BEAM-304: a platform of base editing therapeutics for patients with phenylketonuria

FASEB Genome Engineering: Research and Applications

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Michael Packer[1], Bethany Winans[1], Christopher Fincher[1], Xiao Wang[2], Dominique Leboeuf[1], Jeremy Decker[1], Adam Camblin[1], Serena Moge[1], Marlena Sorbello[1], Lei Johnson[1], Kelly Colletti[1], Rodrigo Laureano[1], Rebecca Ahrens-Nicklas[2], Kiran Musunuru[2], Gopi Shanker [1]

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Beam THERAPEUTICS

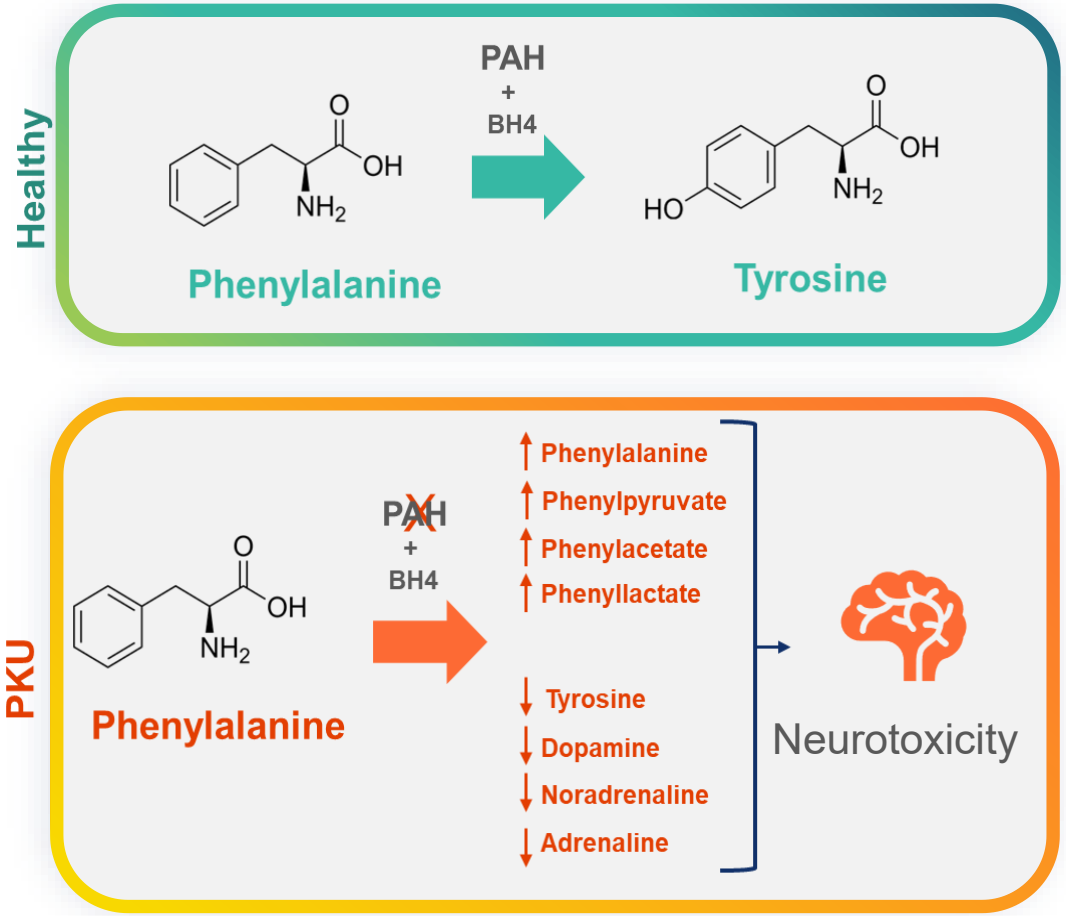
DISCLOSURE

- I am a Beam employee and shareholder

PKU: Disease overview & current standard of care

Phenylketonuria (PKU) is a genetic metabolic disease in which failure to metabolize phenylalanine leads to neurotoxicity

- PKU is inherited via recessive mutations in the *PAH* gene (global incidence of 1:24,000 births[1])
- Loss of hepatic phenylalanine hydroxylase (PAH) activity results in failure to metabolize Phe into Tyr
- Elevated blood Phe results in neurotoxicity through mechanisms including deficiencies of other amino acids and neurotransmitters

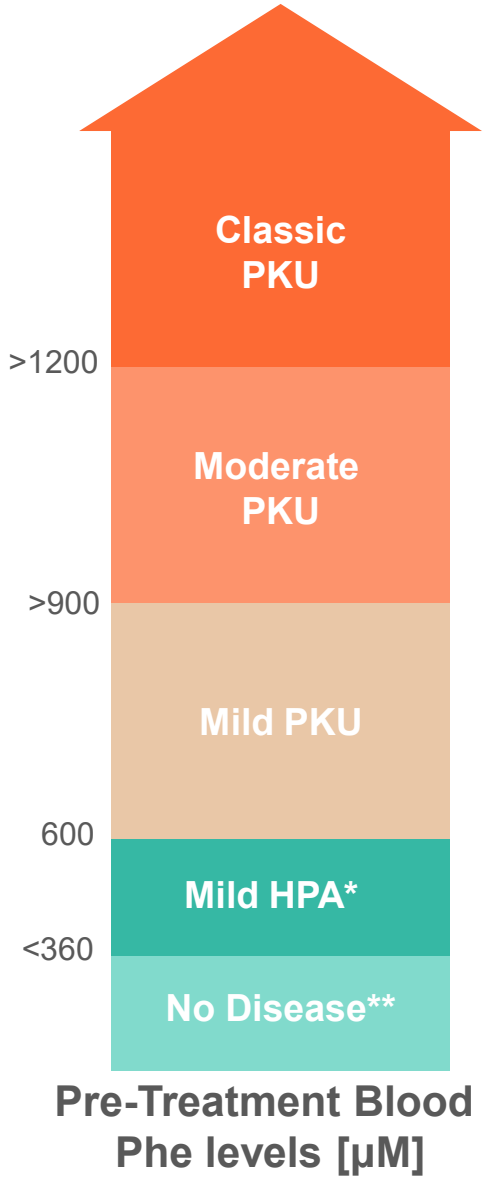


1. Hillert, Alicia et al. The American Journal of Human Genetics, Volume 107, Issue 2, 234 – 250

Neurotoxic manifestations of elevated blood Phe vary over the lifetime of patients with PKU

- Patients are often identified by newborn screening and can be loosely categorized by blood Phe level and/or genotype

