PLUVIA

Pluvia Biotech as

Non-confidential company presentation
April 2024

Pluvia in a Nutshell

- Preclinical seed-stage biotech spin-out from University of Bergen (Norway), founded in 2015 by Prof. Aurora Martinez based on extensive knowledge of Pharmacological Chaperones to restore natural enzymatic activity
- Developing novel oral therapy for Phenylketonuria (PKU) treating the underlying cause of disease
- Lead candidate shows robust pre-clinical Proof of Concept in PKU models and clean safety
- Targeting a ±€15M Series A round to show Clinical Proof of Concept in both Phase 1 and Phase 2 to enable subsequent licensing
- Predictable short clinical pathway thanks to Phe-levels as an accepted biomarker by regulators
- PKU is an established, sizeable and growing market (USD 610m; 10YoY CAGR >6%) with high unmet need (dietary burden, insufficient treatment options)

Team With Hands-On Experience and Expertise

Willem van Weperen, CEO
Senior biotech leader with more than 25 years of experience in development and commercialization of therapies for patients with rare diseases in companies like Genzyme, Amicus, Myokardia and Intercept.

Aurora Martinez, CSO and Co-founder
MSc, PhD. Professor, Department of Biomedicine, Univ. of Bergen. Expertise in structural biology and early-stage drug discovery applied to mechanisms and treatment of phenylketonuria and parkinsonisms.

Ann Kari Grindheim, Director non-clinical
MPharm, PhD. >10 years experience from cell biology and biotechnology research and development. Several years of experience with drug development for PKU.

Torgeir Vaage, CFO
More than 15 years of combined experience from biotech and financing. Multiple CFO and CEO roles in early-stage life science companies. Former senior equity analyst ABG Sundal Collier / Handelsbanken, management consultant AT Kearney

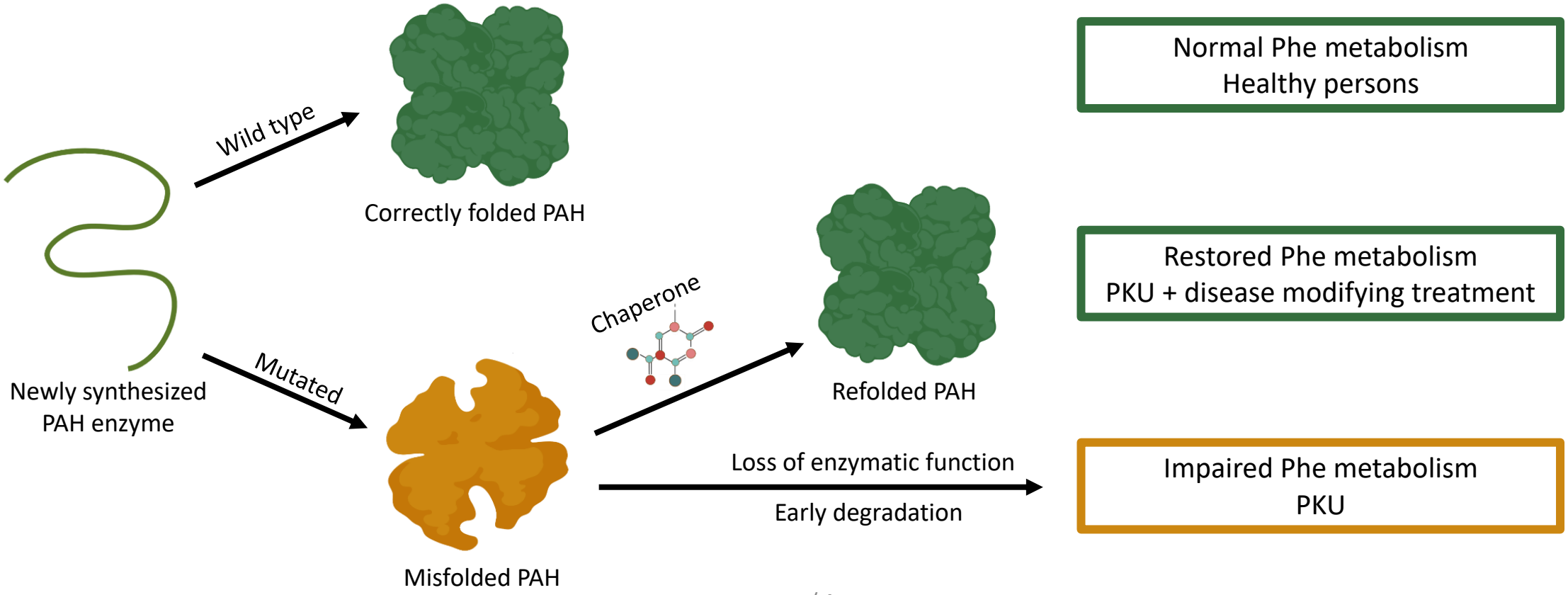
Mikael Thomsen, Drug dev. Consultant
Over 25 years of drug development experience from pharma and biotech, responsible for progressing numerous compounds from preclinical through phase I/II as well as being a successful biotech entrepreneur.

Karina Prestegård, Senior researcher
MSc, PhD. >10 years experience from work with animal models of disease. Expertise in planning, executing and analyzing animal experiments using mouse models for PKU.

