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Interim Report H1 2017
Reporting period January – June 2017

Halle (Saale), 31 August 2017

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Content

1. **Corporate introduction**
2. Results January – June 2017
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At a glance

- Alzheimer's disease – a worldwide health crisis
- New concept for treatment – target pGlu-Abeta (N3pG), involved in initiation and progression of disease
- Glutaminyl Cyclase (QC) catalyzes formation of N-terminal pGlu-Abeta from N-terminal **Glutamate**
- Products under development
  - PQ912, a small molecule inhibitor of QC, Phase-SAPHIR study, top line data reported 11 June 2017
  - PBD-C06, a pGlu-Abeta specific mAB, preclinical
- Strong IP position on medical use and composition of matter
- Experienced management
- "PBD" Euronext

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
- 27 Oct 2014: IPO at Euronext/ Amsterdam, raise of € 23.2m
- 2015: Initiation Phase-2 clinical development of PQ912 (SAPHIR trial)
- 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
- June 2017: PQ912 delivers positive pharmacodynamic and efficacy results in SAPHIR trial in early stage AD patients

Major investors (> 3%)

BB BIOTECH

AVIVA INVESTORS

IBG

EDMOND DE ROTHSCHILD INVESTMENT PARTNERS

TVM | Capital

HBM Healthcare Investments

LSP Life Sciences Partners

Biogen

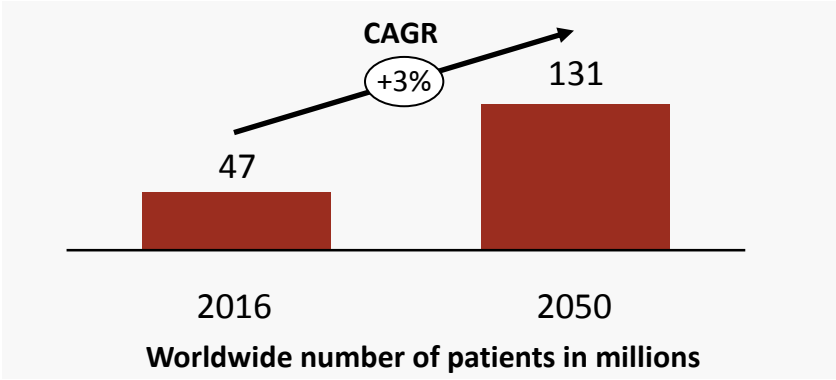
J.P.Morgan

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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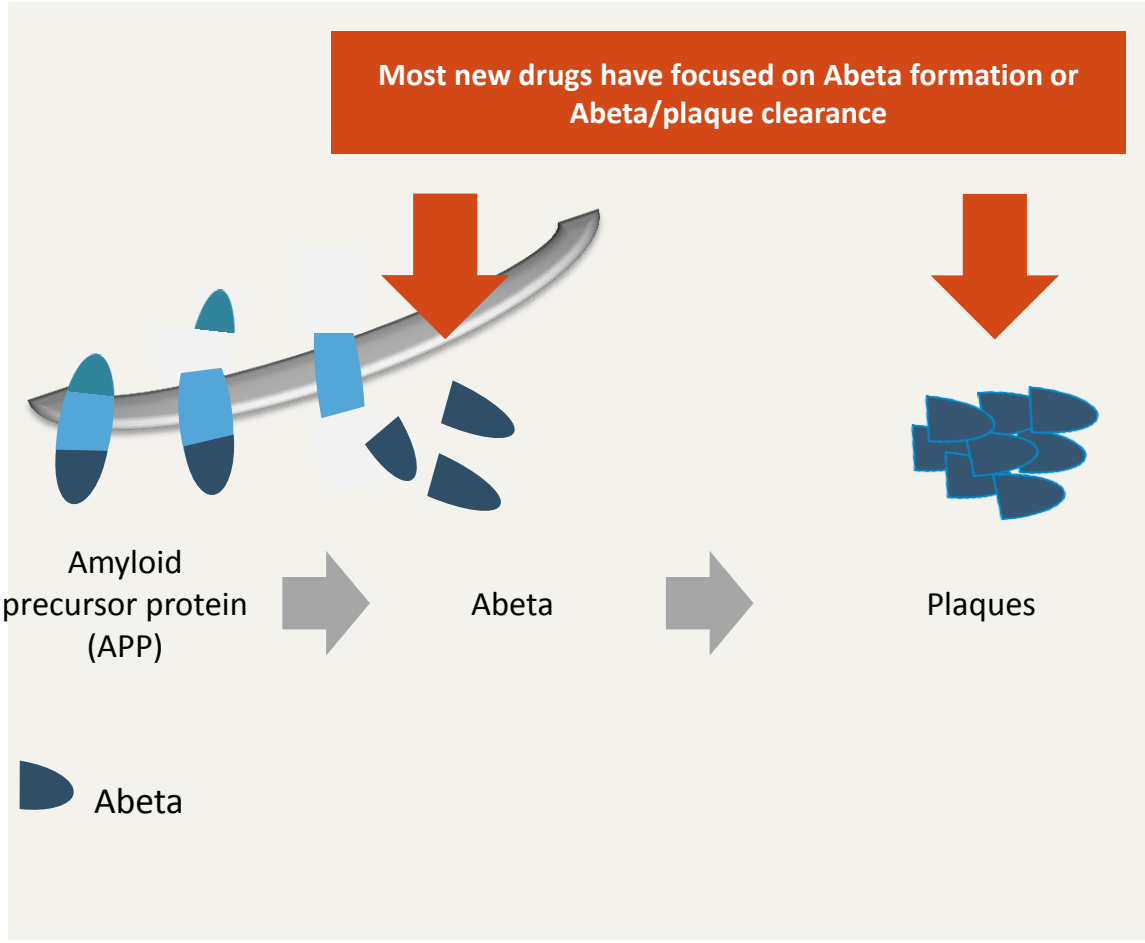
Original Abeta approach