- Symptoms/sequelae of elevated blood Phe (generally >360 µM)
  - In children: impaired brain development, intellectual disability and seizures
  - In adults: cognitive impairment (e.g., confusion, headaches, impaired decision making), anxiety, depression and ADHD
  - During pregnancy: microcephaly in their newborns (even if newborn does not have *PAH* mutations)



*HPA: hyperphenylalaninemia
**Normal Phe <120; treatment target <360

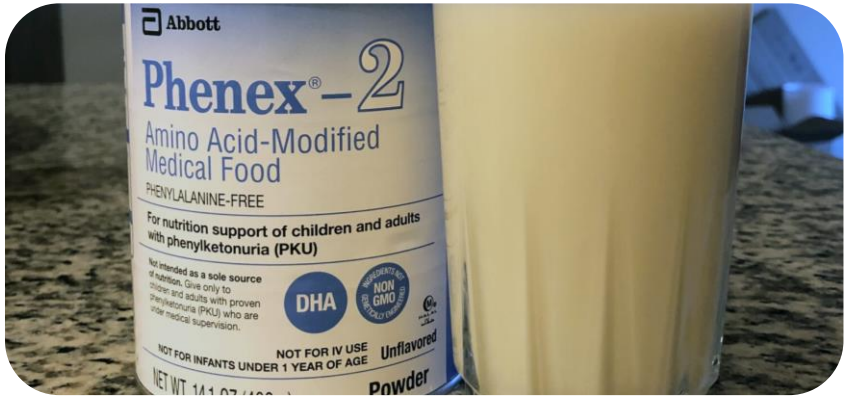
PKU management requires marked diet restriction and medical food; therapies can increase Phe tolerance in some patients

- **Lifelong, Phe-restricted diet:** Phe exists in most foods (meat, dairy, grains, vegetables and fruits), severely restricting diet and requiring medical food to enable adequate protein intake
- **BH4 therapy:** a cofactor used to stimulate PAH enzyme in those with residual enzymatic activity
- **Enzyme substitution therapy:** ~65% of patients achieve Phe <360 µM, but requires frequent injections and comes with risk of side effects (including anaphylaxis)

Most classical PKU patients can handle only 5-10 g of protein/day from diet

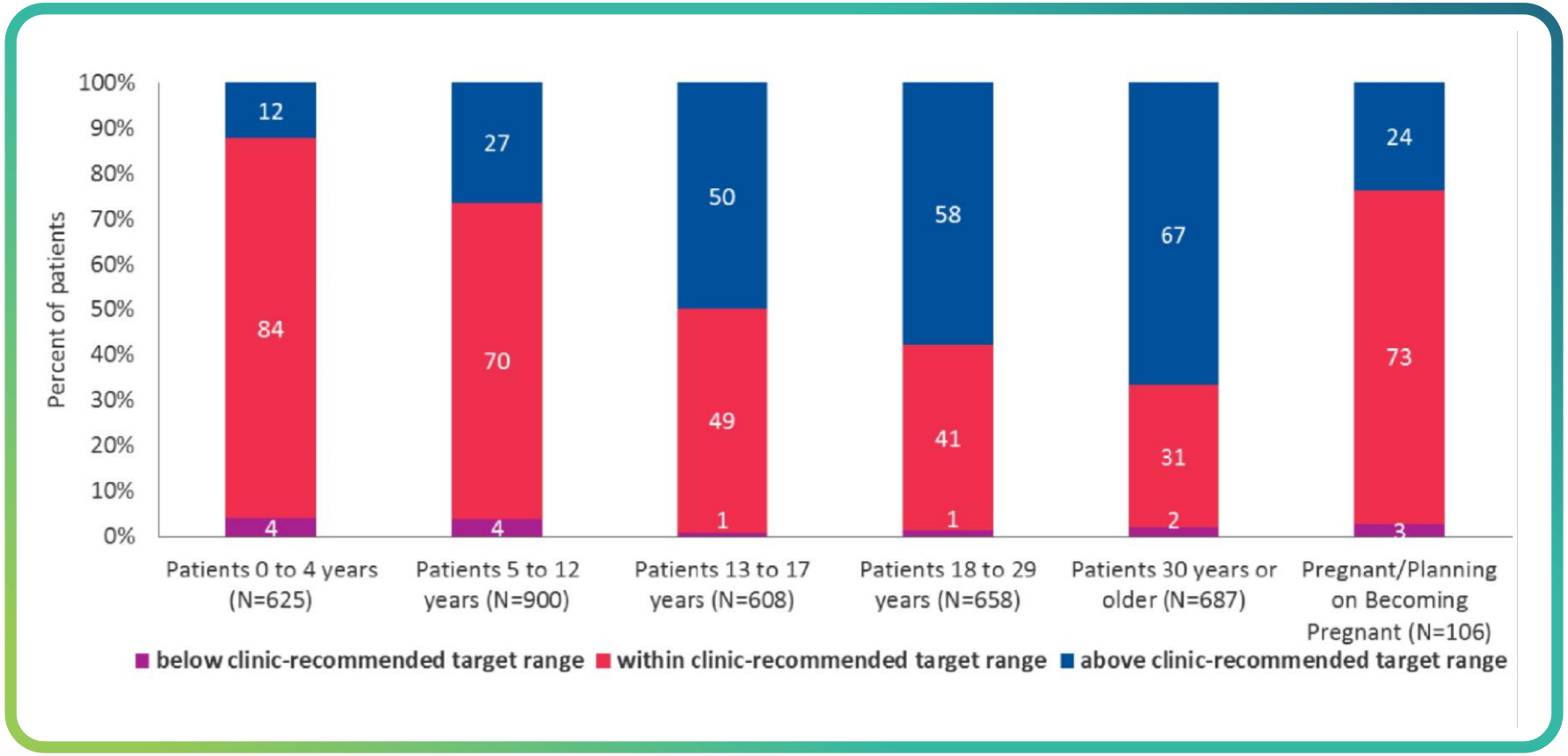
1 slice cheese	1 drumstick	1 slice bread	1 egg
6.5 g	18 g	3 - 4 g	6.5 g

Most protein intake for PKU patients comes from medical formula



Sources: U.S. Department of Agriculture. Agricultural Research Service/Food Data Central/Food Search; PBS Wisconsin; Thomas J., et al, Mol Genet Metab. 2018;124(1):27. Epub 2018 Mar 31.

