probiodrug

The 2017 financial year
Full year results

Halle (Saale), 03 April 2018

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Content

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 (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 AD' patients, presented in November 2017 at CTAD 2017

Major investors

BB BIOTECH

AVIVA INVESTORS

IBG

EDMOND DE ROTHSCHILD INVESTMENT PARTNERS

TVM | Capital

HBM Healthcare Investments

LSP Life Sciences Partners

Biogen

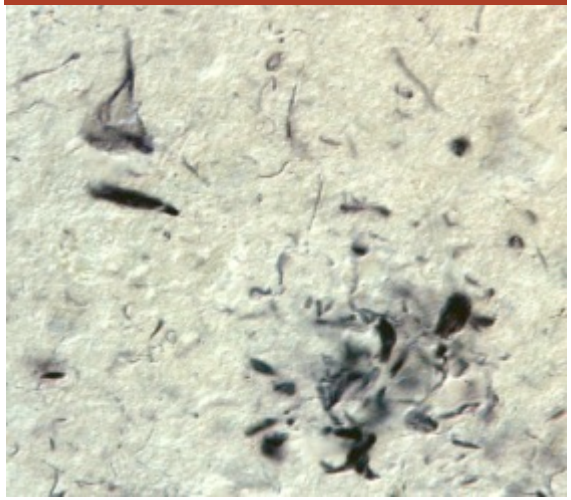
J.P.Morgan

Experienced management team

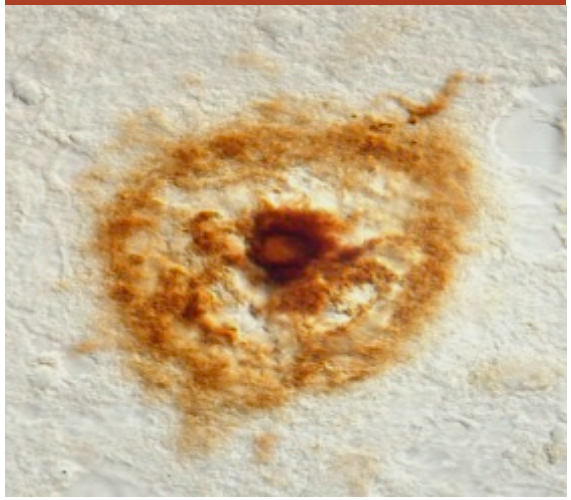
Management team		Biography
Konrad Glund, PhD CEO Co-founder Chairman of the management board		▪ Co-founder of Probiodrug, CEO since 2006 ▪ Led development of DPP 4 inhibitors, transactions with Merck, Novartis, OSI and Ferring ▪ COO & VP business development OSI (Prosidion) in 2004-2006 ▪ > 10 deals at OSI, including phase 1 deal with pharma
Hendrik Liebers, PhD CFO Member of the management board		▪ Longstanding track record in venture and private capital, CFH and IBG ▪ Numerous board seats in biotech companies ▪ > 20 financing rounds, M&A transactions, trade sales
Inge Lues, PhD CDO Member of the management board		▪ Advisor to biotech companies and public research institutions ▪ Family office E. Merck KG ▪ EVP member of the Pharma Board, Merck KGaA ▪ Head Global Drug Discovery and Non-Clinical Development; Head, Business Area Team, CNS Pharma, Merck KGaA
Frank Weber, MD CMO		▪ Global Clinical Advisor of InterMune ▪ Chief Medical Officer at Merck KGaA ▪ Several medical affairs and clinical development management positions at American Cyanamid/Lederle, Synthelabo, Merck KGaA