Probiodrug targets toxic structures in Alzheimer's Disease



Considerations*

- Most new drug treatments have targeted Abeta or plaques
- Therapies have focused on:
  1. Reduction of Abeta formation
  2. Clearance of existing Abeta or plaque
- To date, several drug development attempts based on this original Abeta approach have failed – except one Abeta antibody in an early trial - others are ongoing and have yet to show benefit

* Company analysis, Mullard A Nat Rev Drug Discov 2012

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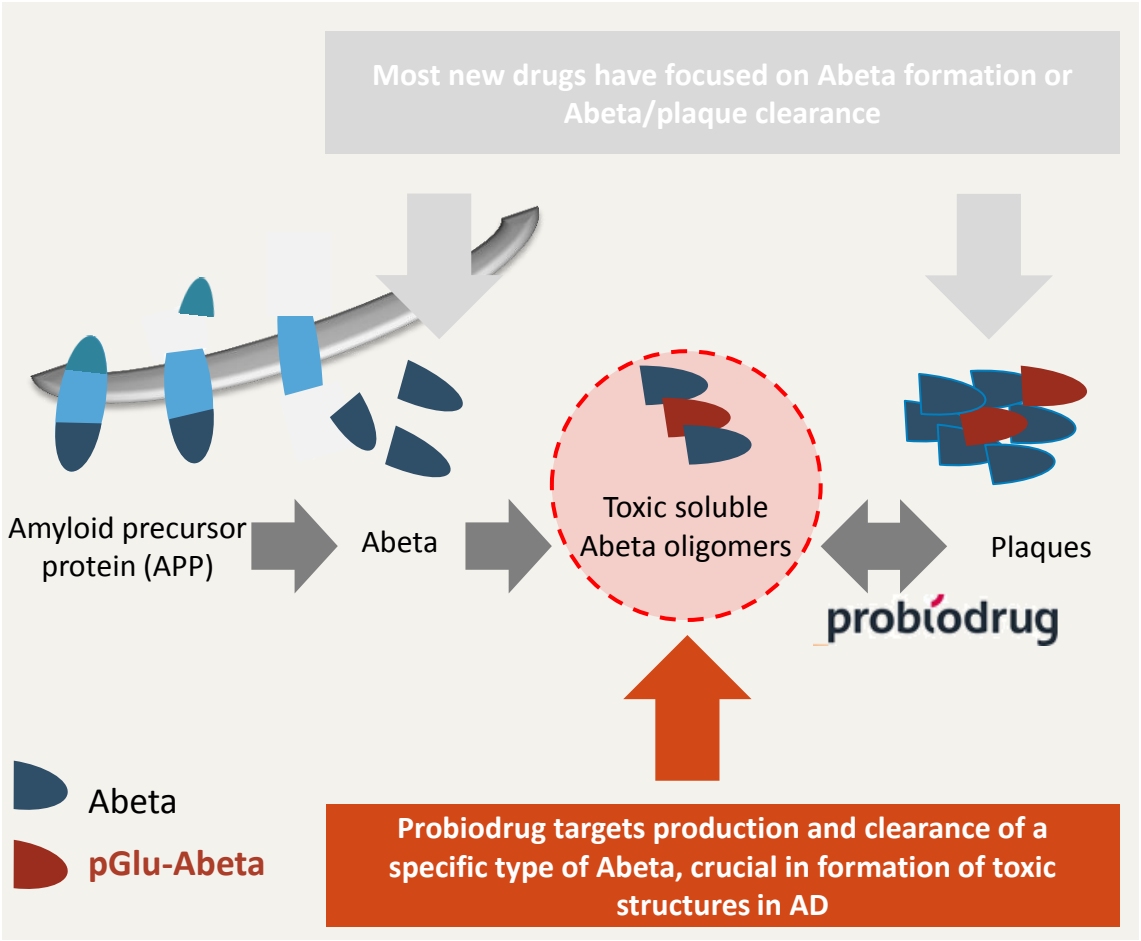
Probiodrug's **differentiated** approach

