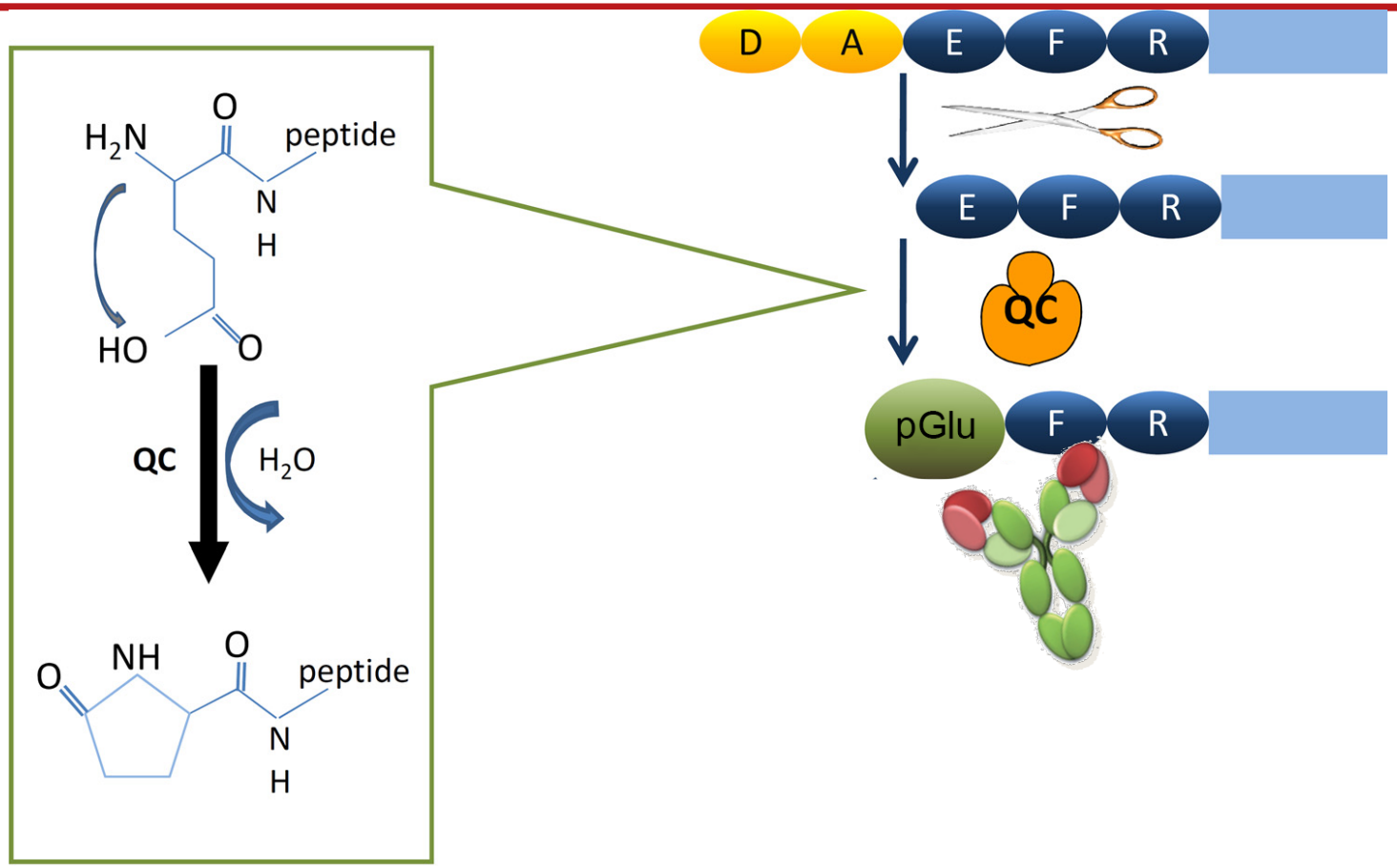
Target pGlu-Abeta: antibody approach



Probiodrug's complementary approach with a pGlu-Abeta specific antibody

Jawhar, S., Wirths, O., Bayer, T.A. JBC 286, 45, 2011; modified

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Emerging landscape of disease modifyers in AD

