PTC Therapeutics PKU Deep Dive

July 19, 2023

Patient Living with PKU

Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. All statements contained in this presentation, other than statements of historic fact, are forward-looking statements, including statements with respect to (i) 2023 total revenue guidance and (ii) 2023 net product revenue guidance for the DMD franchise, statements with respect to the future expectations, plans and prospects for PTC, including with respect to the expected timing of clinical trials and studies, availability of data, regulatory submissions and responses and other matters, future operations, future financial position, future revenues, projected costs; and the objectives of management. Other forward-looking statements may be identified by the words, "guidance", "plan," "anticipate," "believe," "estimate," "expect," "intend," "may," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions.

PTC's actual results, performance or achievements could differ materially from those expressed or implied by forward-looking statements it makes as a result of a variety of risks and uncertainties, including those related to: the outcome of pricing, coverage and reimbursement negotiations with third party payors for PTC's products or product candidates that PTC commercializes or may commercialize in the future; expectations with respect to potential regulatory submissions and commercialization of sepiapterin for phenylketonuria, or PKU, and potential development and regulatory milestone payments that PTC may be obligated to make with regards to sepiapterin; expectations with respect to Upstaza, including any regulatory submissions and potential approvals, commercialization, manufacturing capabilities and the potential financial impact and benefits of its leased biologics manufacturing facility and the potential achievement of development, regulatory and sales milestones and contingent payments that PTC may be obligated to make; PTC's ability to maintain its marketing authorization of Translarna for the treatment of nmDMD in Brazil, Russia, the European Economic Area (EEA) and other regions, including whether the European Medicines Agency (EMA) determines in future annual renewal cycles that the benefit-risk balance of Translarna authorization supports renewal of such authorization; PTC's ability to complete Study 041, which is a specific obligation to continued marketing authorization in the EEA; PTC's ability to utilize results from Study 041, a randomized, 18-month, placebo-controlled clinical trial of Translarna for the treatment of nmDMD followed by an 18- month open-label extension, to support a marketing approval for Translarna for the treatment of nmDMD in the United States and a conversion to a standard marketing authorization in the EEA; expectations with respect to the commercialization of Evrysdi under our SMA collaboration; expectations with respect to the commercialization of Tegsedi and Waylivra; significant business effects, including the effects of industry, market, economic, political or regulatory conditions; changes in tax and other laws, regulations, rates and policies; the eligible patient base and commercial potential of PTC's products and product candidates; PTC's scientific approach and general development progress; PTC's ability to satisfy its obligations under the terms of its lease agreements, including for its leased biologics manufacturing facility; PTC's ability to satisfy its obligations under the terms of the secured credit facility with Blackstone; the sufficiency of PTC's cash resources and its ability to obtain adequate financing in the future for its foreseeable and unforeseeable operating expenses and capital expenditures; and the factors discussed in the "Risk Factors" section of PTC's most recent Annual Report on Form 10-K, as well as any updates to these risk factors filed from time to time in PTC's other filings with the SEC. You are urged to carefully consider all such factors.

As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. There are no guarantees that any product will receive or maintain regulatory approval in any territory, or prove to be commercially successful, including Translarna, Emflaza, Upstaza, Evrysdi, Tegsedi, Waylivra or sepiapterin.

The forward-looking statements contained herein represent PTC's views only as of the date of this presentation and PTC does not undertake or plan to update or revise any such forward-looking statements to reflect actual results or changes in plans, prospects, assumptions, estimates or projections, or other circumstances occurring after the date of this presentation except as required by law.