Pharmacological Chaperone Concept

Pharmacological chaperone therapy (example PKU)

Oral compound that stabilizes and rescues the activity of mutant Phenylalanine Hydroxylase (PAH)



Lead Indication: PKU

- Phenylketonuria (PKU) is the most common inborn error of metabolism (1:10 000 to 1:20 000)
- Caused by dysfunction of PhenylAlanine Hydroxylase (PAH) enzyme, leading to loss of ability to metabolize Phenylalanine (Phe)
- Consequence: normal food = neurotoxic
- In untreated PKU, toxic levels of Phe cause mental retardation
- PKU requires life-long treatment, including burdensome strict diet

Suboptimal Treatment Options for PKU Patients

Current, basic standard of care:

- Since 1960s: **Diet without Phe**
  - Avoids mental retardation, but…
  - Bad taste and smell
  - High psychological & social burden
  - Low quality of life

> *"Adding **10g of protein** per day would be a **game changer for my family**"*
> — Parent of PKU Patient

> *"If my boys could **just eat a slice of normal bread** or a serving of regular pasta it would be huge"*
> — Parent of PKU Patient

> *People think this isn't too bad, I look okay. But this is **a lifelong burden.** It's a challenge to think straight, to plan my day.*
> — Adult PKU Patient

Additional treatments:

- **Kuvan (sapropterin, BH4 => now generic):**
  - Is the cofactor of PAH for mild/moderate PKU
  - Requires patients to remain on diet
  - Targets a subgroup of the patients (20% - 30%)
  - Net price originally at $80-120k/pt/yr, peak sales $457M in 2020
- **Palynziq (pegvaliase):**
  - Pegylated, non-human enzyme (Phenylalanine Ammonia Lyase)
  - Can give strong allergic reactions (Black Box warning)
  - Approved for adults only (market share is 10-15%)
  - Net price at $160-200k/pt/yr, peak sales $304M in 2023

PKU is an Attractive Commercial Opportunity

Base case peak sales opportunity: ±$750M across the US and Europe

US Peak Sales Potential in PKU ($m)

Penetration	Annual price per patient ($)							
	60,000	80,000	100,000	120,000	140,000	160,000	180,000	200,000
5%	28	37	47	56	65	74	84	93
10%	56	74	93	112	130	149	168	186
15%	84	112	140	168	196	223	251	279
20%	112	149	186	223	261	298	335	372
25%	140	186	233	279	326	372	419	466
30%	168	223	279	335	391	447	503	559
35%	196	261	326	391	456	521	587	652
40%	223	298	372	447	521	596	670	745

EU Peak Sales Potential in PKU ($m)

Penetration	Annual price per patient ($)							
	20,000	40,000	60,000	80,000	100,000	120,000	140,000	160,000
5%	14	27	41	55	68	82	95	109
10%	27	55	82	109	136	164	191	218
15%	41	82	123	164	204	245	286	327
20%	55	109	164	218	273	327	382	436
25%	68	136	204	273	341	409	477	545
30%	82	164	245	327	409	491	572	654
35%	95	191	286	382	477	572	668	763
40%	109	218	327	436	545	654	763	872

Assumptions

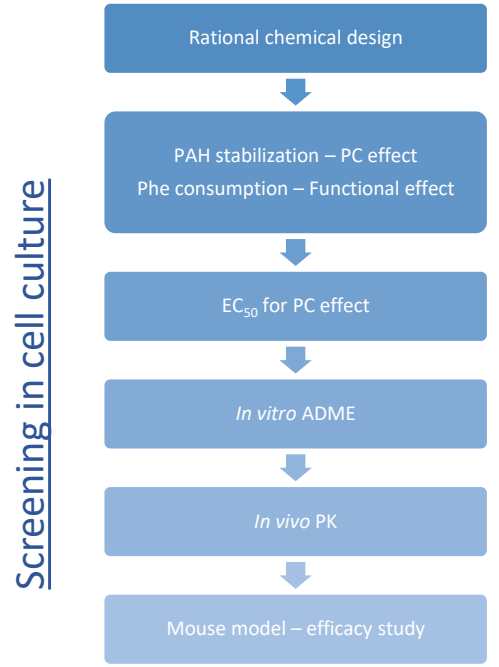
Number of patients
- There are c. 16,500 – 17,300 patients in the US and ±25,000 PKU patients in Europe (70% of which are adults)
- Estimated that ± 65% of adult patients are 'out-of-clinic'
- This results in 9,310 accessible paediatric and adult PKU patients in the US and 13,625 in Europe

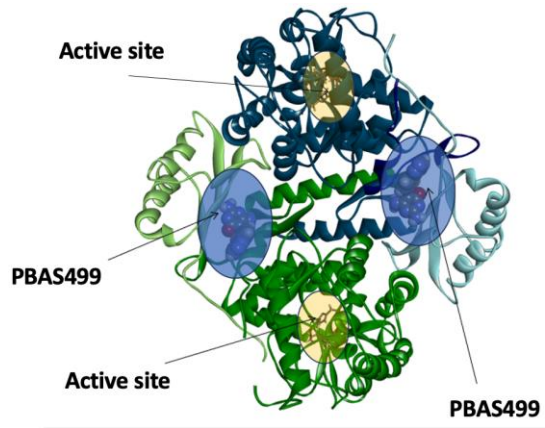
Price
- As a benchmark, Kuvan had an average price of ±$100k / year in the US before LoE (with an average patient weighing 50 – 55kg) – although could be up to $ 180k/year for adults (generics are currently priced at a ±80% discount)
- Meanwhile, Palynziq is priced at ±$200k / year in the US
- **US price** assumed at **$180k/year**, in line with Palynziq
- **European price** discounted to **$100k/year** vs. US in line with other indications

Penetration
- Assuming a **40% response rate** for the product (with potential for upside), **market penetration** would be capped accordingly to **25%** at peak

Drug Discovery Pathway to Development Candidate

- Initial stabilizers of PAH were identified by high-throughput screening of a large commercial compound library
- Initial hits were the basis for chemical derivatization to obtain improved PCs for PAH
- A total of >400 compounds have been synthesized in the medicinal chemistry campaign
- This work in PKU resulted in 1 lead compound (PBAS499), now nominated as development candidate, with 2 additional molecules as back-up
- PBAS499, predicted to be a structurally important allosteric binder:
  - binding between regulatory and catalytic domain
  - binding site different from active site where BH4 binds