The AD Paradigm

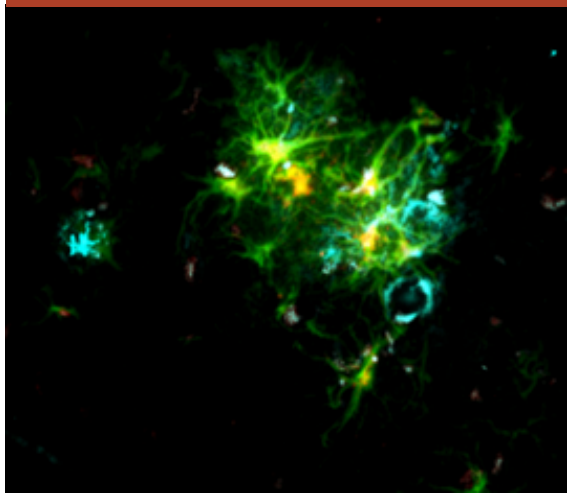
Neurofibrillary Tangles



Abeta plaques



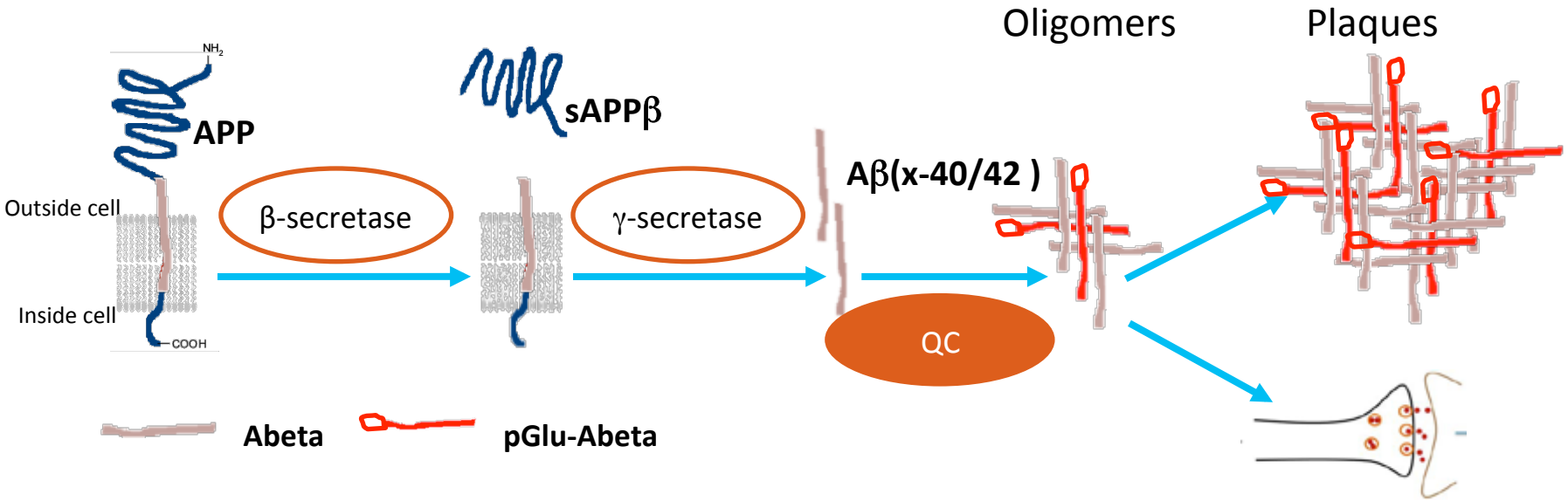
Neuroinflammation



- There are three pathological hallmarks of AD in the brain:
  - **Plaques** formed from Amyloid beta ("**Abeta**"), a small protein fragment, originated from the precursor protein APP
  - **Tangles** are misfolded forms of a protein called **Tau**
  - **Neuroinflammation**
- Many new drug development programs target Abeta

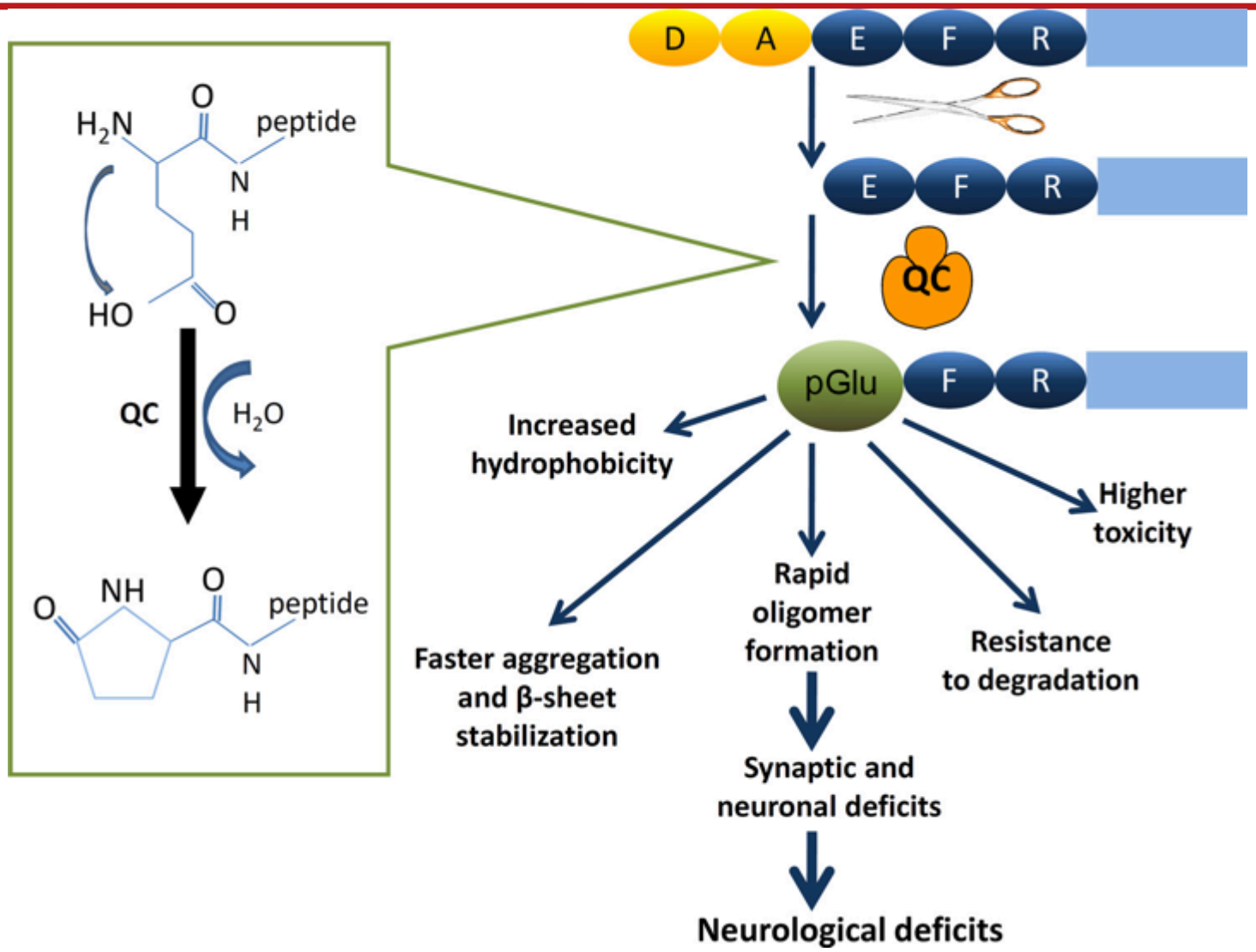
A **different** approach

Targeting post-translationally modified Abeta – pGlu Abeta



- **pGlu-Abeta** is crucial in the formation of synapto-/neurotoxic toxic oligomers
- **Oligomers** act directly on synaptic activity
- **pGlu-Abeta** is formed by the enzyme Glutaminyl Cyclase (QC)
- **PQ912** inhibits Glutaminyl Cyclase (QC)