Given the burdens of managing PKU, many patients are unable to consistently maintain target blood Phe concentrations



The above analysis predates broader use of BH4 and enzyme substitution therapies. However, recent publications still indicate similarly suboptimal control of Phe

Sources: E.R. Jurecki et al. / Molecular Genetics and Metabolism 120 (2017) 190–197
N. Longo et al. / Value in Health (2025) 28S56

BEAM-304 platform is being developed to address unmet need for patients with PKU

Target profile for successful clinical uptake of PKU gene therapy:

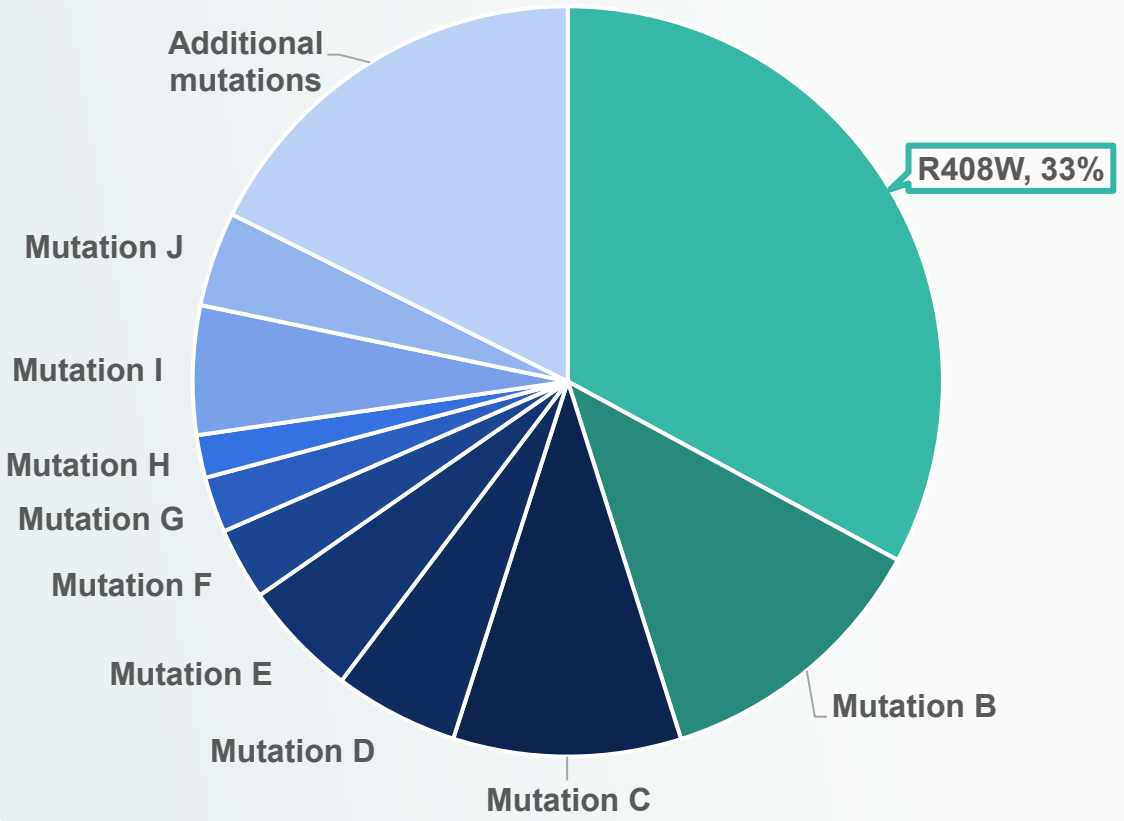
Plasma Phe is a surrogate endpoint for full approval in U.S. and EU

Diet normalization can be demonstrated in clinical setting

Preclinical Development of BEAM-304A as a Potential Base Editing Treatment Targeting the R408W Variant in PKU

PAH-p.R408W is the most common variant in patients with PKU globally and in US, and can be corrected by an adenine base editor

~20,000 PKU Individuals in U.S.



HGG Advances

REPORT

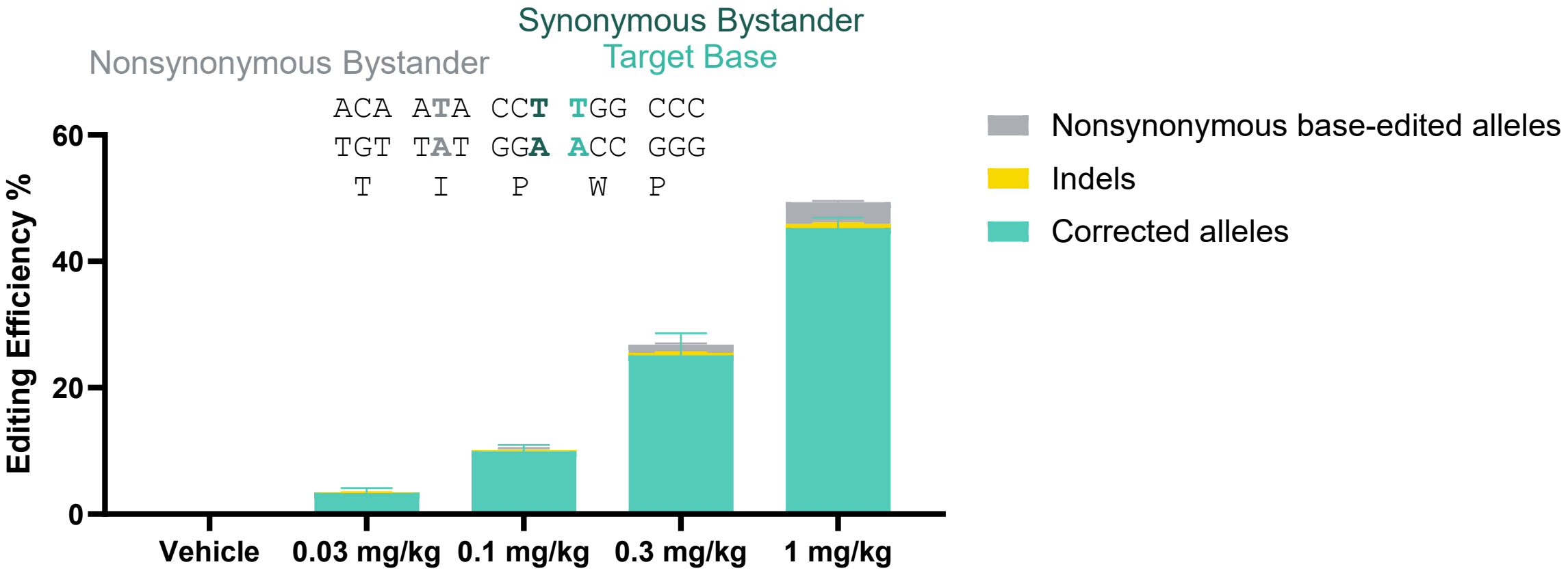
A base editing strategy using mRNA-LNPs for *in vivo* correction of the most frequent phenylketonuria variant