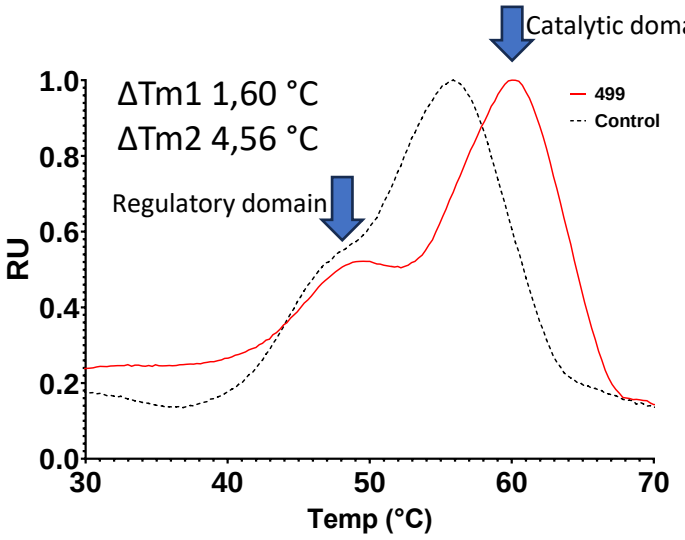




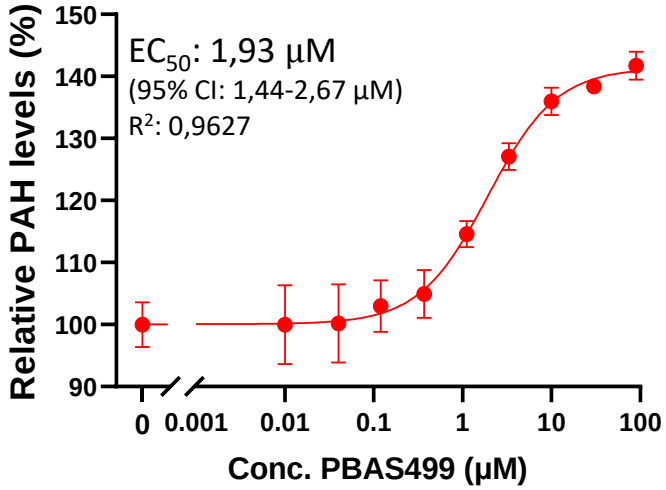
Demonstrating the Chaperone Mechanism of Action

Pharmacological Chaperone effect of lead compound PBAS499 demonstrated in vitro

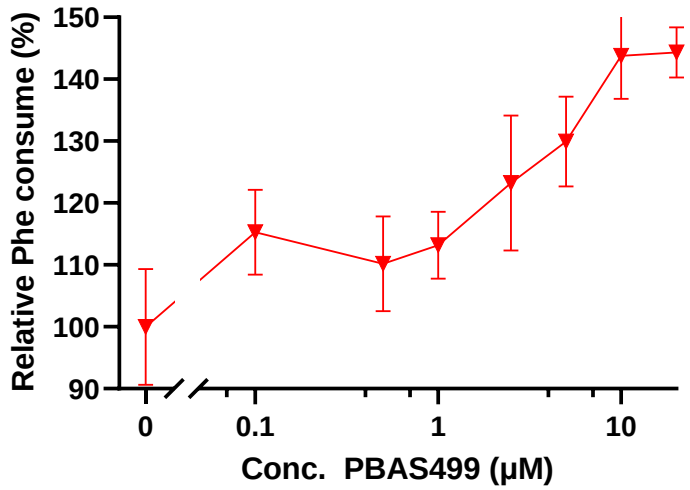
Differential scanning fluorimetry (DSF)



PAH protein level in cell culture



Phe consumption in cell culture



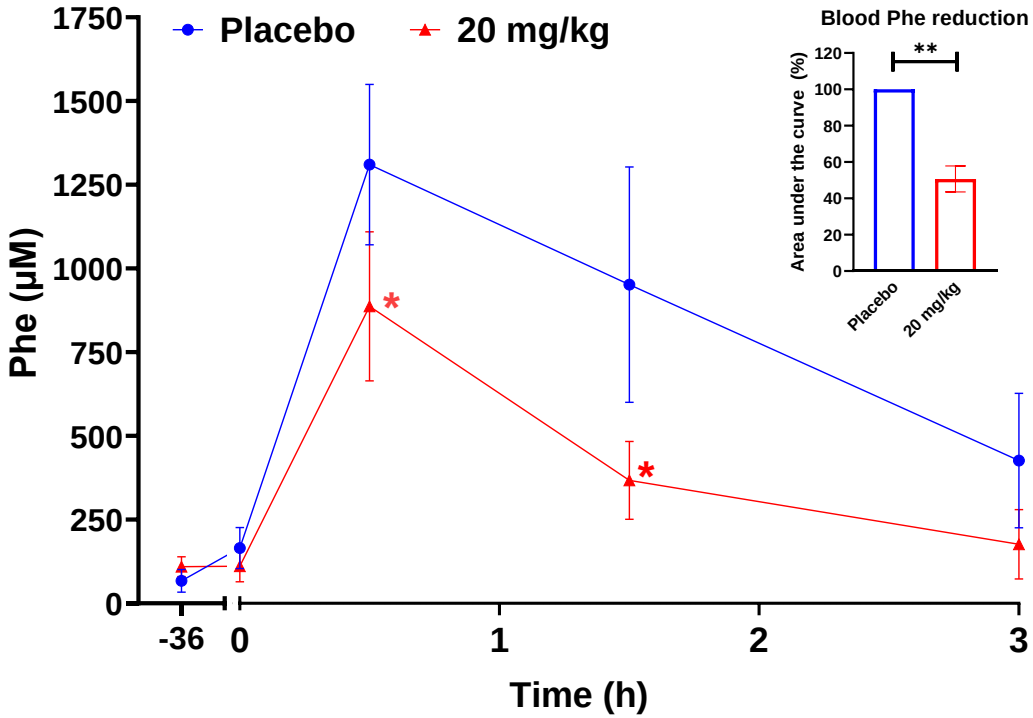
Stabilization of protein conformation demonstrated by DSF