Immunotherapy

Passive

- **Aducanumab (BIIB037): Phase 3**
  - early AD
- **Crenezumab: Phase 3**
  - mild to moderate AD
- **Gantenerumab: Phase 3**
  - mild AD
- **BAN2401/E2609: Phase 2**
  - mild to moderate AD

Active

- **CAD106: Phase 2/3**
  - mild to moderate AD
- **Vanutide cridificar (ACC-001): Phase 2**
  - mild to moderate AD
- **ACI-24: Phase 1/2a**
  - mild to moderate AD

Modulating Abeta production

- **Verubecestat (MK-8931): Phase 3**
  - Beta secretase inhibitor, prodromal AD
- **AZD3293: Phase 2/3**
  - Beta secretase inhibitor, mild AD
- **E2609: Phase 2**
  - Beta secretase inhibitor, prodromal or mild to moderate AD
- **JNJ54861911: Phase 2a**
  - Beta secretase inhibitor, prodromal AD
- **CNP520, Phase 1/2a**
  - Beta secretase inhibitor, prodromal AD
- **CHF-5074: Phase 2**
  - Gamma secretase inhibitor, mild AD
- **NIC5-15: Phase 2**
  - Gamma secretase inhibitor, mild to moderate AD

Modulating pGlu-Abeta levels

- **PQ912: Phase 2**
  - small molecule QC inhibitor, mild AD
- **LY3002813: Phase 1b**
  - pGlu-Abeta mAB, mild AD
- **PBD-C06: preclinical**
  - pGlu-Abeta mAB

Tau

- **ABBV-8E12: Phase 2, anti-tau-AB**
  - early AD, progressive supranuclear palsy (PSP)
- **ACI-35: Phase 1, p-tau vaccine**
  - mild to moderate AD

* Selection - Source: Company announcements, clinicaltrials.gov

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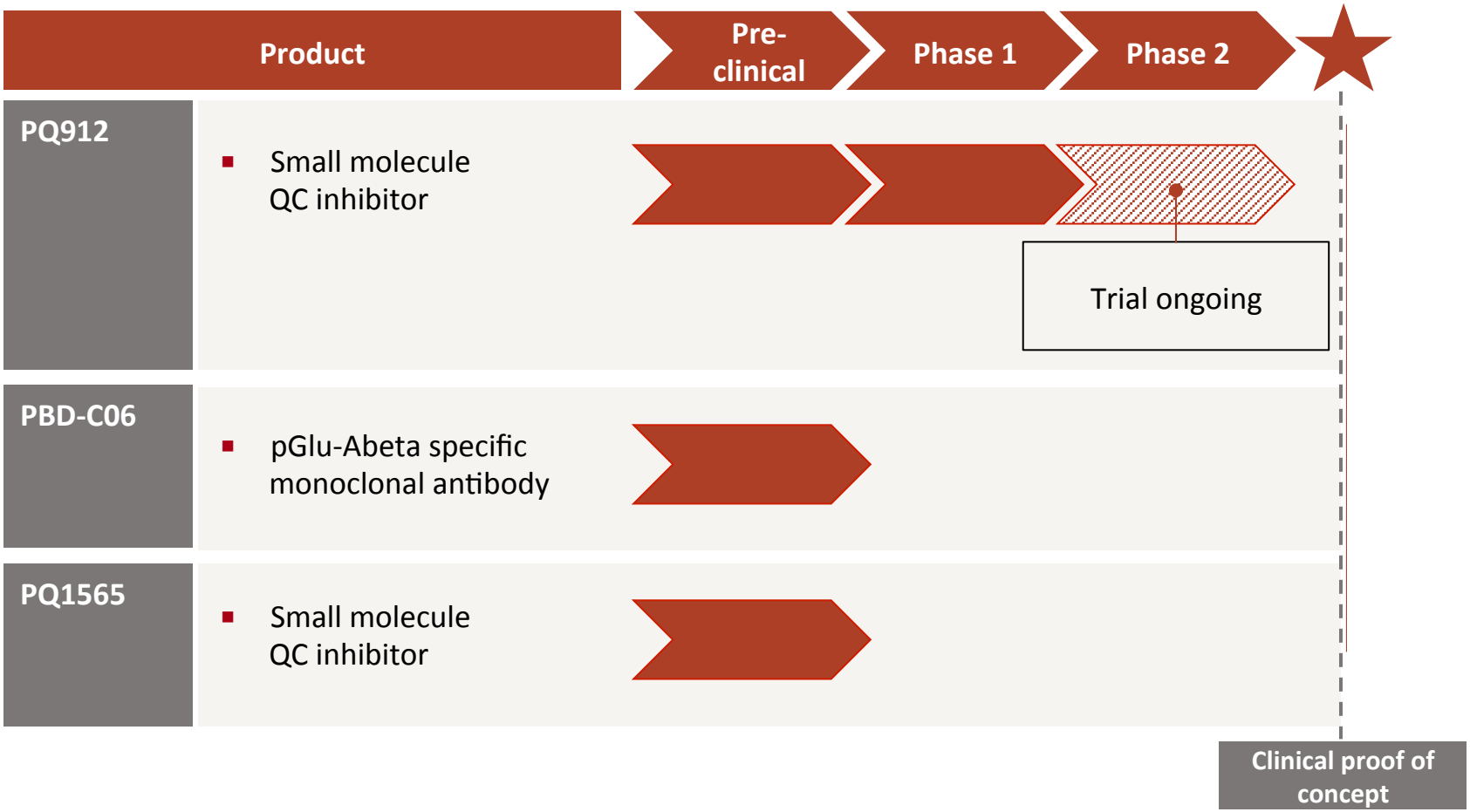
Focused proprietary pipeline