Dominique L. Brooks,[1,2,3] Madelynn N. Whittaker,[1,2,3,4] Hooda Said,[5] Garima Dwivedi,[6] Ping Qu,[1,2,3] Kiran Musunuru,[1,2,3,11,*] Rebecca C. Ahrens-Nicklas,[3,7,8,11] Mohamad-Gabriel Alameh,[5,9,10,11] and Xiao Wang[1,2,3,11]

- Musunuru lab established preclinical proof-of-concept for LNP-mediated base editing in PKU
- In collaboration, we optimized a novel LNP, editor mRNA, and gRNA to yield BEAM-304A to correct the PAH-p.R408W variant

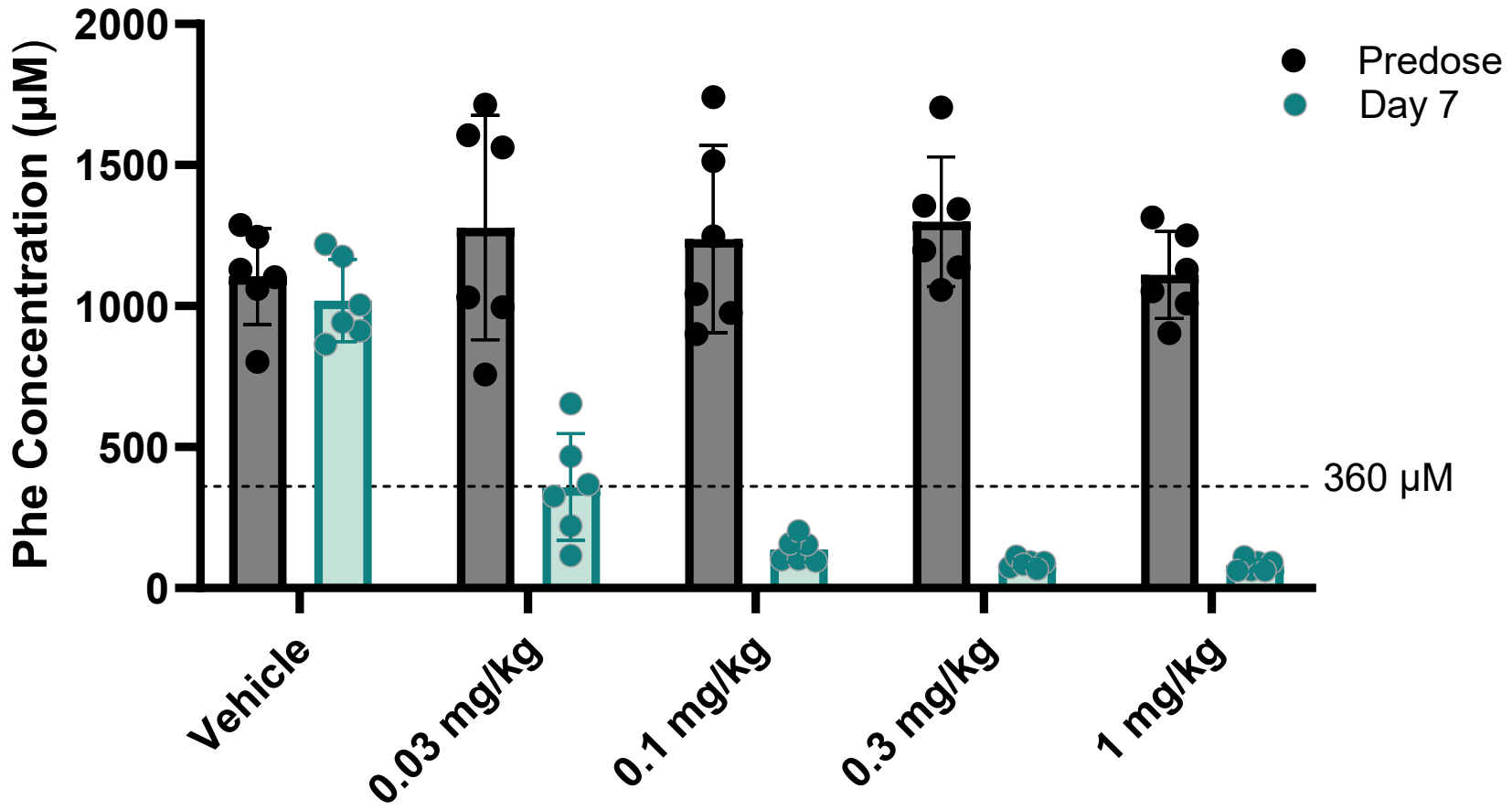
Source: Beam internal data; Hillert, Alicia et al. The American Journal of Human Genetics, Volume 107, Issue 2, 234 – 250; Stone WL, Los E. Phenylketonuria (PKU). StatPearls Publishing; 2025 Jan

A single dose of BEAM-304A yielded potent and precise editing in liver of homozygous R408W mice



The I406T nonsynonymous bystander is associated with classic PKU, but occurs at low frequency and is no more deleterious than the already present R408W variant