Probiodrug targets toxic structures in Alzheimer's Disease

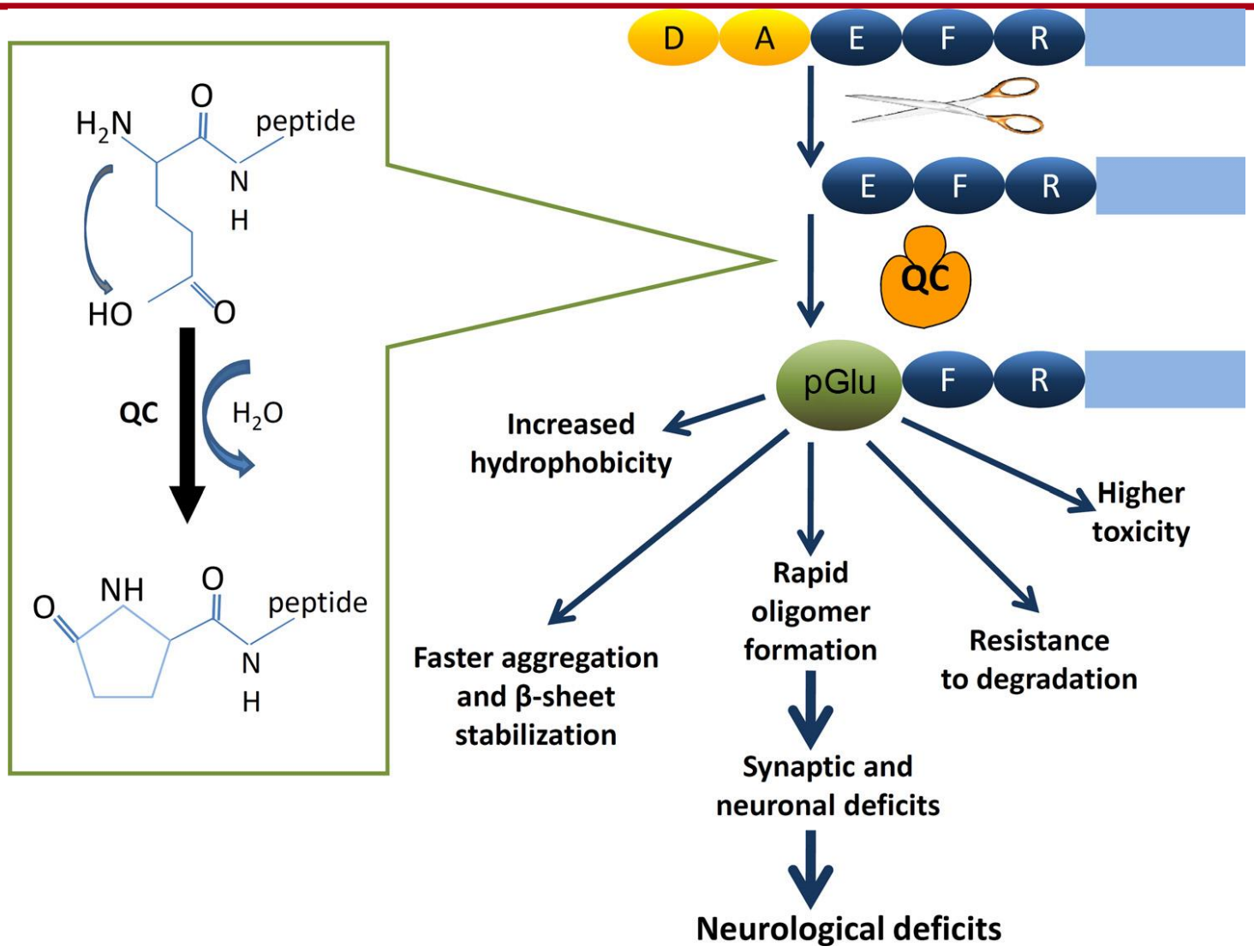


Considerations*

- 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

pGlu-Abeta - N-modified Abeta



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