pGlu-Abeta - N-terminal modified, toxic Abeta



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

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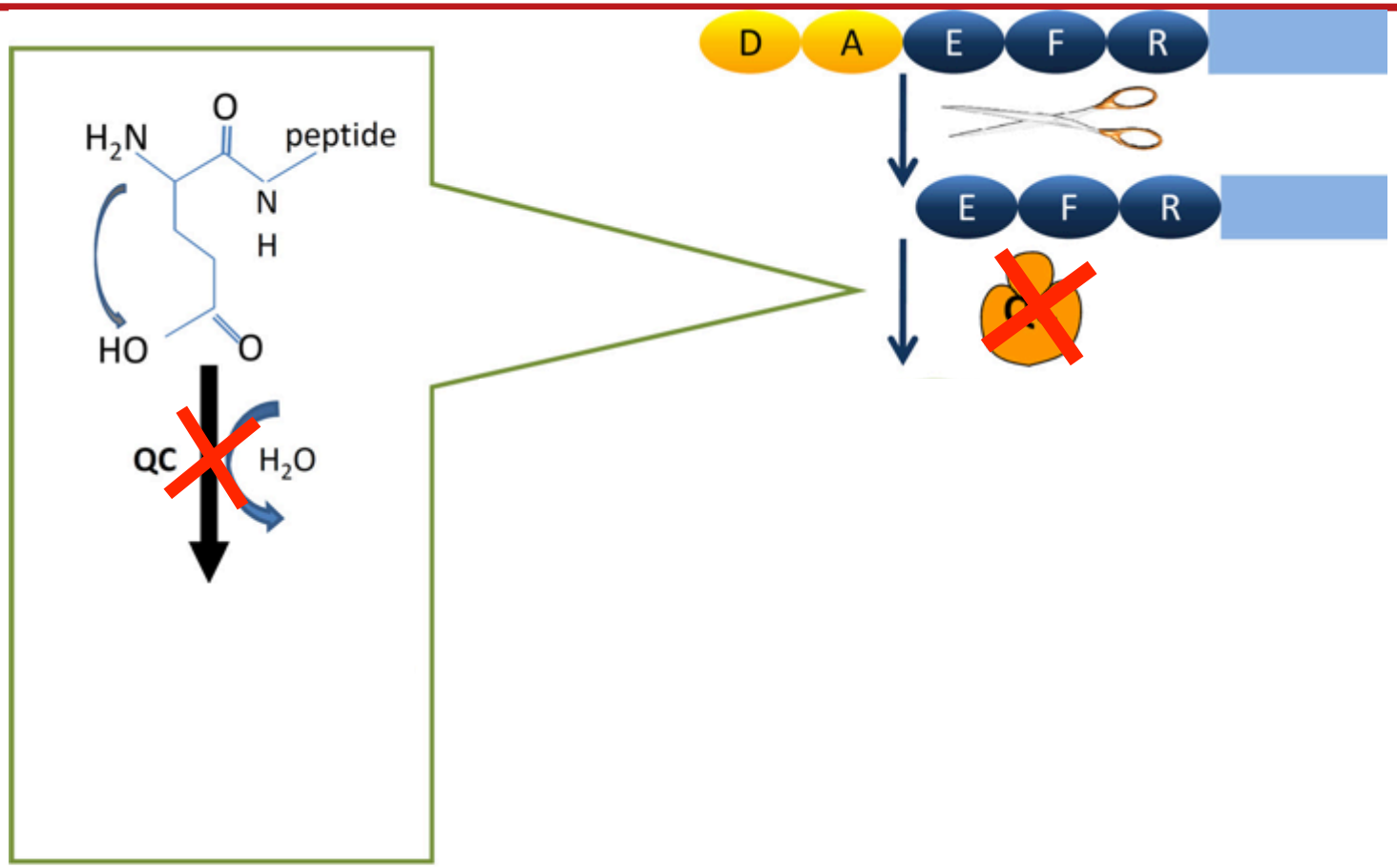
Target pGlu-Abeta: small molecule approach (QC inhibitor)