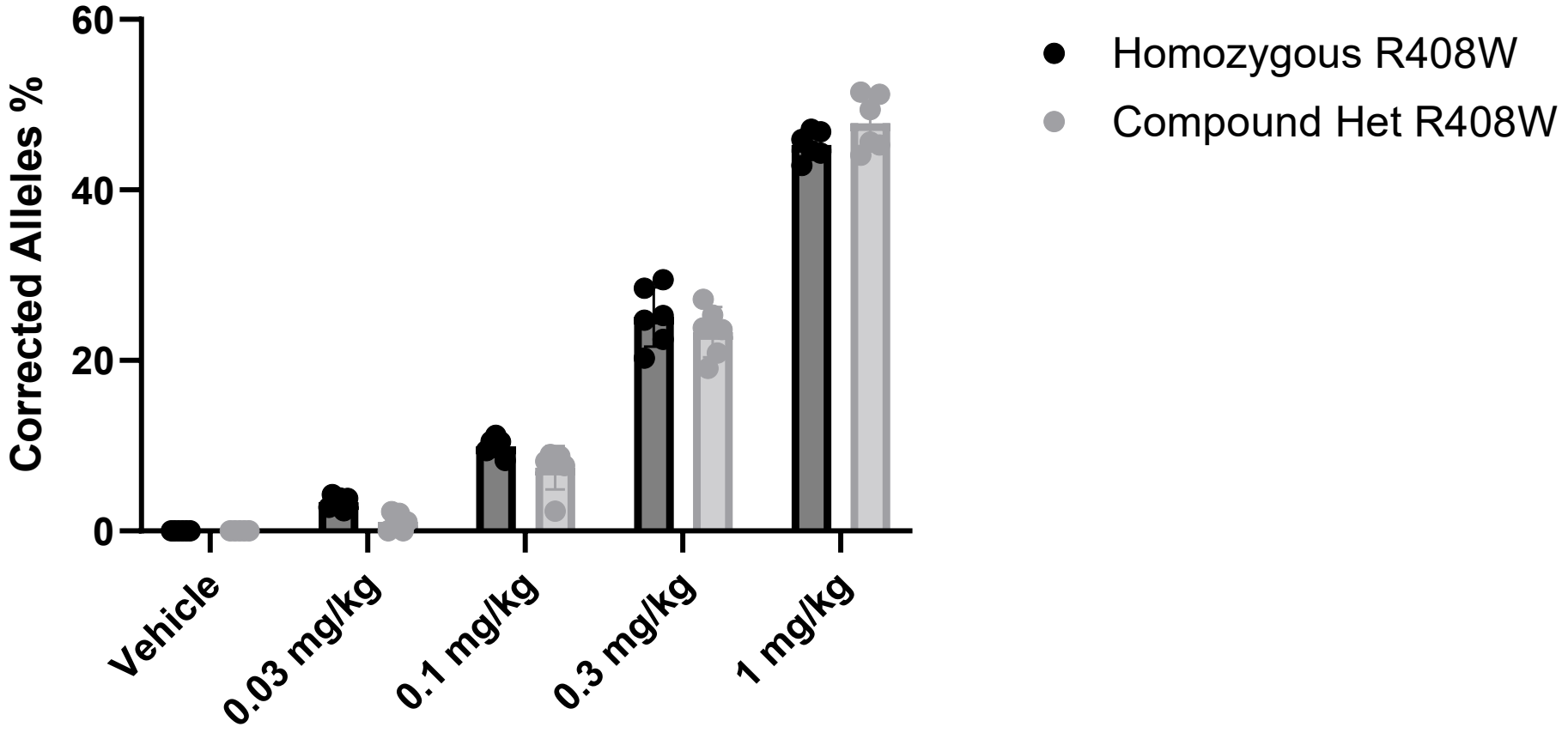
A single dose of BEAM-304A yielded dose dependent reductions in plasma Phe in homozygous R408W mice



Dose levels ≥0.1mg/kg reduced plasma Phe <360 µM* despite consumption of standard protein-containing feed

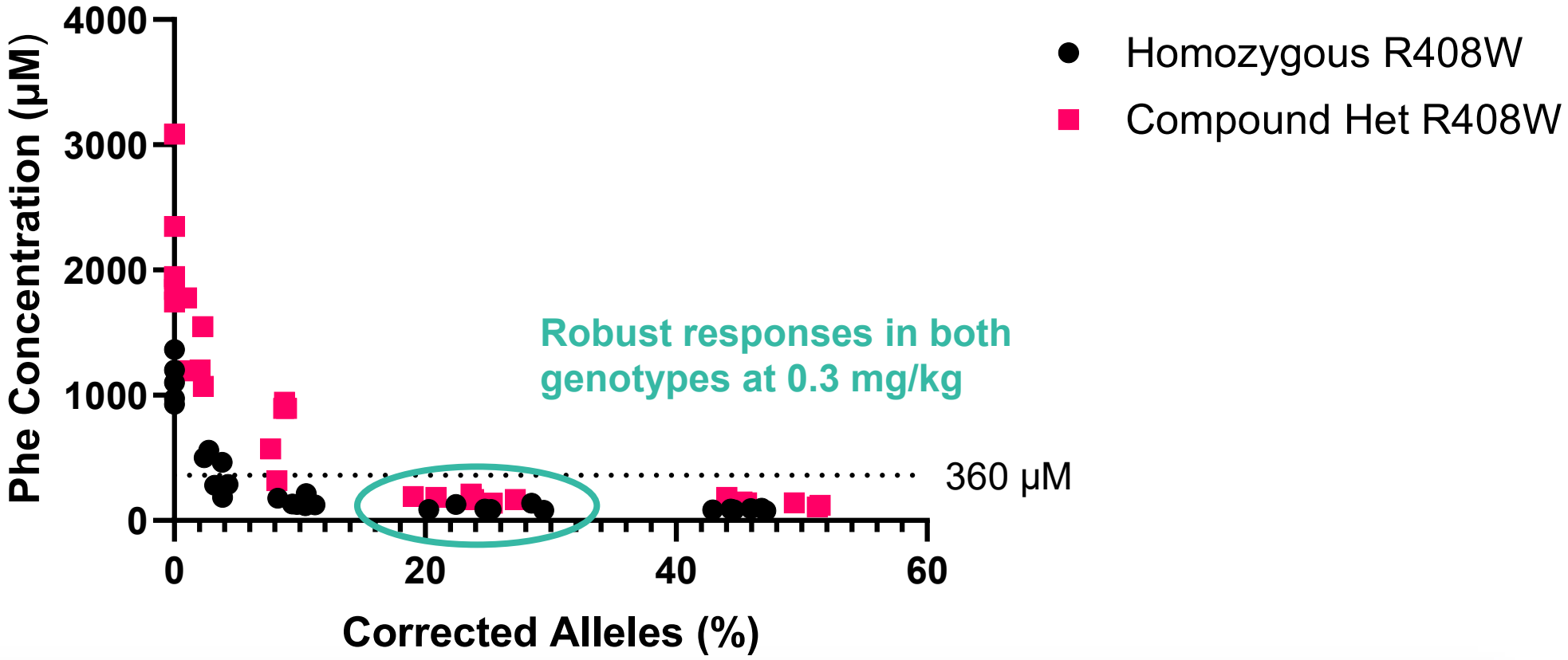
*Normal Phe <120 µM; treatment target <360 µM

BEAM-304A yielded similar liver editing in homozygous and compound heterozygous R408W mice



Results were consistent with expectations for an NGS method specific to the targeted R408W allele

Plasma Phe <360µM was achieved in both compound heterozygous and homozygous R408W mice