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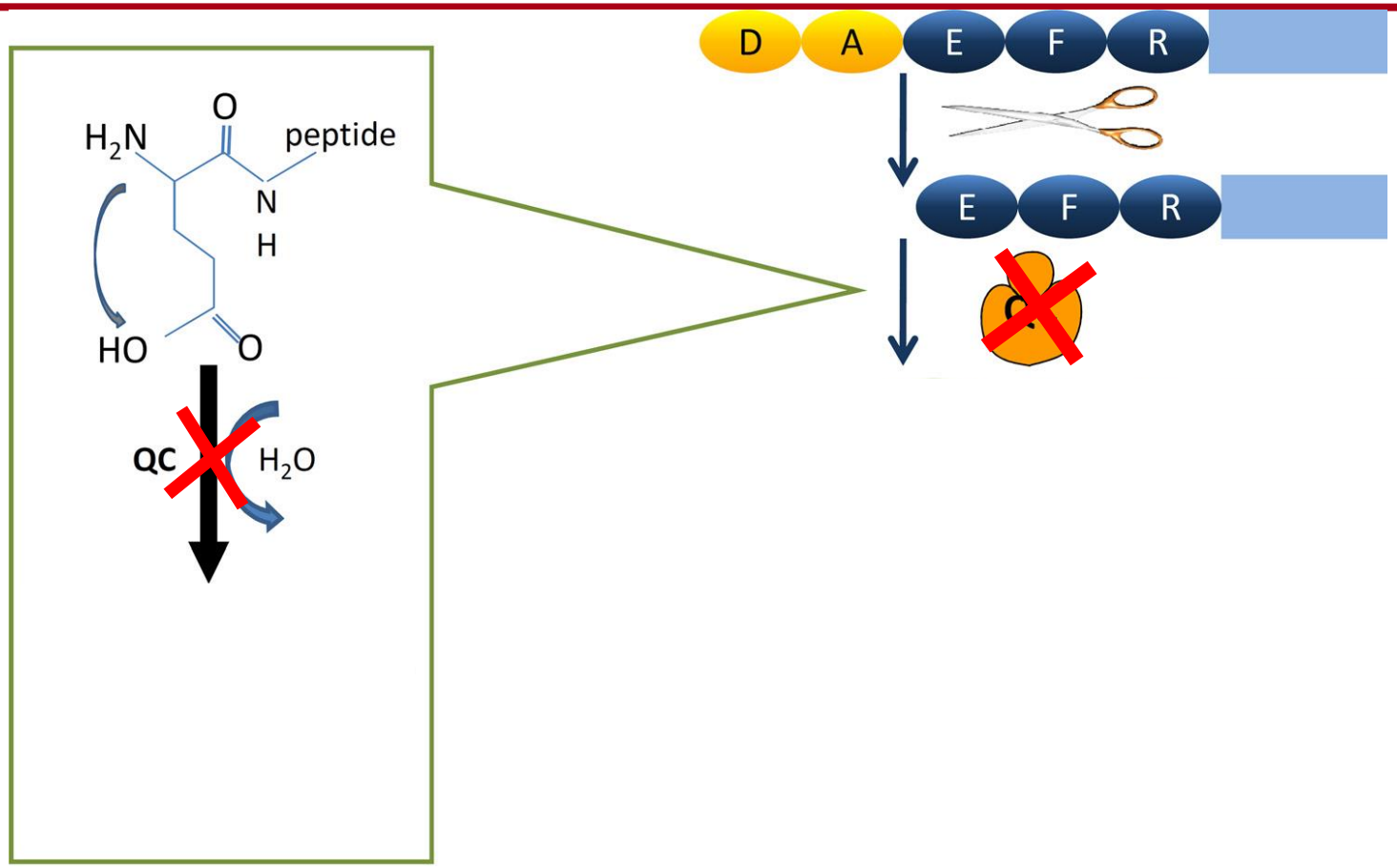
Target pGlu-Abeta: small molecule approach (QC inhibitor)



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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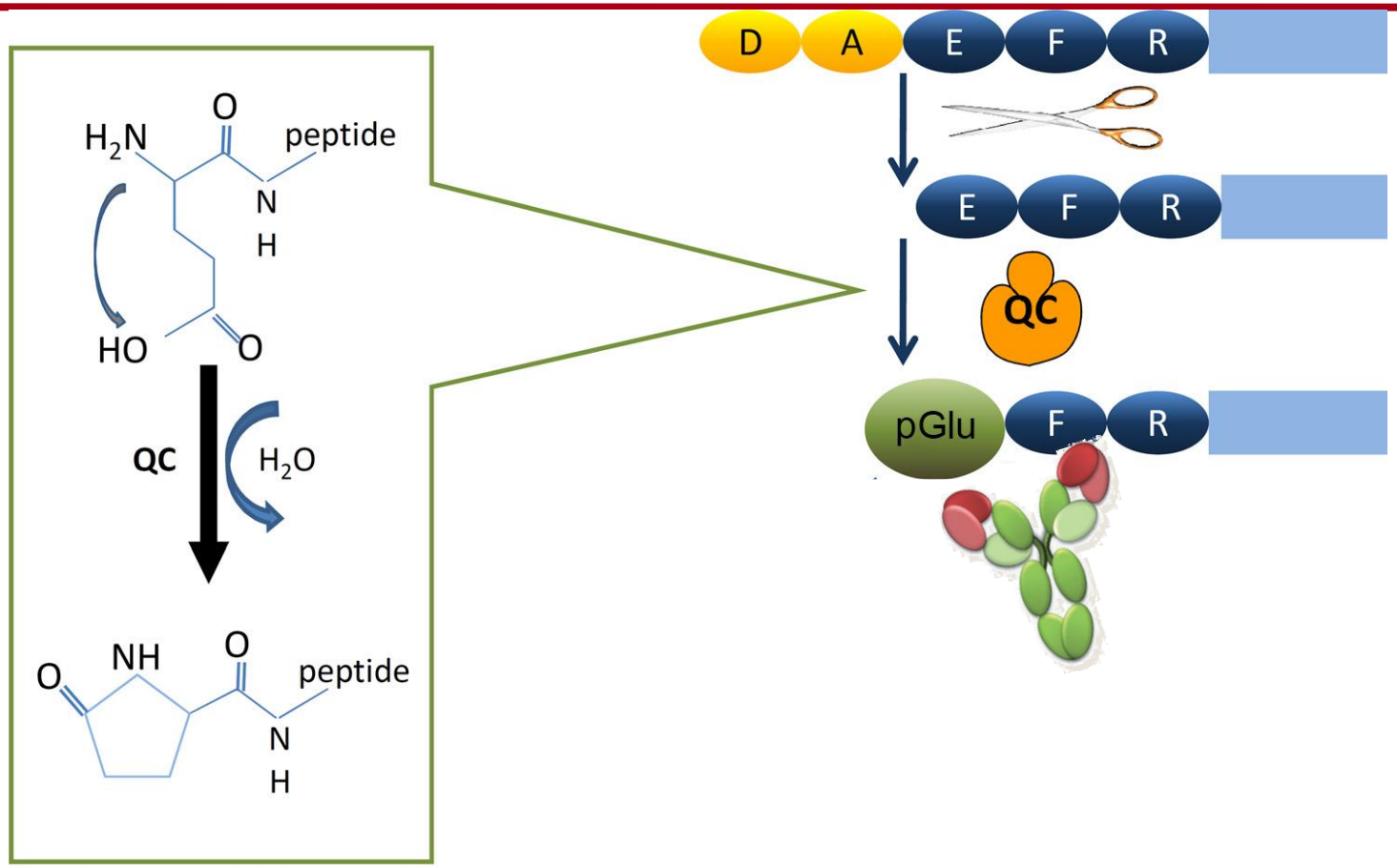
Target pGlu-Abeta: antibody approach