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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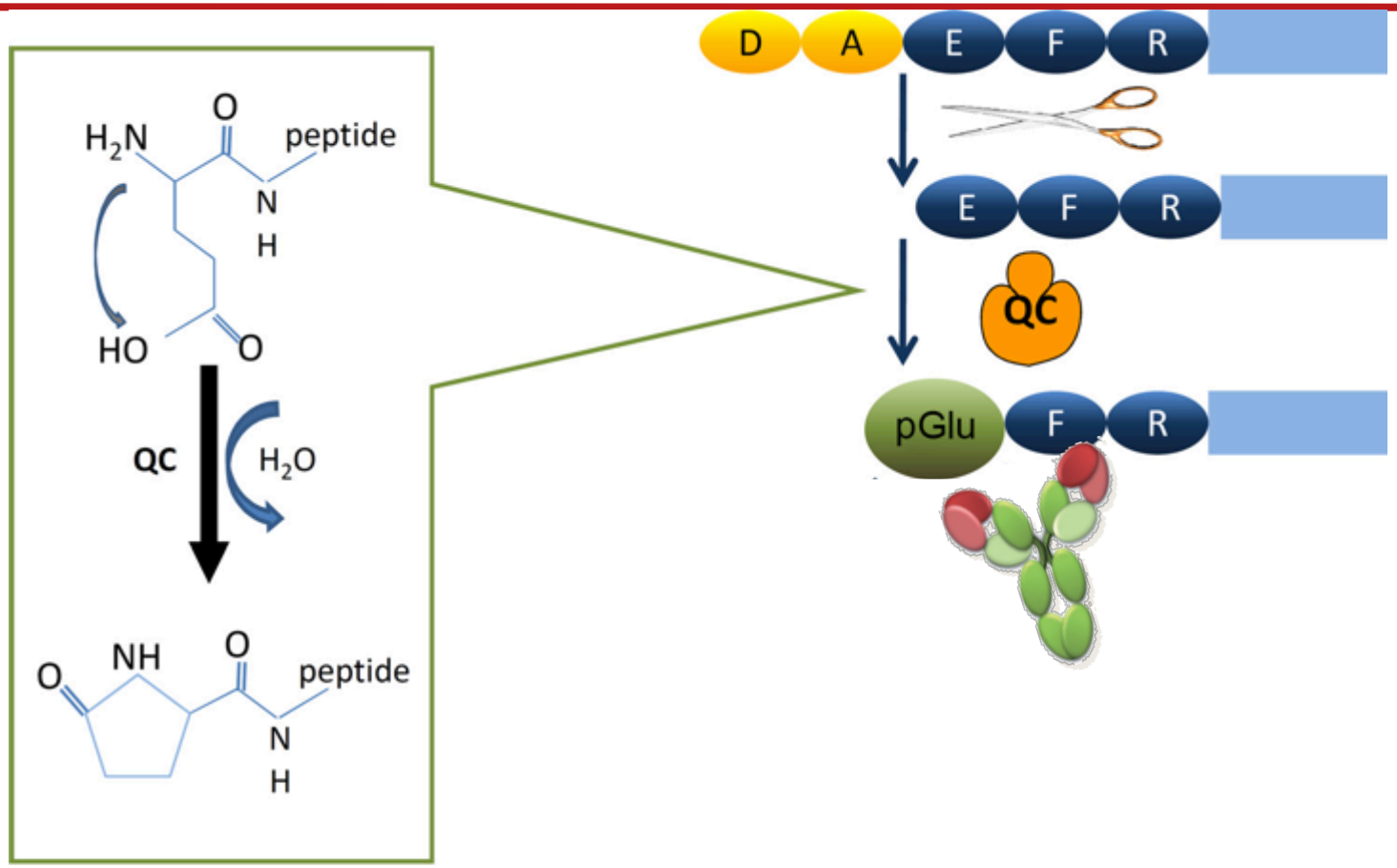
Target pGlu-Abeta: antibody approach



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

- **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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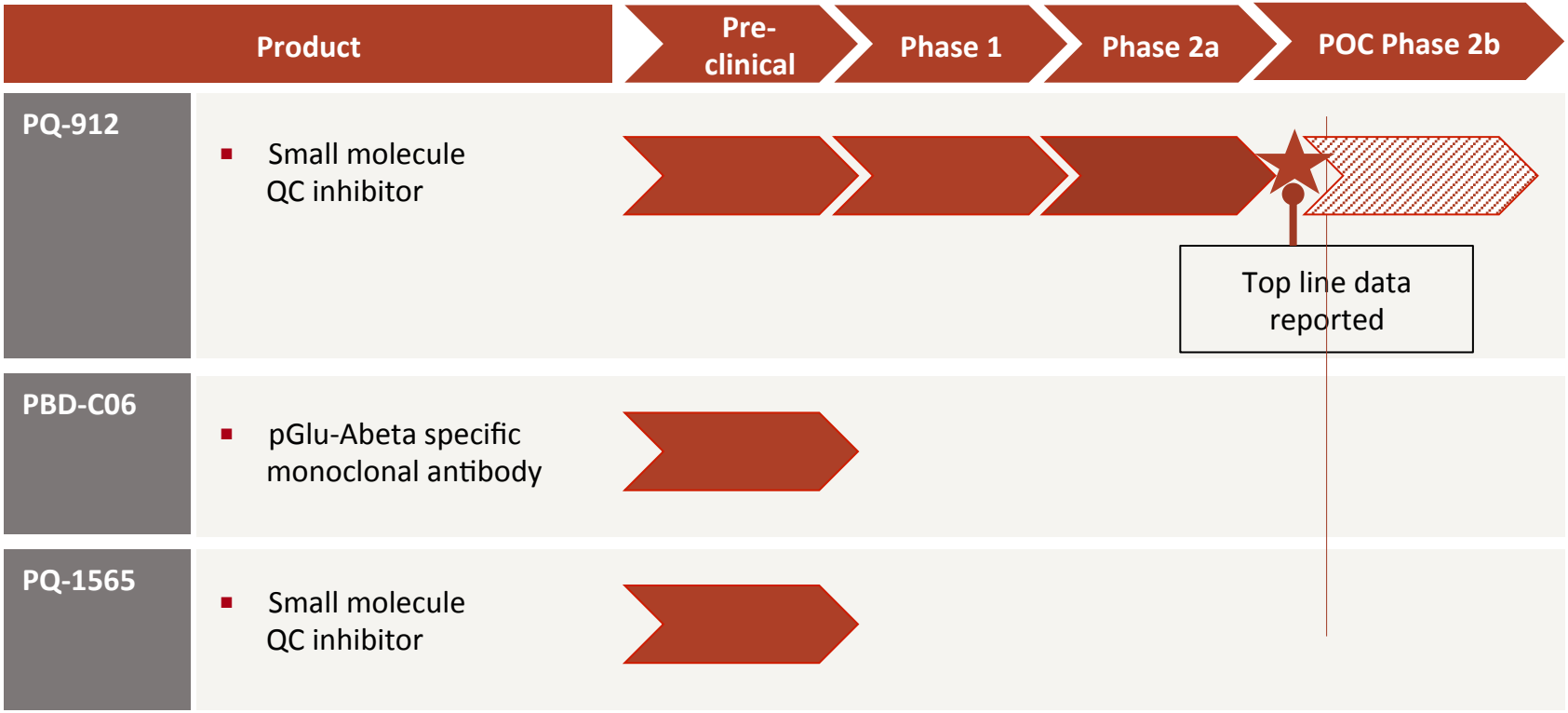
Focused proprietary pipeline