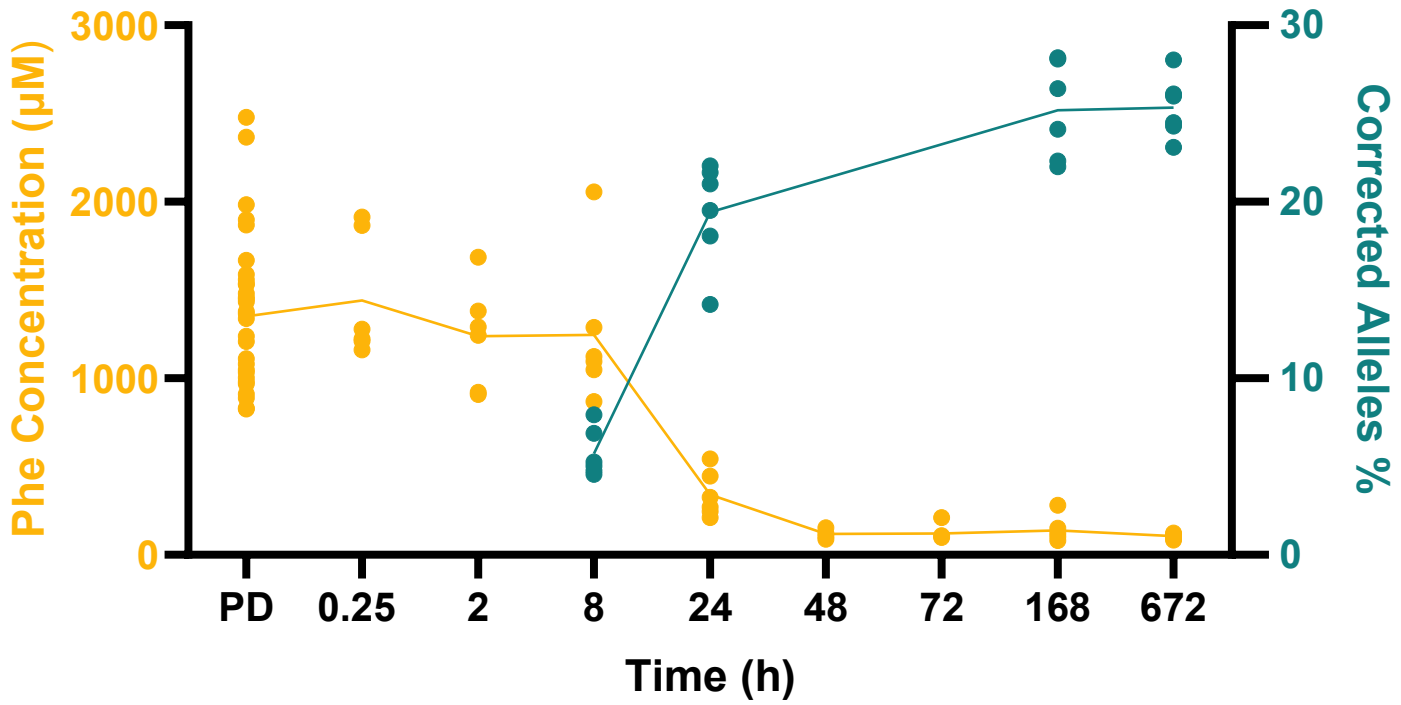


Differences in Phe response between genotypes may be driven by:

1. **Higher baseline plasma Phe in compound heterozygous mice**
2. **Fewer editable *PAH* gene copies in compound heterozygous mice**

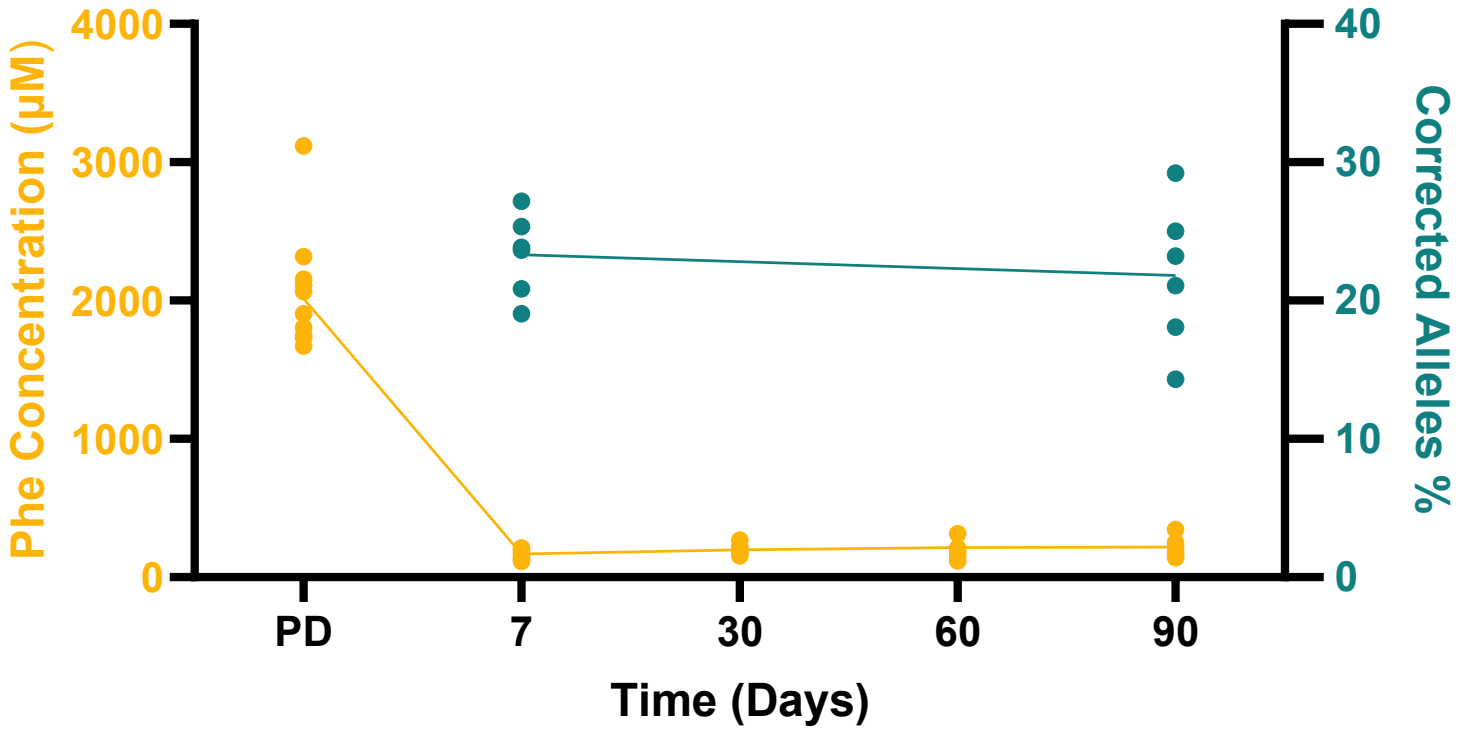
Liver editing and reductions in plasma Phe occurred rapidly after administration of BEAM-304A

- Homozygous R408W mice were administered a single dose of 0.3mg/kg
- Liver editing was detectable by 8 hours, and reached maximum by 7 days
- Plasma Phe reductions were apparent by 24 hours, and stabilized by 48 hours