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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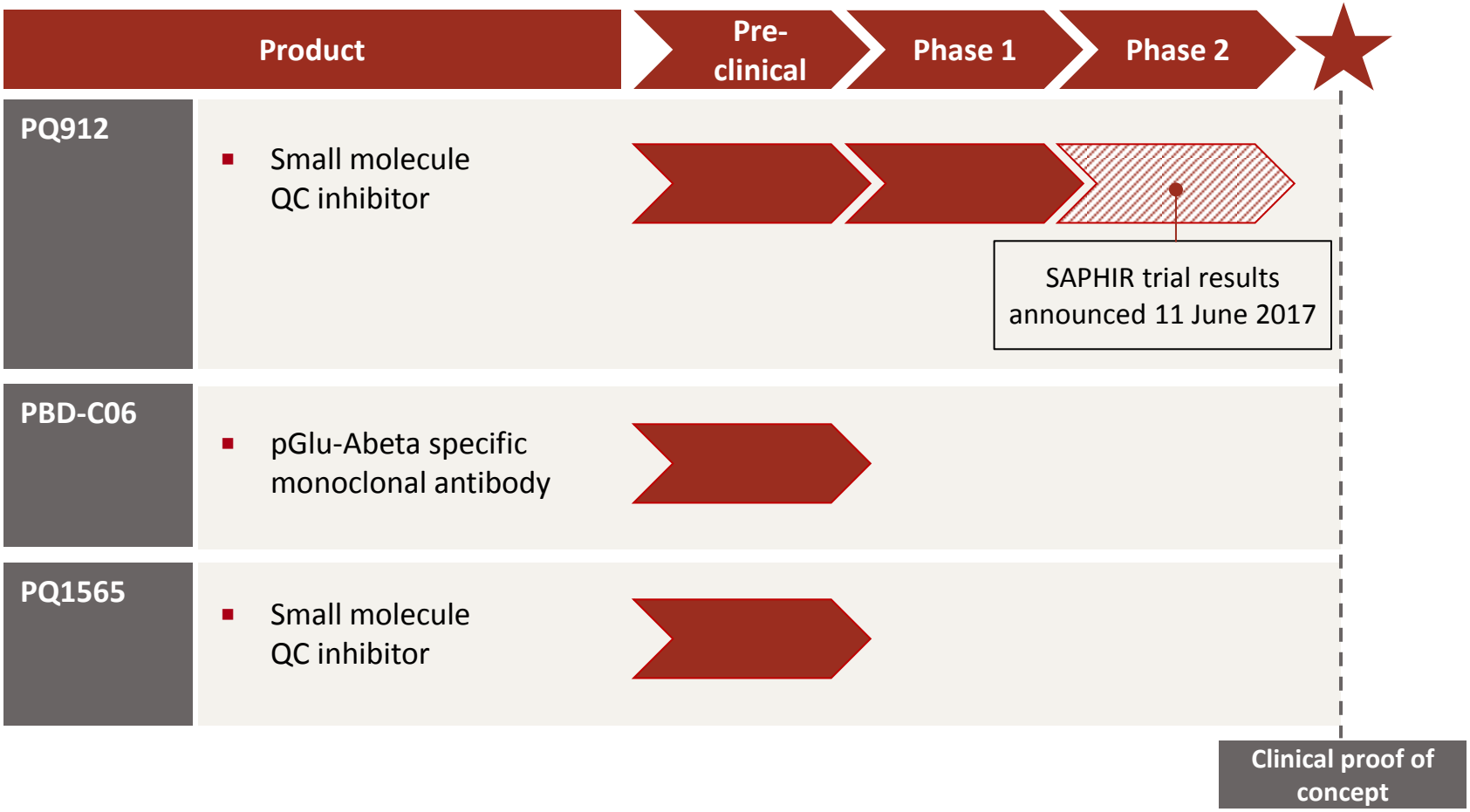
Anti pGlu-Abeta strategies– the emerging new field in AD treatment