Presenters

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Agenda

1 **Overview of PTC and Sepiapterin**

2 Clinical Practice in PKU

3 Commercial Landscape for Sepiapterin

Continued Success Across Our Commercial Portfolio

translarna™ ataluren

Distributed in 50+ countries with continued growth from new patients and geographic expansion

Emflaza® (deflazacort)
6 mg | 18 mg | 30 mg | 36 mg tablets
22.75 mg/mL oral suspension

First and only corticosteroid for all US DMD patients with growth from new patient starts and favorable access

Evrysdi® risdiplam

Established market leadership in all major markets with continued growth expected

Upstaza™ (eladocagene exuparvovec)

First EMA-approved disease-modifying treatment for AADC deficiency for patients 18 months and older

Tegsedi® (inotersen) injection 284 mg/1.5 mL

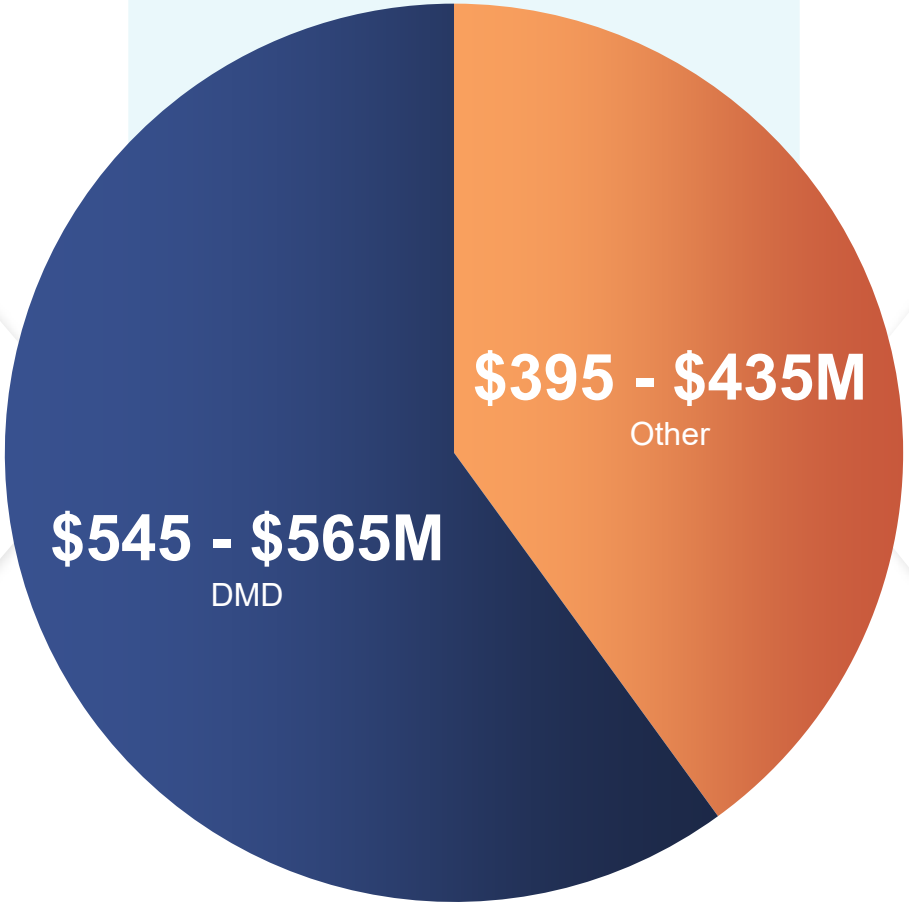
For treatment of hATTR with LATAM patients benefiting through early-access programs

waylivra® (volanesorsen) injection 285 mg/1.5 mL

For treatment of FCS and FPL, with LATAM patients benefiting through early-access programs

Strong Commercial Revenue Guidance for 2023

$940M-$1B



translarna™ ataluren

Emflaza® (deflazacort)
6 mg | 18 mg | 30 mg | 36 mg tablets
22.75 mg/mL oral suspension

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Upstaza™ (eladocagene exuparvovec)

waylivra® (volanesorsen) injection 285 mg/1.5 mL

PTC THERAPEUTICS®

Substantial Pipeline Progress Expected in H2 2023

Clinical Trials

PIVOT HD

SUNRISE LMS

CARDINALS

*Regulatory Activities**

Upstaza (eladocagene exuparvovec)