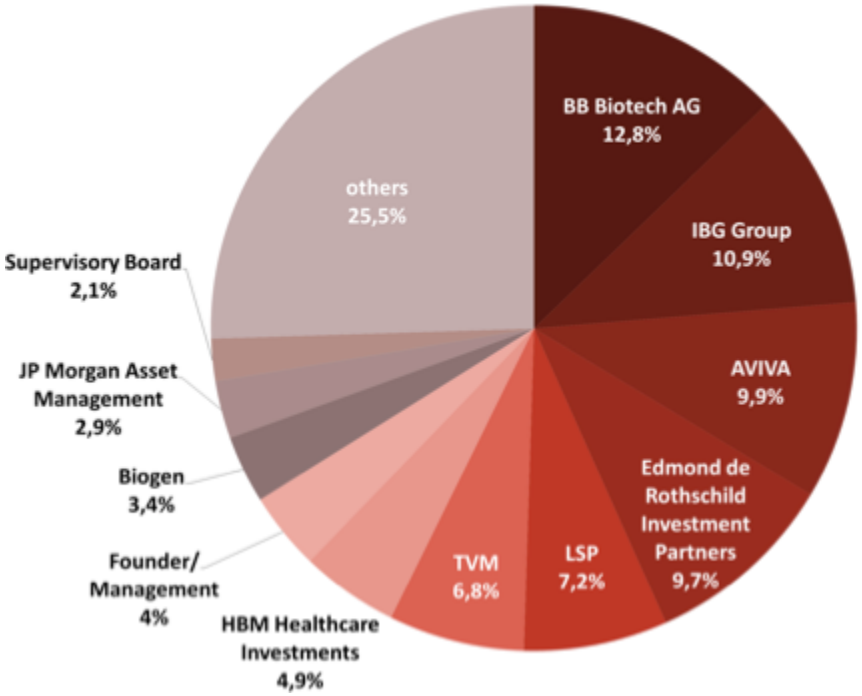


The Probiodrug Share

KEY INFORMATION

- ISIN: DE0007921835
- WKN: 792183
- Ticker Symbol: PBD
- Type of shares: Bearer shares
- Number of shares: 8,208,009
- Stock exchange: Euronext Amsterdam
- Liquidity Provider: Kempen & Co.
- Listing Agent: Kempen & Co.
- First trading day: 27 October 2014

Major Shareholder*



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

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2. **Results 2017**
3. Outlook
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Highlights 2017 (1)

- 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

Highlights 2017 (2)

- 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 had 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.

Results are presented at various conferences and/or are published in peer-reviewed journals - See Appendix for operational review

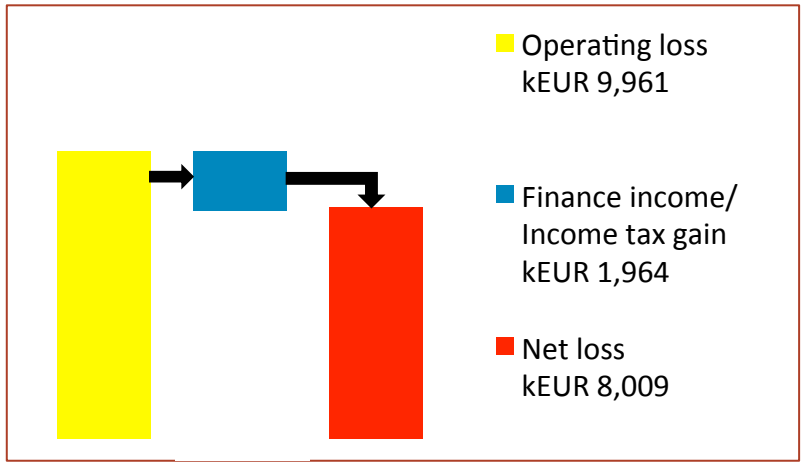
Key financial figures (according to IFRS)

In EUR k	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

- Expenditures in line with company`s projections
- Net loss without income tax gain in line with expectations
- Operating loss primarily driven by R&D expenses
- Finance income/income tax gain driven by release of provision after the successful settlement of the potential tax liability from 2004



Equity

- Equity amounts to EUR 8,923k (2016: EUR 16,376k), corresponding to an equity ratio of 82,9%.