- pGlu-Abeta (N3pG) - preclinically validated target critical to the formation of toxic oligomers involved in the initiation and progression of AD,
- pGlu-Abeta (N3pG) – first positive clinical data in AD patients accomplished
- Two players in the anti pGlu-Abeta field:
  - Probiodrug: leading the small molecule approach via QC inhibitors
  - Lilly: leading the antibody approach, followed by Probiodrug
- **Probiodrug**: **PQ912 first in class QC inhibitor**, first patient trial finished with encouraging results (3 months treatment), long term trial in preparation
- Lilly: LY3002813 first in class antibody, after having shown encouraging results in a 3 month AD patient trial, progressed in a long term trial in patients beginning in 2016

Focused proprietary pipeline

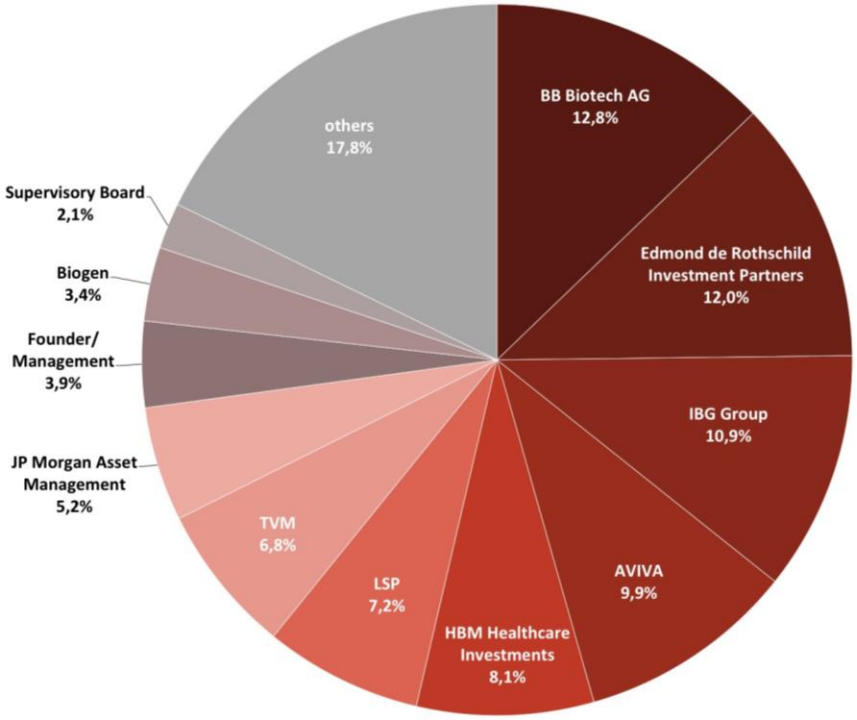


The Probiodrug Share

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

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Key Highlights January to June 2017

- PQ912 delivers positive pharmacodynamic and efficacy results in a Phase-2a-study in early stage AD patients
- Successful settlement of the longpending potential tax liability
- PQ912 demonstrates efficacy in preclinical Huntington`s disease model
- Publication of PQ912 pharmacology paper in a peer reviewed journal
- 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 – all proposed resolutions approved
- 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

Key financial figures January – June 2017 (according to IFRS)

In EUR k, unless otherwise stated	Jan - June 2017	Jan - June 2016	Jan - Dec 2016
Earnings, Financial and Net Assets Position			
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

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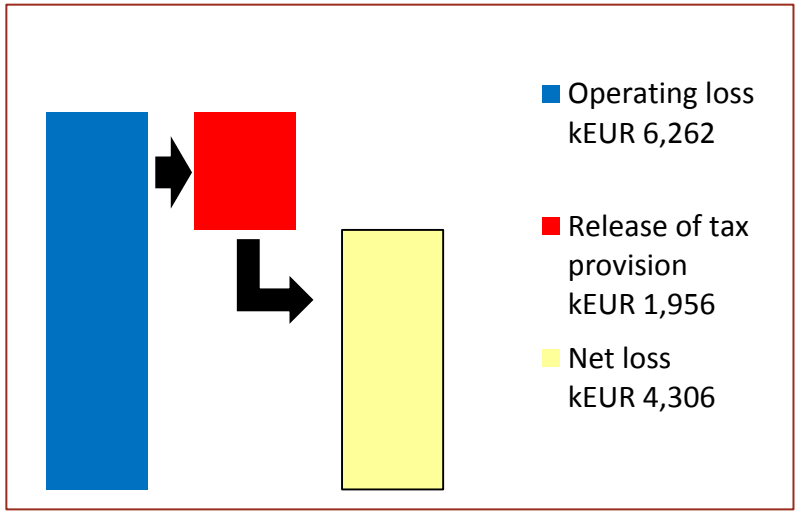
Details of the Financial Results January – June 2017 (according to IFRS)