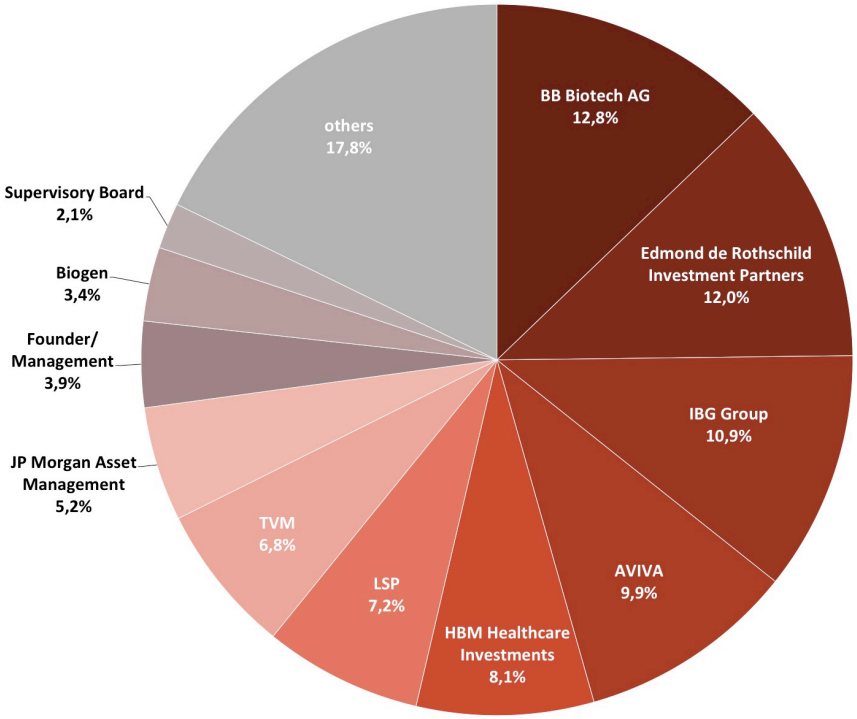


The Probiodrug Share

KEY INFORMATION

- ISIN: DE0007921835
- WKN: 792183
- Ticker Symbol: PBD
- Type of shares: Bearer shares
- Number of shares: 8,186,735
- Stock exchange: Euronext Amsterdam
- Liquidity Provider: Kempen & Co.
- Listing Agent: Kempen & Co.
- First trading day: 27 October 2014

SHAREHOLDER (> 3%)*



* Calculated on the basis of the notifications received from the shareholder so far