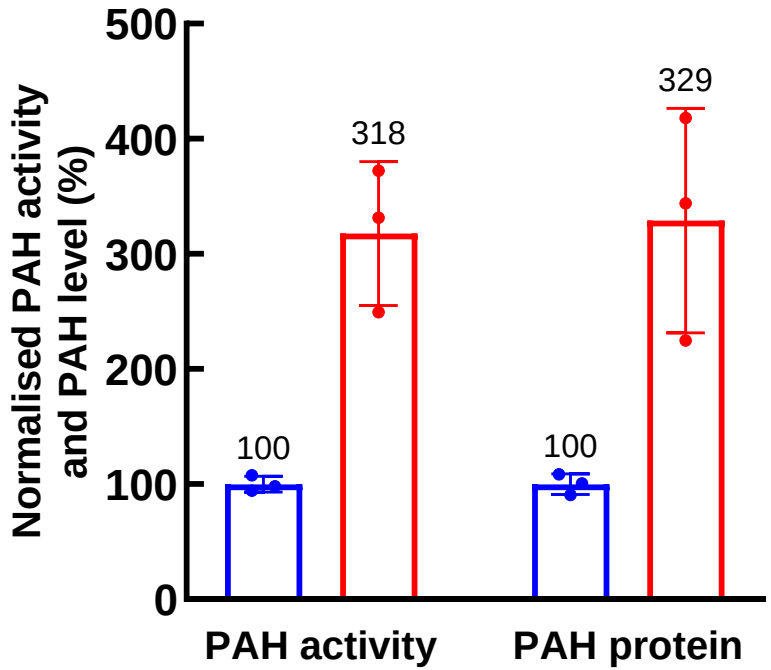
Increased PAH protein levels in cell culture

Increased Phe consumption in cell culture medium

Preclinical PoC of PBAS499 Monotherapy

PBAS499 strongly decreases Phe-levels in the mouse model with human PAH-R261Q mutation



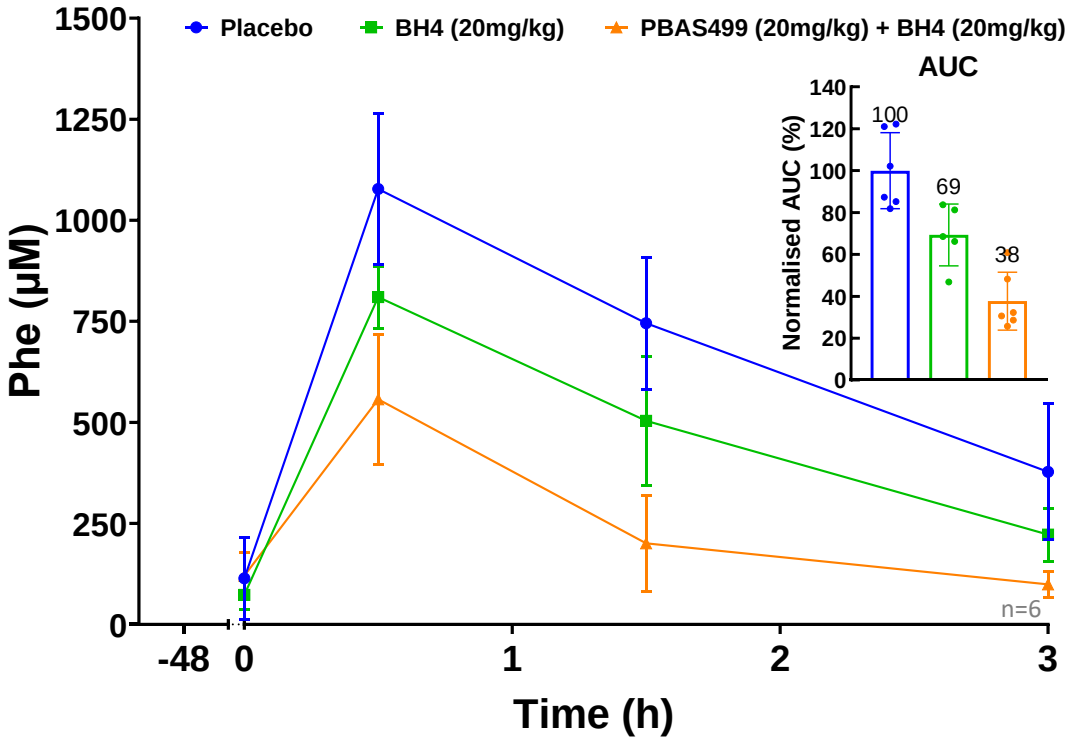


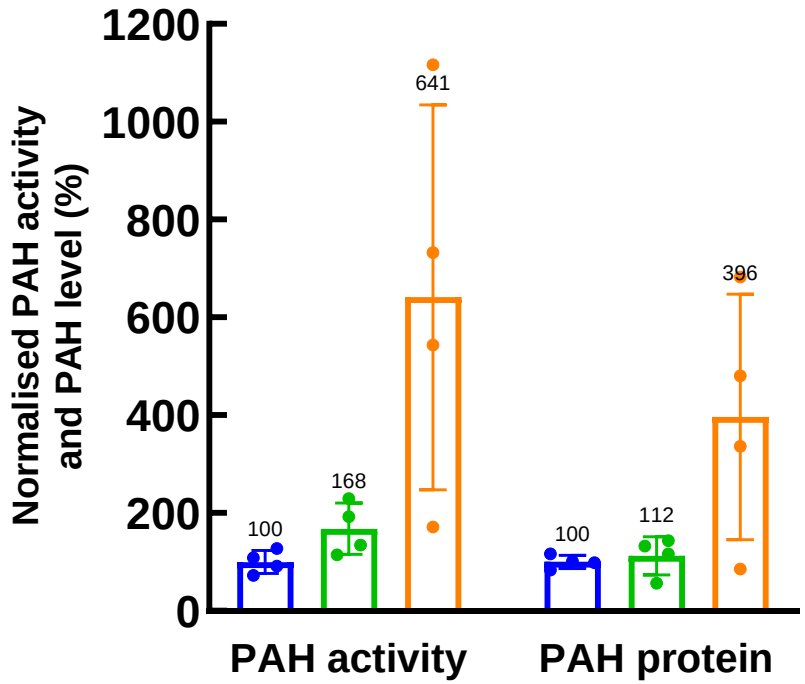
49% blood Phe reduction with PBAS499 at 20 mg/kg