Net loss

- Operating loss in line with expectations primarily driven by R&D expenses for the SAPHIR study
- Income from release of tax provision after successful settlement of potential tax claim

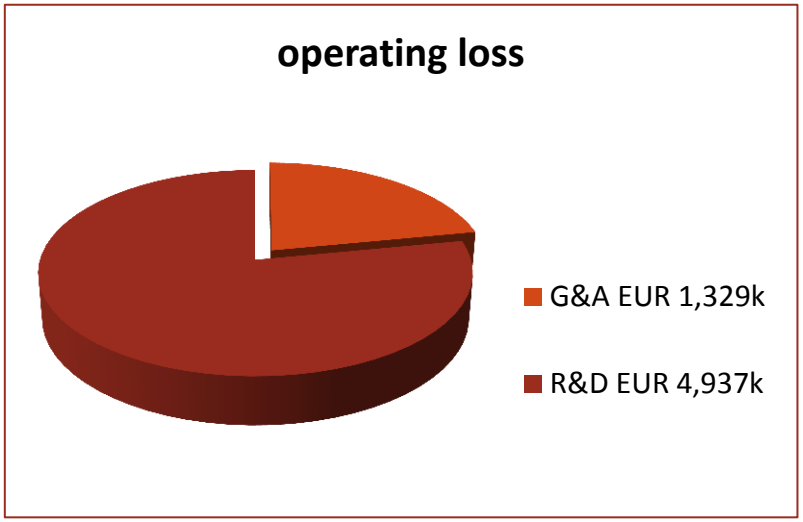


Equity

- Equity amounts to EUR 12,211k (end of 2016: EUR 16,376k), corresponding to an equity ratio of 81.6% (end of 2016: 73.2%).

Cash

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



Operational Review (1)

PQ912 - SAPHIR Phase-2a trial design

- Trial ongoing in 7 EU countries
- Study chair: Philip Scheltens, Amsterdam
- Total: 120 patients

  Early stage Alzheimer's Disease at screening

  MMSE* score: 21-30 inclusive

  Positive AD signature - either a and b or c:

  a. Abeta level in CSF below cut-off 638 ng/L AND total tau >375 or p-tau level above cut-off >52 ng/L
  b. Tau/A-beta ratio in CSF >0,52
  c. Positive amyloid PET if available

- "Treatment naïve": no other Alzheimer drug as co-medication
- 1:1 randomization
- 12 weeks treatment, 4 weeks follow up
- Recruitment completed mid December 2016
- **Top line date announced 11 June 2017**

Objectives and read-outs

- **Primary objective:** To assess safety and tolerability of PQ912 compared with placebo
- **Exploratory objectives:** set of readouts tailored by Probiodrug to optimize basis for capturing efficacy signals – which will determine further development route
- **Cognitive readouts:** Neuropsychological Test Battery to test short term memory improvements known to tightly correlate with synaptic activity
- **Physiological function assessments:** EEG and rested state functional MRI to measure synaptic plasticity and neuronal connectivity
- **Molecular biomarkers in CSF:** pGlu-Abeta, Abeta pattern, Abeta oligomers, synaptic/axonal biomarkers and inflammatory markers, αB-crystallin

*Mini-Mental State Examination

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Operational Review (2)

Update PQ912

- 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.

- June 2017 - First line results of Phase-2a SAPHIR study in early AD patients announced - Encouraging results of the Phase-2a SAPHIR Study
  - 120 patients randomized, 60 to placebo arm and 60 to PQ912 arm.
  - Treatment arms well balanced with respect to age, gender, disease severity and APOE4 status. Mean MMSE (Mini-Mental State Examination) score at baseline was 25.5 (min-max 21-30).

Operational Review (3)

Update PQ912 - Results of the Phase-2a SAPHIR Study in early stage AD patients

- **Safety**
  - No statistically significant differences of PQ912 vs placebo between number of patients experiencing an adverse event (PQ912 n=49, placebo n=45) or number of patients with a serious adverse event (PQ912 n=8; placebo n=5).
  - Patients in treatment arm showed a significantly higher discontinuation rate due to SAE or grade 3 adverse events compared to patients in the placebo arm (PQ912 n=6; 2 withdraw consent, 4 stopped medication but are completers; placebo n=0, p=0.027)

- **Tolerability**
  - Total number of patients non-adherent to randomized treatment for any reason was higher in the treatment arm (PQ912 n=26; placebo n= 2; $p<0.01$).
  - Skin and gastrointestinal organ system related adverse events observed in higher frequency in PQ912 arm compared to placebo. Dose reductions prescribed by the investigator identical in treatment and placebo arm (both n=5). Skin effects occurred during first 60 days.