Content

1. Corporate introduction
2. **Results 2016**
3. Outlook
4. Q & A

Highlights 2016

2016

- Favourable results of chronic toxicology studies with Glutaminyl Cyclase (QC) inhibitor PQ912 announced
- Encouraging combination data of PQ912 with pGlu-Abeta specific antibody PBD-C06 generated
- Innovative Phase 2 study design of PQ912 in early Alzheimer's disease presented
- SAPHIR Phase 2 study of PQ912 fully enrolled in December 2016
- Promising new findings for Probiodrug's Glutaminyl Cyclase – inhibitor in an inflammation animal model announced
- Abeta aggregate-clearing by PBD-C06 with and without complement mutation in an Alzheimer's mouse model announced
- Key patents on Glutaminyl Cyclase (QC) inhibition, PQ912 and the pGlu-Abeta targeting monoclonal antibody program for the treatment of Alzheimer's disease granted

Highlights 2016 – cont.

2016

- Capital raise of EUR 14.9 million executed in October 2016
- Cash and cash equivalents of EUR 21.9 million as of 31 December 2016
- Net loss of EUR 13.9 million compared with EUR 13.5 million in 2015 – in line with company expectations

Post-period Highlights

- There were no significant events subsequent to the reporting period

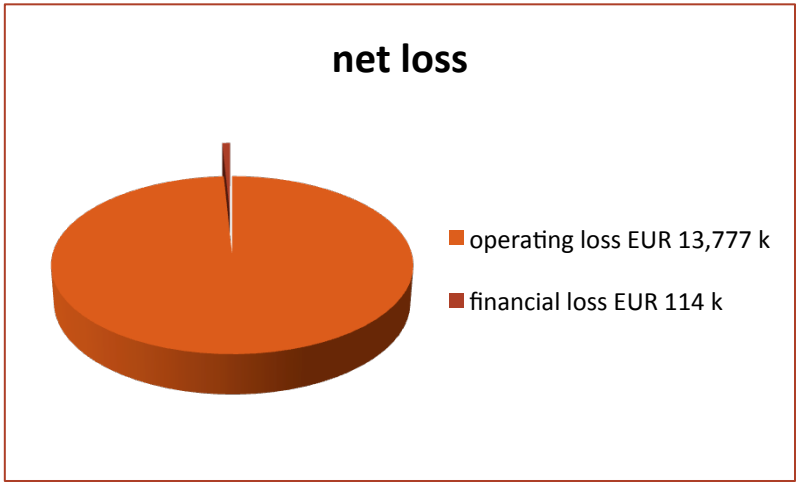
Key financial figures (according to IFRS)

In EUR k	2016	2015
Earnings, Financial and Net Assets Position		
Operating loss	-13,777	-13,393
Net loss for the period	-13,891	-13,505
Equity (end of the year)	16,376	16,133
Equity ratio (end of the year) (in %)	73.2	73.8
Balance sheet total (end of the year)	22,366	21,866
Cash flows used in operating activities (year)	-13,255	-12,147
Cash flows used in operating activities (monthly average)	-1,105	-1,012
Cash flows used in investing activities (year)	-124	-10
Cash flows provided by financing activities (net)	13,915	12,598
Cash and cash equivalents at the end of period	21,897	21,361
Personnel Total number of employees (incl. Board of management) (end of the year)	13	16
Average number of employees (incl. Board of management)	14.5	15.8
Probiodrug-Share Loss per share (basic and diluted) (in EUR)	-1.82	-1.97
Number of shares issued (end of the year)	8,187	7,442

Details of the Financial Results (according to IFRS)

Net loss

- Net loss in line with expectations
- Operating loss primarily driven by R&D expenses
- Increase in operating expenses reflects primarily investments in PQ912
- Financial loss largely driven by the costs incurred from accrued interest on the disputed tax liability