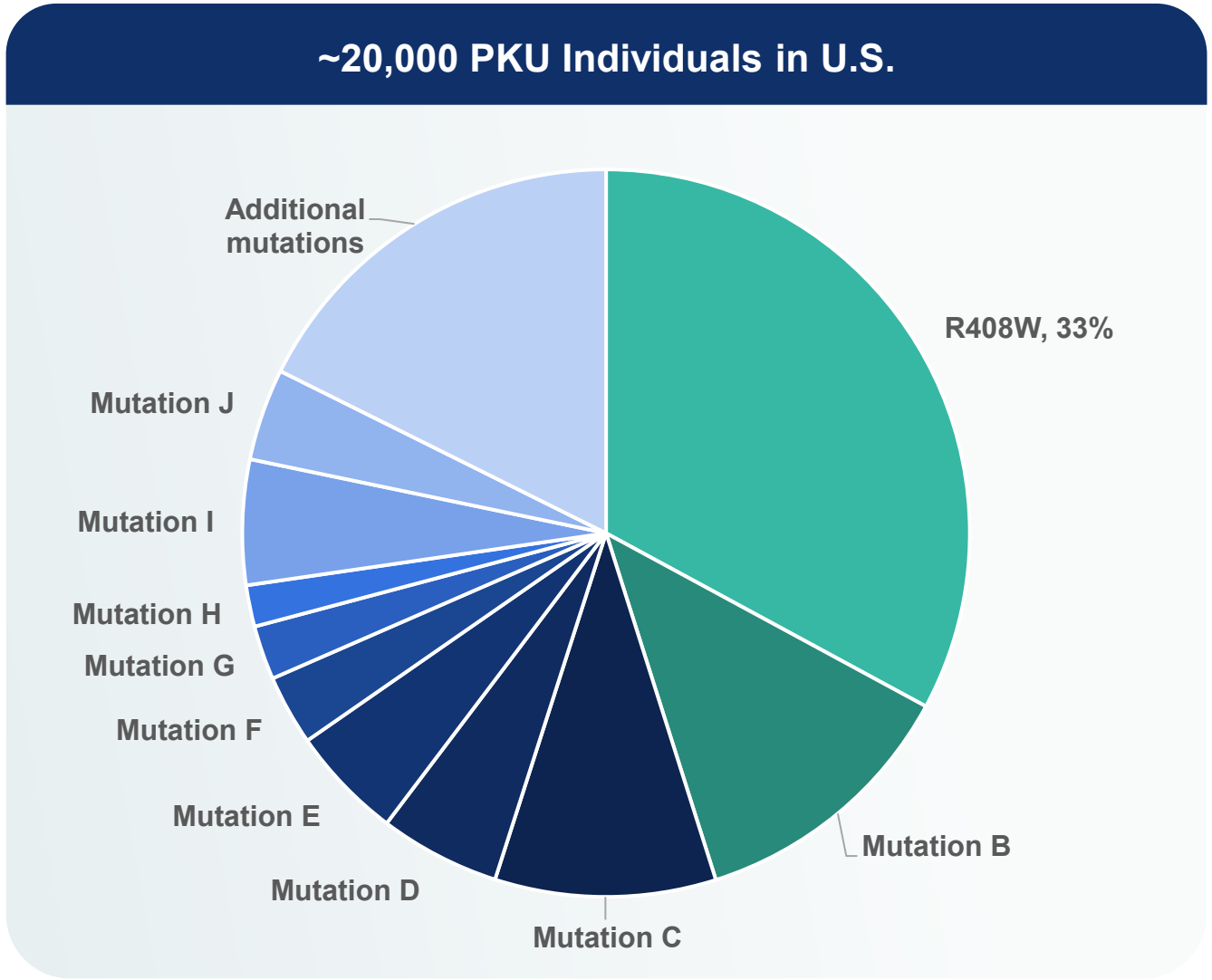
Liver editing and reductions in blood Phe were durable at least 90 days after a single dose of BEAM-304A

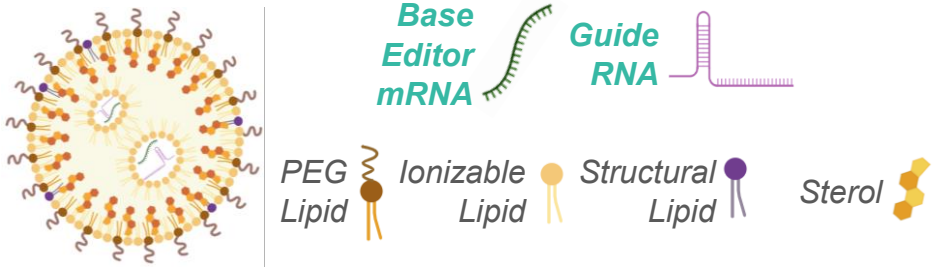
- Compound heterozygous R408W mice were administered a single dose of 0.3mg/kg
- Liver editing and plasma Phe were stable from D7 through D90



Further Development of a BEAM-304 Base Editing Platform for PKU

BEAM-304B targets a second mutation using the same LNP but a different adenine base editor mRNA and gRNA