- **Conclusion**
  - With a view on the high dose applied, confidence that with lower doses showing still quite high levels QC-inhibition and slower titration scheme the drug will be safe and well tolerated in AD patients

Operational Review (4)

Update PQ912 - Results of the Phase 2a SAPHIR Study in early stage AD patients

- **Pharmacodynamics and efficacy**
  - Very strong target engagement (QC inhibition), confirming the finding in Phase-1 in elderly healthy volunteers of more than 90%
  - Reduction of numbers of patients with detectable levels of synaptotoxic pGlu-Abeta oligomers in CSF while in placebo number of patients with detectable levels of pGlu-Aeta oligomers increased
  - Strong trends to reduce the level of the synaptic marker neurogranin, and a significant reduction of inflammatory marker YKL40, which are both enhanced in early AD
  - EEG (electroencephalogram) – compared to placebo, significant effect at the first level of EEG analysis: significant reduction in theta power which is increased in AD ($p=0.002$; Cohen's $D = -0.29$)
  - Short term memory – analysis via NTB (Neuropsychological Test Battery):
    - Significant improvement in 'one card back', ($p=0.050$, Cohen's $d = 0.24$) a test to assess working memory
    - The 'Detection' test, a measure of attention, showed a meaningful but not significant difference (Cohen's $d=0.2$)

- **Conclusion**
  - Data strongly supporting (a) the hypothesis of pGlu Abeta being synaptotoxic and (b) the effect of Glutaminyl Cyclase (QC)-inhibitors on inhibiting/ reversing this pathology.

Operational Review (5)

Update PQ912 - Results of the Phase 2a SAPHIR Study in early stage AD patients

- **Overall conclusion:**
  - SAPHIR 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.
  - Results make the program highly attractive for further development.

Operational Review (6)

Update PBD-C06

- Monoclonal antibody targeting pGlu-Abeta, while leaving non-toxic forms of Abeta untouched
- Currently in preclinical stage
- IgG isotype modified to eliminate complement activation (assumed to be involved in ARIAs) while keeping phagocytosis competency
- 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
- Unique binding mode – recently published
- Positive treatment results in combination with PQ912 in AD animal models presented
- Manufacturing process of this molecule is running

PQ1565

- Second QC-inhibitor with attractive drug-like properties
- Currently in preclinical stage
- Compound ready for regulatory toxicology studies

Operational Review (7)

Publications/ Presentations

- March 2017: poster/ presentation at Alzheimer's and Parkinson's Diseases Congress (AD/PD™ 2017)
  - *QC- enzyme/CSF Biomarker*
    - Cerebrospinal fluid glutaminyl cyclase (QC) activity correlates with Alzheimer's disease biomarkers and inflammation molecules in AD patients
    - In CSF from AD patients high correlation of QC activity with AD related biomarkers and inflammatory molecules were found
  - *QC-Inhibitor PQ912*
    - Glutaminyl cyclase inhibition by PQ912 in transgenic mice with Alzheimer-like pathology-translation to clinics
    - Based on PK/PD 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
  - *Anti-pGlu-Abeta MAB/QC-I*
    - Murine anti-pyroglutamate-3 Abeta MAB, 07/2a, spares cognition, reduces plaques, and, in combination with glutaminyl cyclase inhibitor PQ912 further improves efficacy
    - 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

Operational Review (8)

Publications/ Presentations

- April 2017: Oral presentation at the 12th Annual HD Therapeutics Conference of the CHDI Foundation
  - *The Glutaminyl Cyclase (QC) inhibitor PQ912 demonstrates beneficial effects in a preclinical Huntington´s disease model*

    - 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.

Operational Review (9)

Publications/ Presentations

- May 2017: Acceptance of PQ912 Pharmacology Paper by Peer Reviewed Journal of Pharmacology and Experimental Therapeutics
  - *Glutaminyl Cyclase Inhibitor PQ912 improves cognition in mouse models of Alzheimer's disease – studies on relation to effective target occupancy*
    - Authored by T. Hoffmann *et al.*; DOI: https://doi.org/10.1124/jpet.117.240614
  - 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 Ki-values in the range between 20 and 65 nM.
  - Chronic oral treatment of hAPPSLxhQC 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.

Corporate Review (1)

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

- Agreement reached 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, 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 end of 2016.
- Probiodrug believed that better arguments spoke against the tax authorities' view and contested claims of the tax authorities. 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, a total amount of EUR 775k (taxes including accrued interest) paid.
- Remaining EUR 1.9 million released.
- Result: this longpending topic brought to its conclusion and Probiodrug could thereby prevent a further distraction of its attention and resources.

Corporate Review (2)

Annual Shareholders' Meeting 2017 on 13 June 2017

- 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

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Outlook

- 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.

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

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

Financial Calendar

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

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Q & A