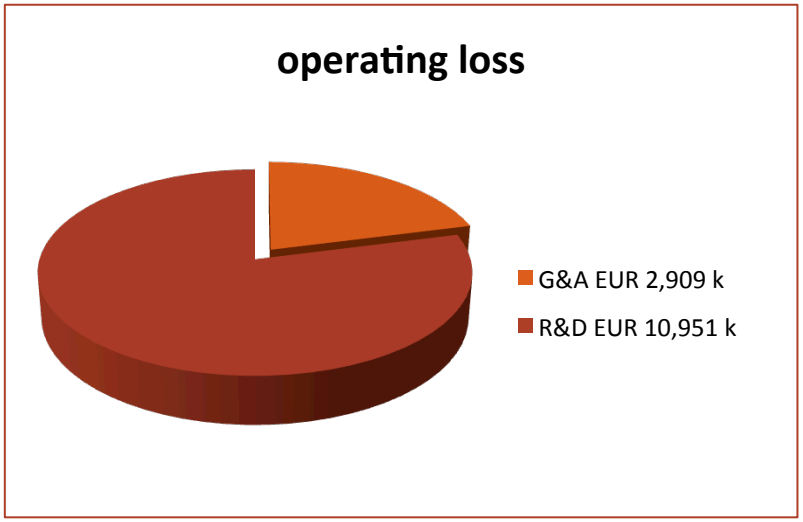


Equity

- Equity amounts to EUR 16,376k (2015: EUR 16,133k), corresponding to an equity ratio of 73,2%.

Cash

- Cash and cash equivalents were EUR 21,897k, compared with EUR 21,361k at the end of 2015



Operational Review (1)

Pipeline Update PQ912

- First QC-inhibitor being tested in humans
- In preceding Phase 1 study with healthy young and elderly volunteers shown to be safe, well tolerated and revealed high QC-inhibition
- SAPHIR is a randomized, double-blind multi-center study
  - Run in seven European countries at about 21 sites
  - Primary endpoint safety and tolerability compared with placebo over a three-month treatment period
  - Set of exploratory read-outs comprising cognitive tests, functional assessments by EEG and functional MRI and new molecular biomarkers in CSF to evaluate the compound's effect on AD pathology
  - Led by internationally renowned experts in AD
  - Lead center is the Alzheimer Center, VU Medical Center (VUmc), Amsterdam
  - Patient recruitment has been completed in mid-December 2016.
  - 120 patients with early stage Alzheimer's disease have been randomised
  - Mini-Mental State Examination (MMSE) and the Cogstate neuro-psychological tests monitored blindly every 30 patients to ensure consistency and reliability of ratings
  - First blinded results at baseline show that mean MMSE scores from the 120 randomised patients is 25.3, mean age is 73 years and gender distribution is 64 female and 56 male
  - Current results indicate a low variability and therefore the high quality of the assessments being used
  - Full unblinded results of the SAPHIR study are expected in the second quarter of 2017

Operational Review (2)

PBD-C06

- Monoclonal antibody targeting pGlu-Abeta, while leaving non-toxic forms of Abeta untouched
- Currently in preclinical stage
- Successfully humanized and de-immunized
- For the first time for an anti-pGlu-Abeta-antibody 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
- Development of the manufacturing process is running

PQ1565

- Second QC-inhibitor with attractive drug-like properties
- Currently in preclinical stage
- GMP process for this molecule is being implemented
- Next development steps in preparation and respective decisions to be made in connection with the readout of SAPHIR

Operational Review (3)

Publications/ Presentations

- March 2016: Two oral presentations entitled "The pyroglutamate modification of toxic A-beta resulted in new therapeutic approaches: Inhibitors of glutaminyl cyclase and highly specific antibodies – A status report" and "Phagocytic characterization and therapeutic efficacy of an Anti-PyroGlutamate-3 A-beta IgG2a antibody in aged APP/PS1dE9 mice" presented at the 14th AAT Symposium on Advances in Alzheimer Therapy in Athens Greece.
  - The data resulted from a collaboration between Probiodrug and a research team led by Professor Hans-Ulrich Demuth from the Department of Drug Design and Target Validation at the Fraunhofer Institute for Cell Therapy and Immunology IZI, Halle (Saale), Germany and the research team led by Professor Cynthia Lemere from the Center for Neurologic Diseases at the Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.