Cash

- Cash and cash equivalents were EUR 10,291k, compared with EUR 21,897k at the end of 2016
- Cash Flow from investing activities: EUR 467k resulting from proceeds from the expiration of a pension liabilities insurance

PQ912 Clinical Development Strategy AD

- Phase 1: Comprehensive single and multiple dose studies

  Focus on mechanism based biomarker, PK / PD model, safety
  Delivered target occupancy model, good safety margins, drug formulation strategy, drug metabolism

- Phase 2a: Pilot double blind study in target AD population

  Focus on safety of high dose, efficacy : CSF, imaging and functional outcomes
  Delivered dosing strategy for long-term studies, proof of principle of target engagement and positive functional AD outcomes for next study

- Phase 2b: Clinical proof of concept study program powered for cognition endpoint

  Focus on clinical efficacy in cognition
  Will deliver clinical proof of concept, using sensitive cognition endpoints according to latest FDA guideline, upside for early approval

- Phase 3: Confirmation of Phase 2b results (if required)

SAPHIR – first in patient Phase 2a study

INTENTION

- Using a high dose of PQ912 resulting in a high QC-occupancy –
  to find **both**
  - early-on safety and tolerability signs
    and
  - any signal on the various sensitive secondary exploratory outcome measures – in a relatively short time frame of 12 weeks

- To guide the design of the next study

SAPHIR Phase 2a trial in early AD patients
Objective: safety and early pharmacodynamic effects

SAPHIR Phase 2a trial design

- Seven EU countries, 21 Sites, PI P. Scheltens Amsterdam
- Total number of patients: 120
  - Early stage Alzheimer's Disease
    - MMSE*: 21-30 inclusive
    - Abeta level in CSF below cut-off 638 ng/L
    - p-tau level in CSF above cut-off >52 ng/L
    - Tau/A-beta ratio in CSF >0,52
    - Positive amyloid PET if available
  - "Treatment naïve": no other Alzheimer drug as co-medication
- 1:1 randomization
- 12 weeks treatment, 4 weeks follow up
- Trial completed in 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
- **Physiological function assessments:** EEG and rested state functional MRI to measure synaptic plasticity and neuronal connectivity
- **Molecular biomarkers in CSF:** Abeta pattern, Neurogranin and inflammatory markers,

*Mini-Mental State Examination

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SAPHIR Phase 2a trial in early AD patients

Safety Results

- No significant differences in the number AE or SAE between active and control arm
- Significantly higher number of patients discontinuing within first weeks of treatment with PQ912 800mg q12h compared to placebo
  - Clinically relevant differences in number of patients with skin and GI effects
  - Events appeared early in the study and were fully reversible
- Overall no major safety concern associated with PQ912
- Safety and tolerability are likely to be improved by lower dose, still showing a high enzyme inhibition, and a slower titration regime.

Summary of exploratory efficacy results in SAPHIR trial

CSF:

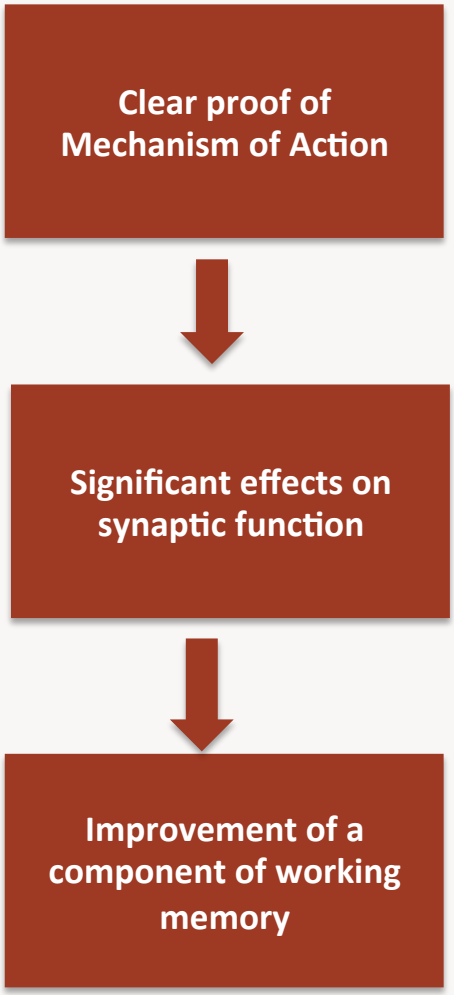
- Strong QC-inhibition, target occupancy about 90%
- Strong trends to reduce the synaptic marker neurogranin, and the inflammatory marker YKL40, which are both enhanced in early AD

EEG:

- Significant effect at the first level of EEG analysis: strong reduction in theta power which is increased in AD
- Post-hoc analysis: significant positive effect on functional connectivity as measured by AEC (amplitude envelope correlation) , p= 0.025, Cohens's d=0.45
  - implicates that PQ912 causes stabilization or improvement of the connectivity of the underlying network, whereas the placebo group declined over time due to disease progression.

NTB:

- Significant improvement in 'one card back', (p=0.050, Cohen's d=0.23) 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)



Results and Conclusions

➢ Results:

- **Primary endpoints**: Safety signal in skin and GI events in the first weeks of treatment period
- **Secondary endpoints**: Very strong target engagement, significant effects on One back Test and on qEEG theta power and encouraging results in the right direction on synaptic and inflammatory CSF markers

➢ Conclusion:

- Although differences between treatment arms were observed we are confident that the drug is safe and well tolerated in the AD population.
- The encouraging positive effects on secondary readouts are supporting the hypothesis of pGlu-Abeta being a synaptotoxic Abeta variant and are making the program attractive to go forward
- Study reveals a positive benefit risk ratio and provides important guidance how to go forward