Increased PAH activity and protein levels in PBAS499-treated mice

Preclinical PoC of PBAS499 Combination Therapy

Even larger effect of PBAS499 in combination with BH4 (Kuvan)* due to different Mechanism of Action





62% blood Phe reduction
with combination of PBAS499 and BH4

Increased PAH activity
– but not PAH protein – in BH4 group

*: *Commercially relevant since BH4/Kuvan is now generically available at low price*

PBAS499 Preclinical Safety

Clean in all in vitro de-risking assays

• Mini-AMES – Mutagenic potential	Not mutagenic
• hERG – Cardiotoxicity	IC_{50} >100 µM
• CYP inhibition – Drug-drug interactions	IC_{50} >25 µM
• Cerep screen – Off-target interactions	No binding

Maximum tolerated dose (MTD) studies

- Exploratory, 3-day dosing, toxicity studies in rats (100, 500, 1000 mg/kg/day) and in dogs (100, 200, 400 and 600mg/kg/day)
- All planned dose levels achieved
- No mortality, serious adverse effects or gross necropsy findings
- PBAS499 seems well tolerated <u>=> large therapeutic window</u>

Strong Protection for PBAS499 and Back-ups

IP:

- ☑ Fresh CoM patent covering PBAS499 filed in August 2023
- ☑ Separate from earlier awarded 2015 patent family
- Potential additional patent filing based on combination with salt(s)

Other protection:

- ☑ Rare Pediatric Disease Designation (RPDD) awarded by FDA
- ☑ US Orphan Drug Designation (ODD) awarded by FDA
- EU ODD filed January 2024

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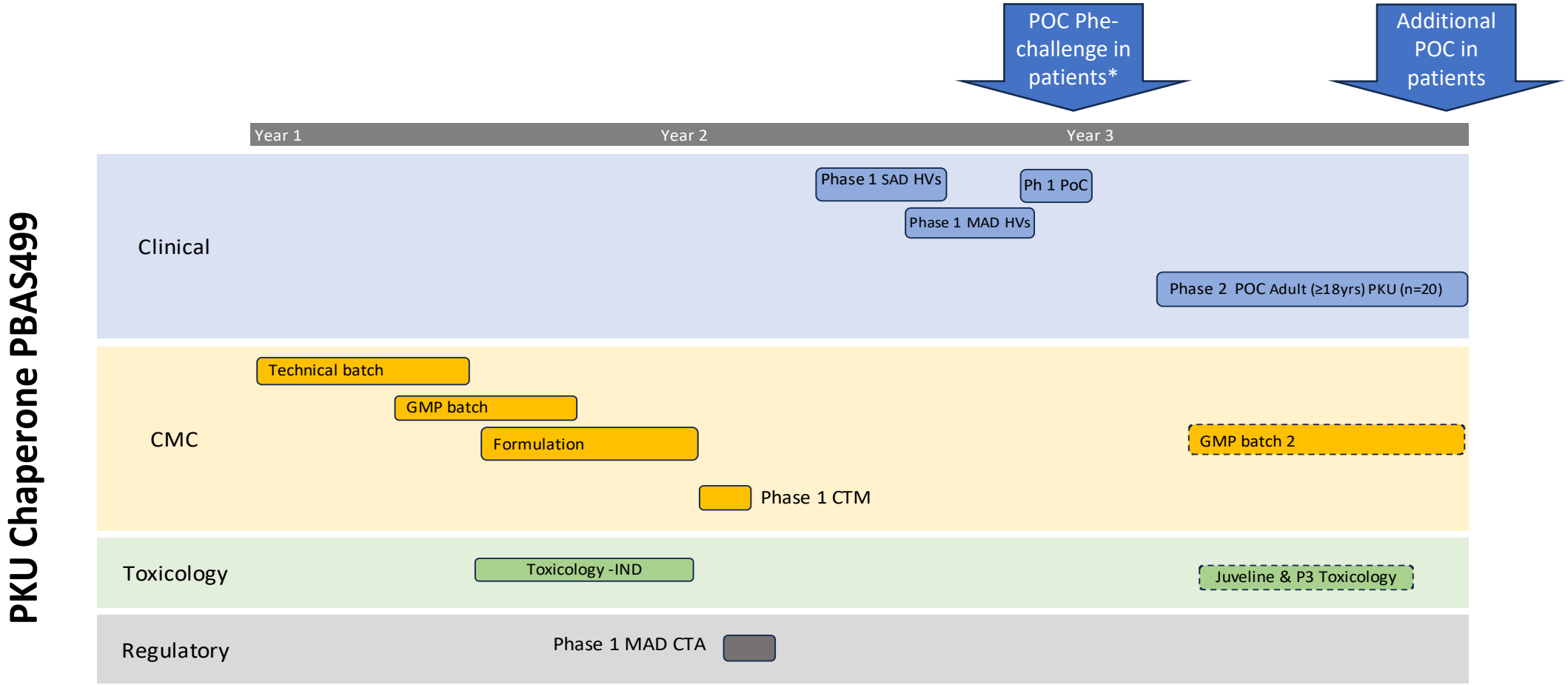
Series A Planning: Deliver Clinical POC in Ph1 and Ph 2