- April 2016: Assessment of its chronic toxicology studies with its lead candidate PQ912, currently under development for AD in a clinical Phase 2 study (SAPHIR) is concluded.
  - The results showed that the toxicology profile of PQ912 in the 6-month rat and 9 month dog studies was absolutely comparable to the results of the previously available 3-month toxicology studies conducted in the same species. No new findings were observed and the minimal to slight non-adverse or questionable changes seen in both the 1-month – and the 3 month-studies were not aggravated after prolonged treatment, thus providing an excellent basis for a sound preclinical safety assessment. In conclusion, the comfortable safety margin is retained.

Operational Review (4)

Publications

- May 2016: Two poster entitled "Quantitative Analysis of truncated Aβ peptide substrates of glutaminyl cyclase in human CSF samples using LC-MS/MS," and "Determination of Aβ Oligomers using a Flow Cytometry-Förster Resonance Energy Transfer (FRET) method," presented at the 1st Meeting of the Society for CSF Analysis and Clinical Neurochemistry in Gothenburg, Sweden
  - Probiodrug is evaluating and establishing new concept-related molecular biomarkers to be used in their ongoing Phase 2a study (SAPHIR). The emphasis is regarded as an important and key cornerstone in the read out hierarchy in clinical studies.

- June 2016: Agreement with the Dutch biotech company Crossbeta Biosciences B.V. announced
  - To utilize Crossbeta's proprietary technology in support of Probiodrug's biomarker development activities. The potential of Crossbeta's unique technology has significant impact to overcome the challenge of establishing and validating sensitive and specific assays for Abeta- and pGlu-Abeta-oligomers to be used in the clinical studies of Probiodrug's lead candidate, Glutaminyl Cyclase (QC) inhibitor PQ912.

Operational Review (5)

Publications

- September 2016: New findings for Probiodrug's Glutaminyl Cyclase – inhibitor in an inflammation animal model were presented at the Summer Frontiers Symposium 2016 'Systems Biology of Innate Immunity', Nijmegen, The Netherlands and the 6th European Workshop on Lipid Mediators, Frankfurt/M, Germany
  - The data resulted from a collaboration between Probiodrug and Ambiotis. The effect of the QC inhibitor PQ912 was investigated in a mouse model of inflammation (thioglycollate induced peritonitis) with special focus on its effect on cell infiltration and release of pro-resolving lipid mediators. The effects seen with PQ912 on recruitment of macrophages and eosinophils, and levels of chemokines and lipid mediators, makes QC inhibition attractive for further evaluation as potential anti-inflammatory drug and/or resolution promoting agent.

- September 2016: First results of a preclinical combination trial targeting pGlu-Abeta announced
  - An additive effect on lowering pGlu-Abeta (pyroglutamate-Abeta) as well as total Abeta was observed with a double-pronged approach of targeting toxic pGlu-Abeta by combining the Glutaminyl Cyclase-inhibitor PQ912 to block pGlu-Abeta formation and the mouse version of the pGlu-Abeta specific antibody, PBD-C06, to increase its clearance in an AD animal model.

Operational Review (6)

Publications

- November 2016: First results of a preclinical study in an AD mouse model with the pyroglutamate-3 Abeta (pGlu3-Abeta)-specific antibody mPBD-C06, comparing versions with and without a mutation eliminating complement activation were presented as a poster at the Society for Neuroscience (SfN) meeting in San Diego, CA, USA
  - The data were generated in collaboration with Cynthia Lemere of Brigham and Women's Hospital, Harvard Medical School, and QPS, Graz, Austria. It was demonstrated for the first time, that microglial activation, analyzed by TSPO microPET, can be reduced by CDC inactivation without impairing the potency of the antibody to clear amyloid deposits.

- December 2016: Innovative Phase II study design of the SAPHIR study was presented at 9th Clinical Trials on Alzheimer's disease (CTAD), San Diego, CA, USA
  - Based on an exploratory analysis of 86 randomised patients, a low standard deviation for the Neuro-psychological test battery and functional EEG at baseline has been observed. The SAPHIR study has been designed and is conducted in collaboration with Philip Scheltens, M.D., Ph.D., the VUmc Amsterdam (NL) and the CRO Julius Clinical (NL).