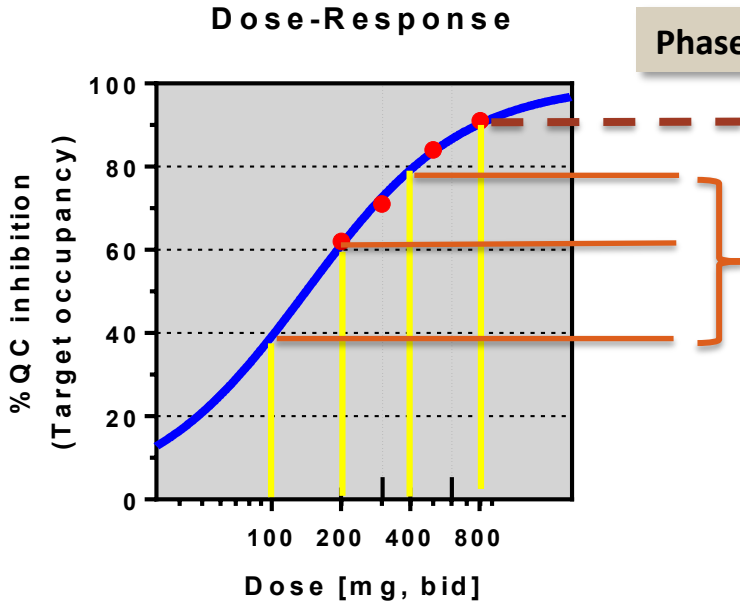
Study reveals a positive benefit risk ratio and provides important guidance how to go forward

Outlook: Overarching Phase 2b Development Strategy

SAPHIR gave highly valuable results regarding dosing and efficacy endpoints / biomarker

- **EU Phase 2b study design - inbuilt newest FDA and EMA guidance for early AD**
  - **Seamless design**:
    - **Stage 1: tolerability dose-titration** (150-600 mg bid): Investigate whether 300 mg bid is adequately tolerated (60 treatment/30 placebo) after 3 month of treatment
    - Re-affirm CSF biomarker and EEG findings from SAPHIR
    - **Stage 2:** if tolerability meets pre-specified criteria (DSMB) - study continues
    - investigate effects on cognition (and BM) with the optimal dose for in total a treatment of 6-7 months duration
    - If safety and biomarker findings positively answered will be used for (Phase 3 planning) and regulatory interaction (end of Phase 2 meetings)
- **US Phase 2b study looking at cognition long-term in collaboration with ADCS/UCSD-** ***synopsis in preparation***
  - mean treatment duration at effective dose 12 months / patient investigating effect on long-term cognition
  - Safety results (interim) will be used for regulatory Phase 3 preparation Efficacy results will be used to kick start phase 3 program
- **If both studies meet primary and key secondary endpoints (sequential testing) option to discuss accelerated / conditional approval**

Dosing option POC study



Phase 2 a: high dose, **90%** Target Occupancy (TO); **800 mg bid**

3 months

Under discussion

Phase 2 POC- Dosing options

- **Doses** between 600 mg bid (titrated) and 100 mg bid
- TO between 40 and 80%
- 70% TO at a dose of 300 mg bid

Longer term treatment

- Pot. adaptive design, futility / interim analyses

● **Target occupancy obtained in Phase 1 in healthy elderly** *(Lues et al 2015)*

EU Phase 2b Study SAPHIR 2 Objective: Clinical Proof of Concept in Cognition – changes possible

Trial metrix and design

- 10 EU countries, PI P. Scheltens, Amsterdam
- Total projected: 250 patients
  - Early stage Alzheimer's Disease
    - MMSE*: 21-30 inclusive
    - CSF amyloid & tau signature positive
  - Patients on SoC or treatment naïve
- 12 weeks treatment with 300mg (bid) for initial safety read out in first 90 patients
- Patients go to individually highest tolerated dose (300 or 600mg bid)
- Minimum treatment duration per patient 36 weeks up to 84 weeks (average 56 weeks)
- Evaluation methodology: Comparison of the slope of progression of cognitive decline

Objectives and read-outs

- **Primary objective:** To assess the efficacy of PQ912 on cognitive function in early AD (NTB)
- **Secondary objectives:** efficacy on activities of daily living, effect on functional EEG and synaptic brain connectivity
- **Exploratory readouts:** CSF based biomarker and MRI imaging of brain and hippocampal volume

Tentative timelines

- **Protocol ready: Q2 2018**
- **FPI: Q4 2018, LPI: Q2 2020, LPO: Q2 2021**
- **Safety futility: Q4 2019; key results Q3 2021**