	Year 1	Year 2	Year 3
Funding	€3-5M	€5M	€5M

**: Innovative Ph1 design with Phe-challenge in selected PKU Adults in Phase 1 Unit in last MAD cohort measuring blood Phe-levels pre- and post-treatment*

Series A Budget supports Clinical POC in 2 to 3 Years

Costs (EURM)	Year 1	Year 2	Year 3	TOTAL
Corporate	0.9	1.0	1.0	**2.9**
Internal R&D	0.6	0.3	0.3	**1.2**
CMC	1.7	1.0	0.0	**2.7**
IND tox	1.6	0.7	0.0	**2.3**
Phase 1 SAD/MAD	0.0	1.7	1.1	**2.8**
Phase 2 POC	0.0	0.0	2.5	**2.5**
Total	**4.8**	**4.7**	**4.9**	**14.4**
Contingency (ca 10%)				1.6
Soft funding				-1.0
SERIES A				**15.0**

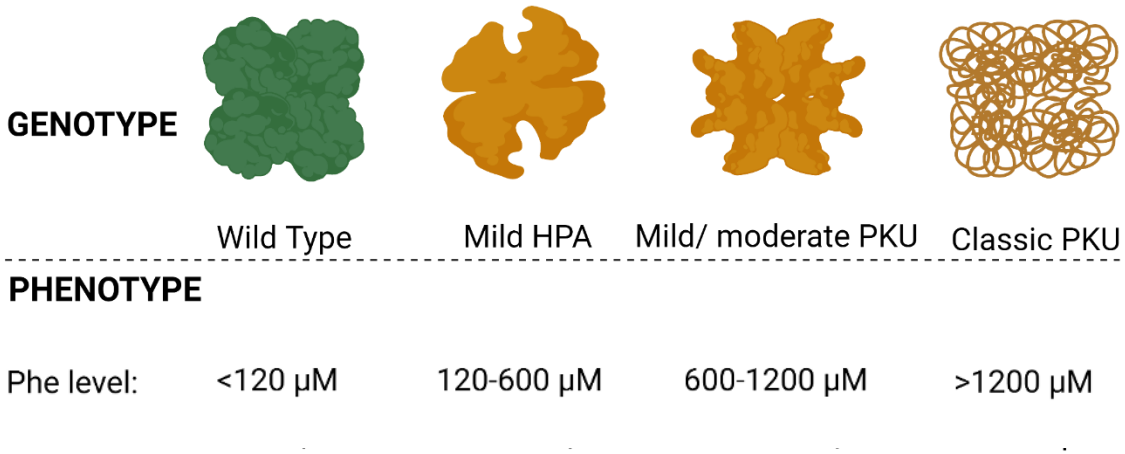
Pluvia's Straightforward Opportunity

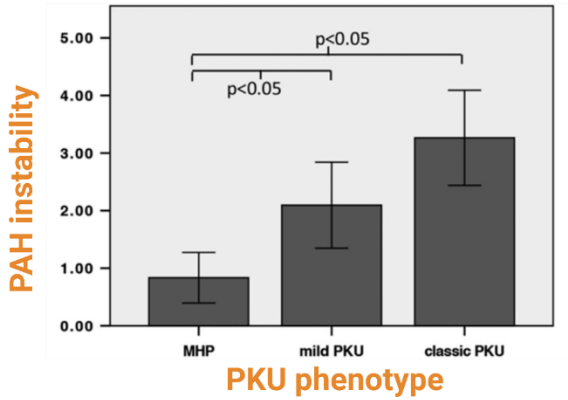
- ☑ High unmet medical need in PKU
- ☑ MoA for PBAS499 demonstrated and modelled
- ☑ Preclinical PoC for PBAS499 as monotherapy and BH4 combo
- ☑ Safety of PBAS499 de-risked in-vitro and in-vivo
- ☑ Oral small molecule with simple and efficient CMC
- ☑ IP filed Aug 2023, US RPDD and ODD obtained, EU ODD expected
- ☑ Short timelines: Phase 1 with PoC in 2025, Phase 2 in 2026
- ☑ Efficient path to market: accepted Phe-reduction endpoint
- ☑ Early interest from rare disease biopharma
- ☑ Small capable team with strong external connections
- ☑ Single digit post-money

Thank you!