Operational Review (7)

IP

- In 2016, IP position further strengthened by important patent applications being granted
  - Patents US 9,156,907 and JP 5,828,762 covering antibody program targeting pyroglutamate Abeta (pGlu-Abeta, also N3pG Abeta) in the US and in Japan, method as well as composition of matter claims.
  - Patent JP 5,934,645 covers PQ912 and surrounding chemical space; this patent has been granted already in the USA, the EU as well as in other important markets. With a patent life expiring in 2030, plus the usual extension for pharmaceuticals, the patent provides a solid protection for PQ912 in Japan and other key markets.
  - Patent JP 5,930,573 covers the general use of QC inhibitors for the treatment of Mild Cognitive Impairment (MCI), granted previously for the treatment of AD and British/Danish dementia in the USA, EU and Japan, thereby broadly protecting the general use of QC inhibition. Importantly, the granted claims of JP 5,930,573, already issued in the US, complement and extend the use of QC inhibitors for MCI.

Corporate Review

Execution of a capital increase via accelerated bookbuild on October 6, 2016

- Increase of share capital from EUR 7,442,487 to EUR 8,186,735, issuing 744,248 new shares
- Representing appr. 10% of the issued share capital at the time of the placement
- Gross proceeds of EUR 14.9 million
- Order book well covered based on strong demand from European and US investors
- New shares placed at EUR 20 per share

Executive Management

- Mark Booth, appointed as Chief Business Officer in March 2016, left the company for personal reasons in August 2016

Supervisory Board

- Shareholder meeting on May 19, 2016, re-elected Dr Erich Platzer, Dr Dinnies von der Osten, Dr Jörg Neermann and Dr Olivier Litzka as Supervisory Board Members.
- The Supervisory Board then re-elected Dr Erich Platzer as chairman and Dr Dinnies von der Osten as vice chairman.
- Dr Olivier Litzka, partner at Edmond de Rothschild Investment Partners (EdRIP) and member of the Supervisory Board since October 2009, stepped down in September 2016 as part of a natural transition.

Content

1. Corporate introduction
2. Results 2016
3. **Outlook**
4. Q & A

Outlook

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

- Continuing the clinical development of PQ912, in particular generate initial patient study data in 2017 and start long-term treatment,
- Continuing the development of PBD-C06,
- Continuing the development of PQ 1565,
- Further scientific analysis of potential second 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.

As a result of the continuing costs being incurred for development activities, the Company projects a net loss for the financial year 2017 which may be lower than that incurred in 2016.

News flow *(selection)*

2015

- ✔ First patient enrolled in PQ912 Phase 2a "SAPHIR" study at leading Alzheimer Center in Amsterdam
- ✔ Additional data on Glutaminyl Cyclases (QCs) in AD published in Acta Neuropathologica
- ✔ Key patents on Glutaminyl Cyclase (QC) inhibition for treatment of AD granted in Japan
- ✔ Data on Probiodrug`s Anti-pGlu-3 Abeta monoclonal antibody presented at the 12th International Conference on Alzheimer's and Parkinson's Diseases (AD/PDTM 2015)
- ✔ PBD-C06 start of development activities to prepare for Phase 1
- ✔ PQ912 Publication of complete Phase 1 results

2016

- ✔ PQ912 results of long term tox studies
- ✔ Promising anti-inflammatory effect by activating the resolution process in an animal model of inflammation.
- ✔ PQ912 POP* combination therapy with PBD-C06
- ✔ Amyloid beta clearing by the murine anti-pGlu-Abeta antibody PBD06 with and without complement mutation

2017

- ☐ PQ912 Phase 2a SAPHIR results
- ☐ PQ912 POP* combi-nation therapy with BACE inhibitor
- ☐ PQ912 Preclinical assessment of potential in Huntington Disease and Down syndrome

* Pre-clinical proof of Principle
Please note: timing of news flow is indicative

Financial Calendar

▪ 12 May 2017	Interim Management Statement Q1 2017
▪ 13 June 2017	Annual General Meeting of Shareholders
▪ 31 August 2017	Interim Report, half year results 2017
▪ 30 November 2017	Interim Management Statement Q3 2017

Content

1. Corporate introduction
2. Results 2016
3. Outlook
4. **Q & A**