*Mini-Mental State Examination

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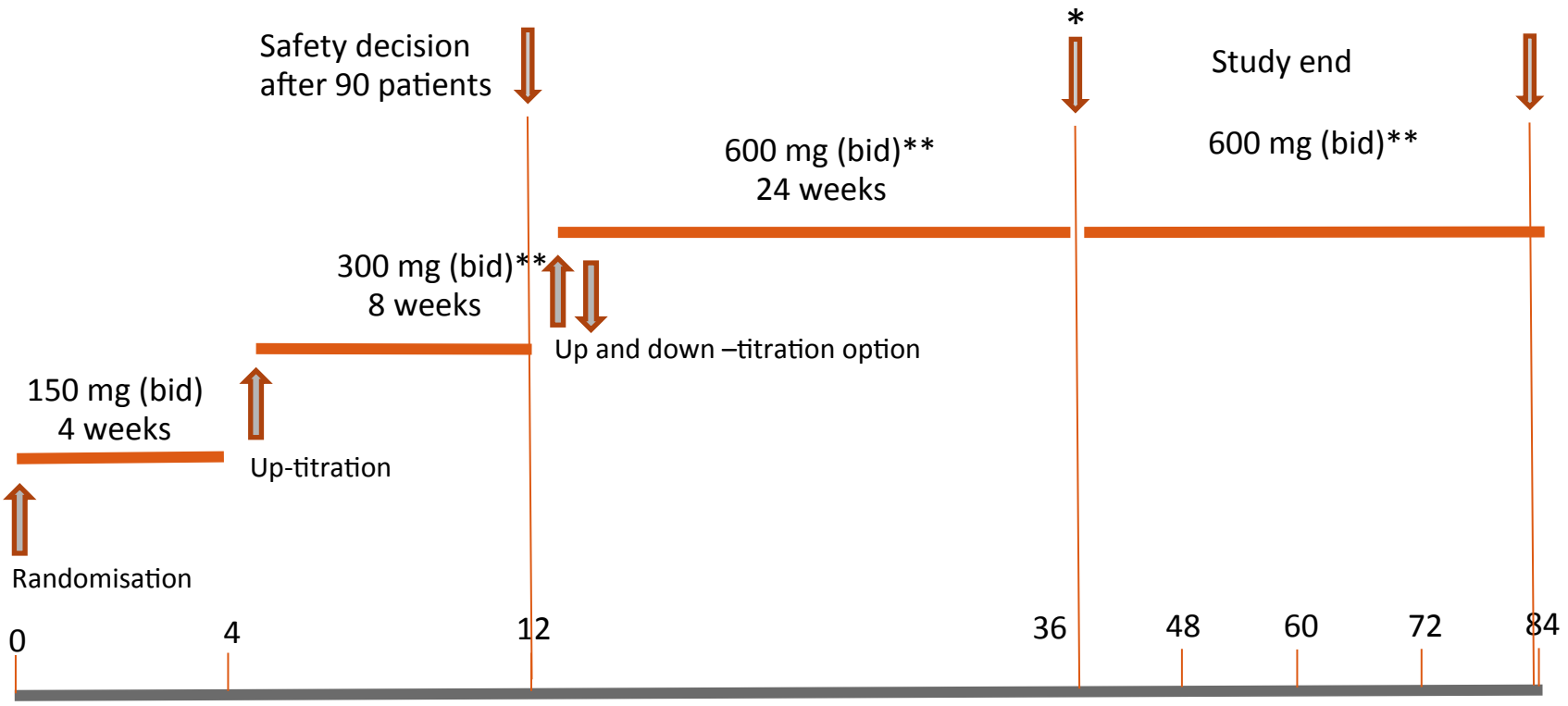
SAPHIR 2 – Patient dosing and time schedule



* All patients will have a study duration of at least 36 weeks on treatment. The earlier randomised patients will continue after week 36 until the last patient in the study reached week 36. Depending on timing for each individual patient this means treatment up to week 36, week 48, week 60, week 72 **or** week 84

** Subjects who experience AEs compromising the tolerance of the treatment or the safety and wellbeing of the subjects can reduce the dose anytime back from 300 mg (bid) to 150 mg (bid) during weeks 5-12 and from 600 mg (bid) to 300 mg (bid) during weeks 13 to 84.

Corporate Review (1)

General Meeting of Shareholders on June 13, 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.

Corporate Review (2)

Supervisory Board

- Shareholder meeting on 13 June 2017, re-elected Dr Erich Platzer, Dr Dinnies von der Osten and Dr Jörg Neermann as Supervisory Board Members.
- 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.

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Outlook

Mid-term focus of Probiodrug's business activities are 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.

News flow *(selection)*

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* combination therapy with BACE inhibitor
- ✔ PQ912 Preclinical assessment of potential in Huntington Disease and Down syndrome
- ✔ **Start planning Phase 2b program with PQ912**
- ✔ PBD-C06 Antibody; Unique selling points published, stably expressing cell line secured
- ✔ SAPHIR Data- Late Breaking Oral Communication at CTAD 2017 in Boston, MA, USA.

2018

- ✔ NIH grant application submitted
- ☐ Secure non-dilutive funding components
- ☐ Apply regulatory agency approvals for European Phase 2b
- ☐ IND filing for PQ912 US trial
- ☐ PQ912 POP* combination therapy with BACE inhibitor

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

Financial Calendar

▪ 15 May 2018	Interim Management Statement Q1 2018
▪ 21 June 2018	Annual General Meeting of Shareholders
▪ 30 August 2018	Interim Report, half year results 2018
▪ 29 November 2018	Interim Management Statement Q3 2018

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Operational Review (1)

PQ912

- January 2017: **Completion of recruitment for the SAPHIR Phase 2a** study of Glutaminyl Cyclase Inhibitor PQ912 in early Alzheimer's disease patients. A total of 120 patients have been randomised, surpassing the 110 patients planned in the study protocol.
- April 2017: Probiodrug announced **Last Patient Last Visit (LPLV)** reached in the SAPHIR Study.
- 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 and/ or 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.

Operational Review (2)

PQ912

- 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.
- November 2017: **CTAD 2017**, Boston, USA: Prof Philip Scheltens, MD, PhD, Principal Investigator of the SAPHIR study, presented the data from Phase 2a SAPHIR Study 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*".

Operational Review (3)

PQ912 - Combination therapies

- March 2017: Probiodrug presented at the **13th International Conference on Alzheimer's and Parkinson's Diseases (AD/PD™ 2017)**

  - 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

    - "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.

Operational Review (4)

PQ912 – Huntington's disease

- April 2017: 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 - most common inherited neurodegenerative disorder where, due to a mutation, the poly-glutamine amino acid sequence is expanded in a protein called huntingtin (HTT).
  - 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 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. 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.

Operational Review (5)

PBD-C06

- Monoclonal antibody targeting pGlu-Abeta, while leaving non-toxic forms of Abeta untouched
- Currently in preclinical stage
- Successfully humanized and de-immunized
- Unique profile - IgG1 isotype − no complement activation to prevent complement triggered inflammation
- 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

PQ1565

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

Operational Review (6)

Publications

- ***13th International Conference on Alzheimer's and Parkinson's Diseases (AD/PD™ 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. Additonally, 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).

Operational Review (7)

Publications

- ***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-β-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".*

Operational Review (8)

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.