Back-up slides

Genotype/Phenotype Spectrum allows for PAH correction





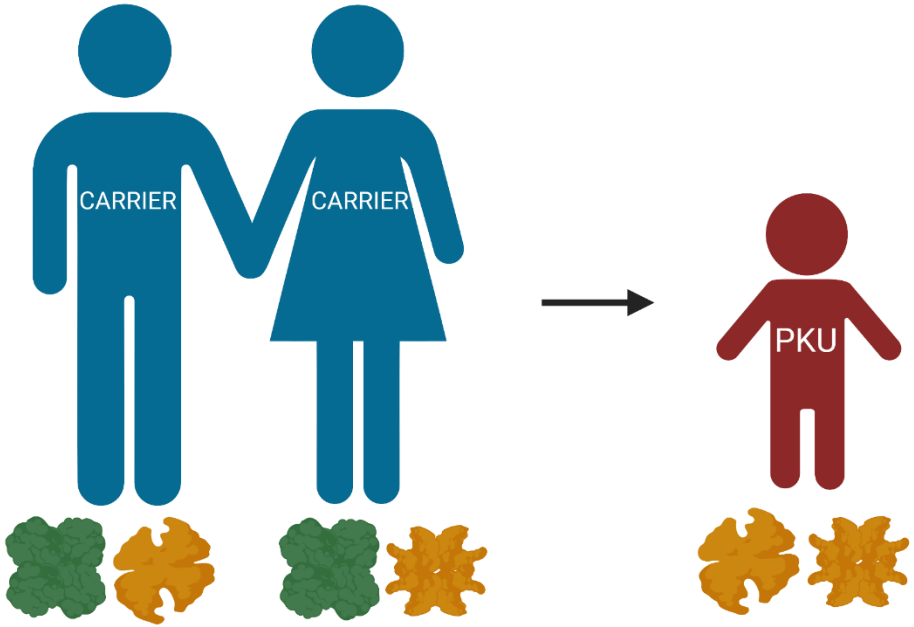
Increased misfolding

↓

Elevated PAH instability

↓

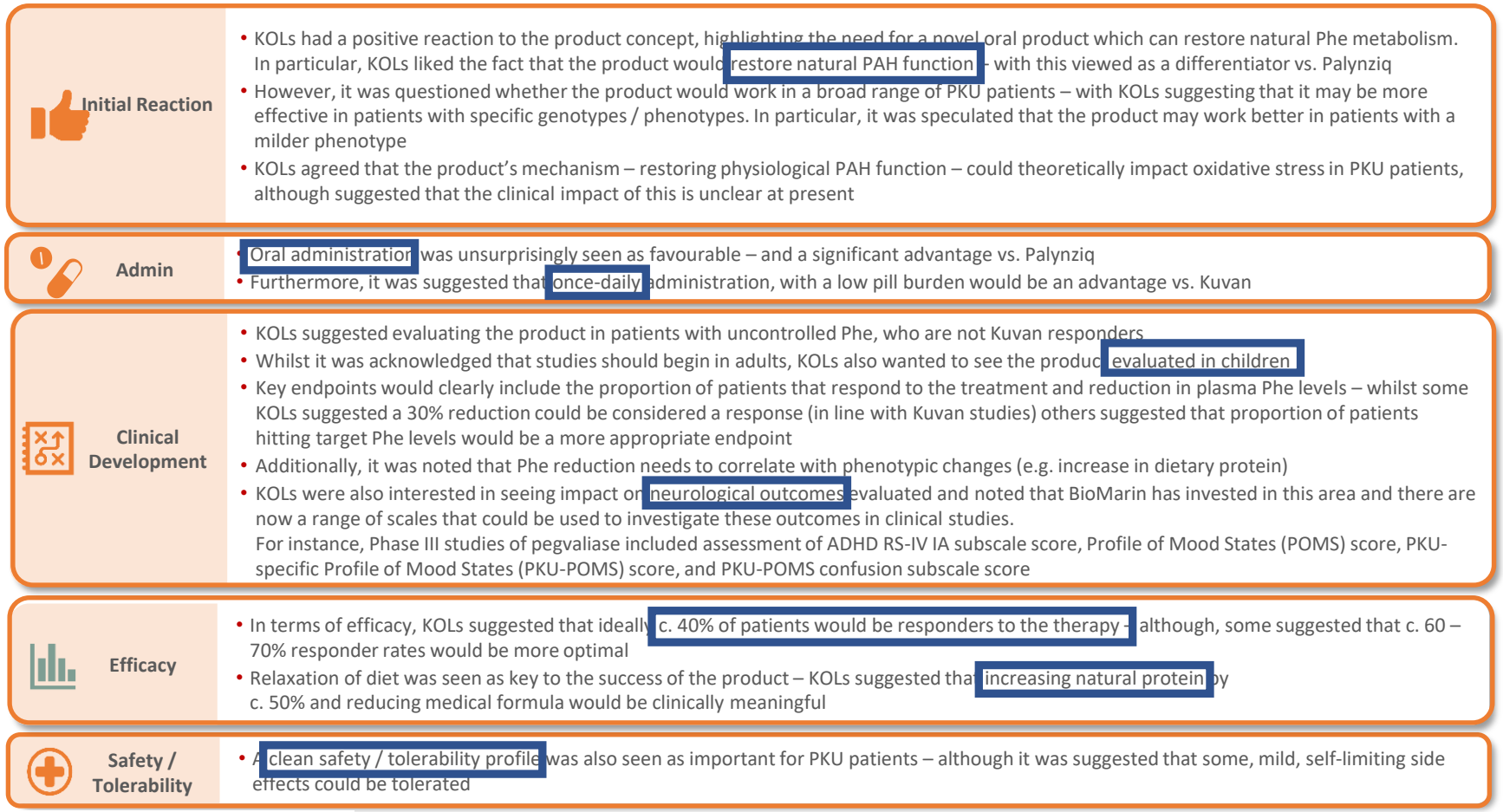
Worse phenotype



- 758 PAH mutations published (Hillert et al. 2020)
- Currently even more reported in BIOPKU database
- Allele Frequency of all missense mutations is ±70%
- >75% of PKU patients have 2 different mutations
- High variability in phenotype (blood Phe-levels)

Attractive Target Product Profile

- KOLs had a positive reaction to the product concept, welcoming a novel, oral product that could restore natural Phe metabolism:



Other Therapeutic Options have Limitations

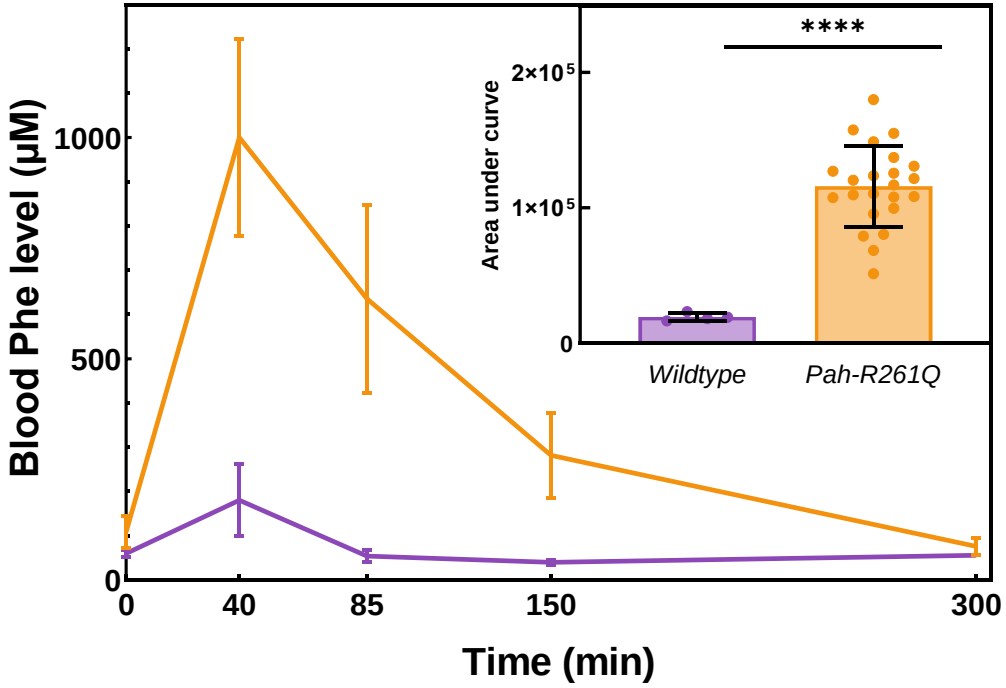
Current and future competitive landscape				Independent of BH4 response	For Adults and Pediatrics	Convenient for patients	Simple manufacturing	**Treating the PAH deficiency**
Marketed								
Kuvan	Biomarin	Approved	Oral small molecule for BH4 responders only Once daily	✗	√	√	√	✗
Palynziq	Biomarin	Approved	SC injection for adults only Once daily, US PI Boxed Warning*	√	✗	✗	✗	✗
In development								
Sepiapterin	PTC	Phase 3 completed	Oral small molecule for BH4 responders only Once daily	✗	√	√	√	✗
SYNB1934	*Synlogic*	*Phase 3 started 2H23*	*Genetically engineered gut bacteria* *=> **Discontinued due to lack of effect (Feb'24)***	√	√	✗	✗	✗
JNT-517	Jnana	Phase 1/2 ongoing	Oral small mol. (aimed at kidney transporter removing all 15 of 20 neutral AAs). Twice daily	√	√	√	√	✗
SAR444836	Sanofi	Phase 1/2 started 3Q23	IV-administered AAV Gene therapy of human PAH gene. Study completion expected in 2027	√	√	√	✗	√
Pharmacological chaperone	**Pluvia**	**Phase 1 early 2025**	**Oral small molecule** **Potentially once daily**	√	√	√	√	√

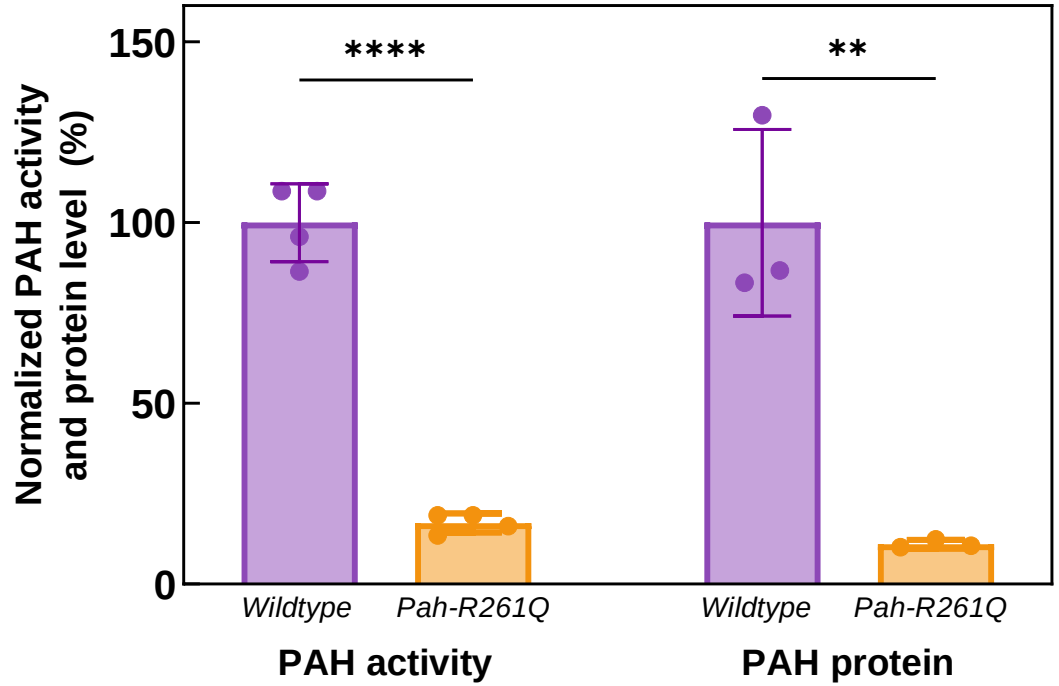
Few are addressing the underlying cause of the disease

*: Palynziq Boxed Warning: "Anaphylaxis at any time". "Requires autoinjectable epinephrine at all times"

Pluvia's Unique Mouse Model* for PKU

Clinically relevant model with prevalent human mutation based on Phe-level as the approved regulatory endpoint





<u>Human</u> mutation: PAH-R261Q

- Causes mild to moderate PKU phenotype in humans
- Elevated blood Phe in mice after a Phe challenge

Clinically relevant characteristics

PAH-R261Q mice have 10-20% PAH activity and protein levels compared to wildtype mice

**: Proprietary PAH-R261Q model is part of a research collaboration with an undisclosed biopharma partner*