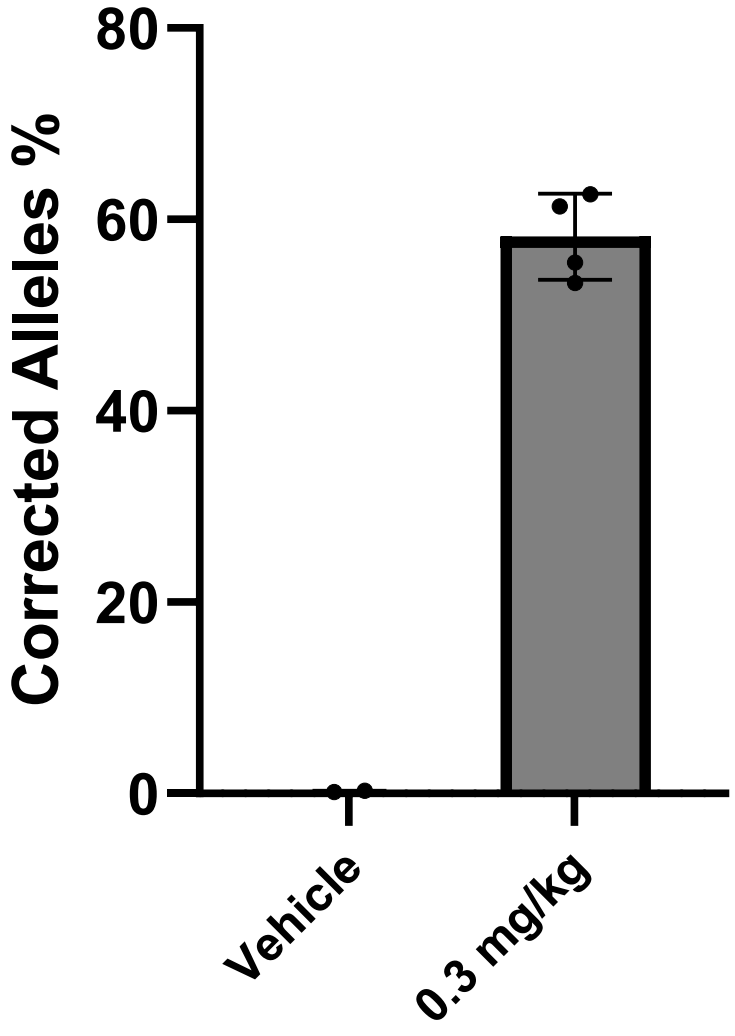


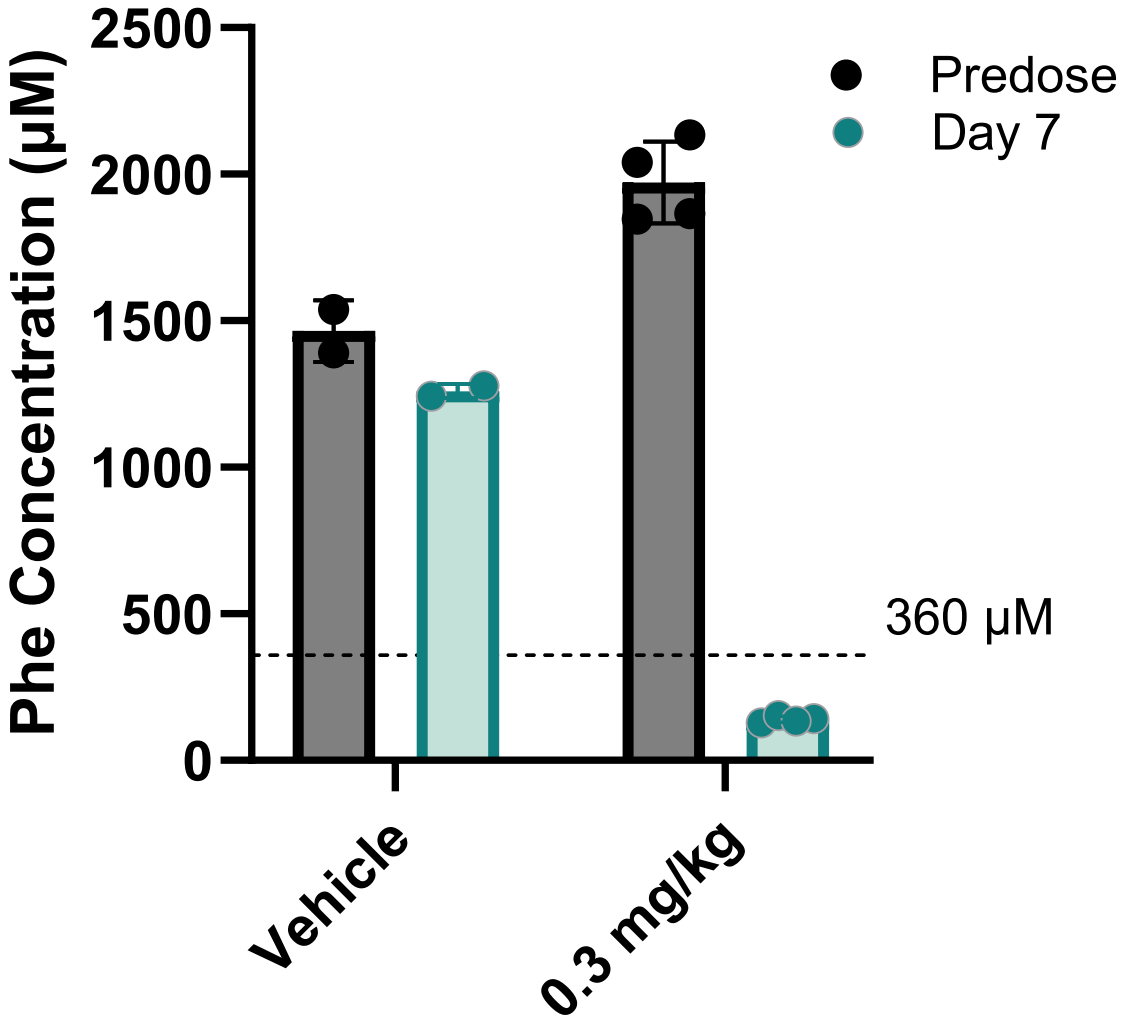


- BEAM-304A and BEAM-304B could address nearly half of US patients with PKU
- Work is ongoing at Beam to develop product variants for additional mutations

Source: Beam internal data; Hillert, Alicia et al. The American Journal of Human Genetics, Volume 107, Issue 2, 234 – 250; Stone WL, Los E. Phenylketonuria (PKU). StatPearls Publishing; 2025 Jan

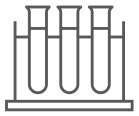
BEAM-304B resulted in potent editing in liver and reductions in blood Phe in compound heterozygous mice





Initial learnings from BEAM-304A expected to provide predictable path for expedited development for future variants (e.g., BEAM-304B)

Efficiencies can be gained across the drug development lifecycle

	Function	Possible synergies
	**Preclinical**	• Platform IND-supporting studies for BEAM-304A • Future nonclinical work focused on unique attributes of editor/gRNA pair (on-target efficacy and off-target assessments)
	**CMC**	• Leverage platform processes and analytical methods • Matrixed approaches to stability, process characterization and qualification
	**Clinical**	• Use of a single master protocol • BEAM-304A dose exploration data could streamline clinical development of subsequent product variants • Pooled analyses of efficacy and/or safety could enable efficient and robust BLA submission packages
	**Regulatory**	• Leverage FDA's umbrella IND framework to streamline submissions

Source: FDA Draft Guidance June 2026 "Leveraging Prior Knowledge in the Development of Human Gene Therapy Products Incorporating Genome Editing" FDA-2026-D-1257

BEAM-304 Phase 1/2 trial designed to achieve early clinical proof of concept in patients with PKU and the R408W mutation

- Beam will initially focus development of BEAM-304 in U.S.
- Initial IND filing enables clinical study of BEAM-304A with potential to expand to other mutations

PHASE 1/2

Open-label, single-ascending dose trial

DOSE EXPLORATION ▶ **DOSE EXPANSION**

KEY ENDPOINTS

- Safety and tolerability
- Reduction of blood Phe concentration

IND cleared in June 2026

Q&A