Upstaza BLA Submission Q3

translarna ataluren

Translarna CHMP Type II Variation Opinion Q3

translarna ataluren

Translarna FDA Type C Meeting H2

MOVE-FA

Vatiquinone FA FDA Type C Meeting H2

aphenity

Sepiapterin NDA Submission Q4

*New or Updated Guidance

PTC THERAPEUTICS

APHENITY Topline Results

APHENITY Topline Results Demonstrate Clinical and Statistically Significant Benefit

aphenity

Achieved primary endpoint in placebo-controlled portion of study with statistically significant ($p<0.0001$) blood phenylalanine (Phe) reduction

Demonstrated substantial Phe reduction in both the overall primary analysis population (63%) and the subset of classical PKU patients (69%)

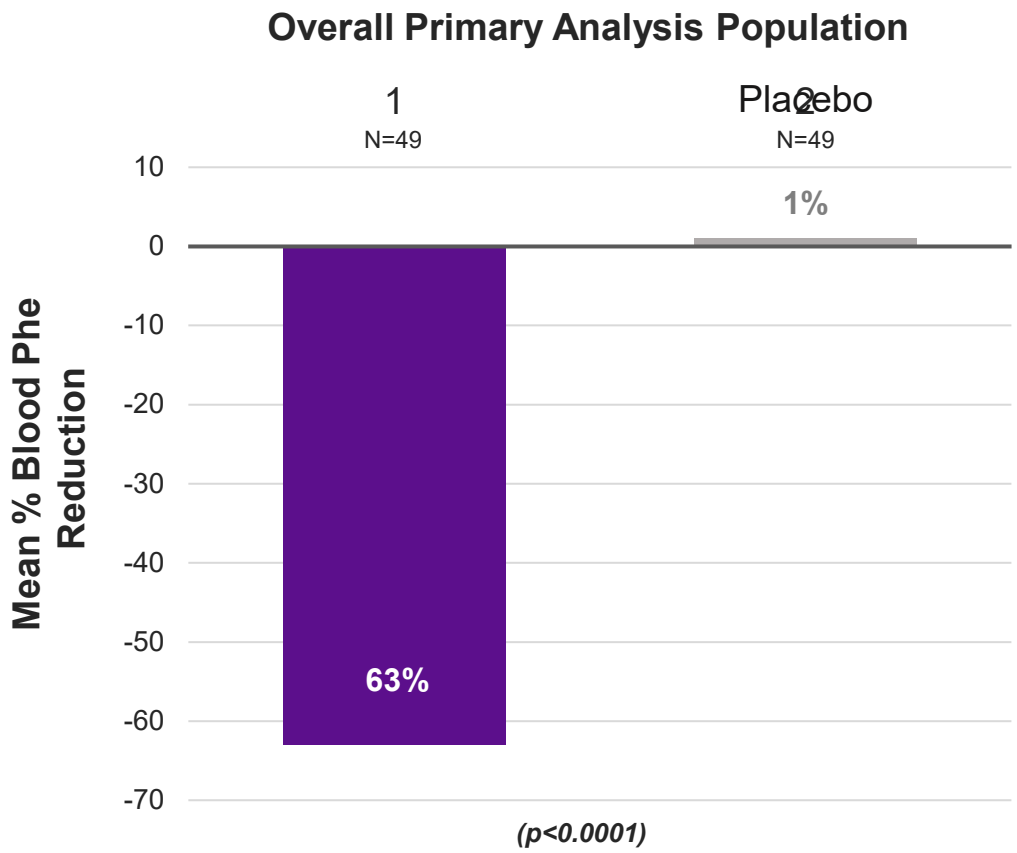
Achieved Phe reduction sufficient to bring **84% of study patients within US guidelines** for Phe reduction <360 µmol/L

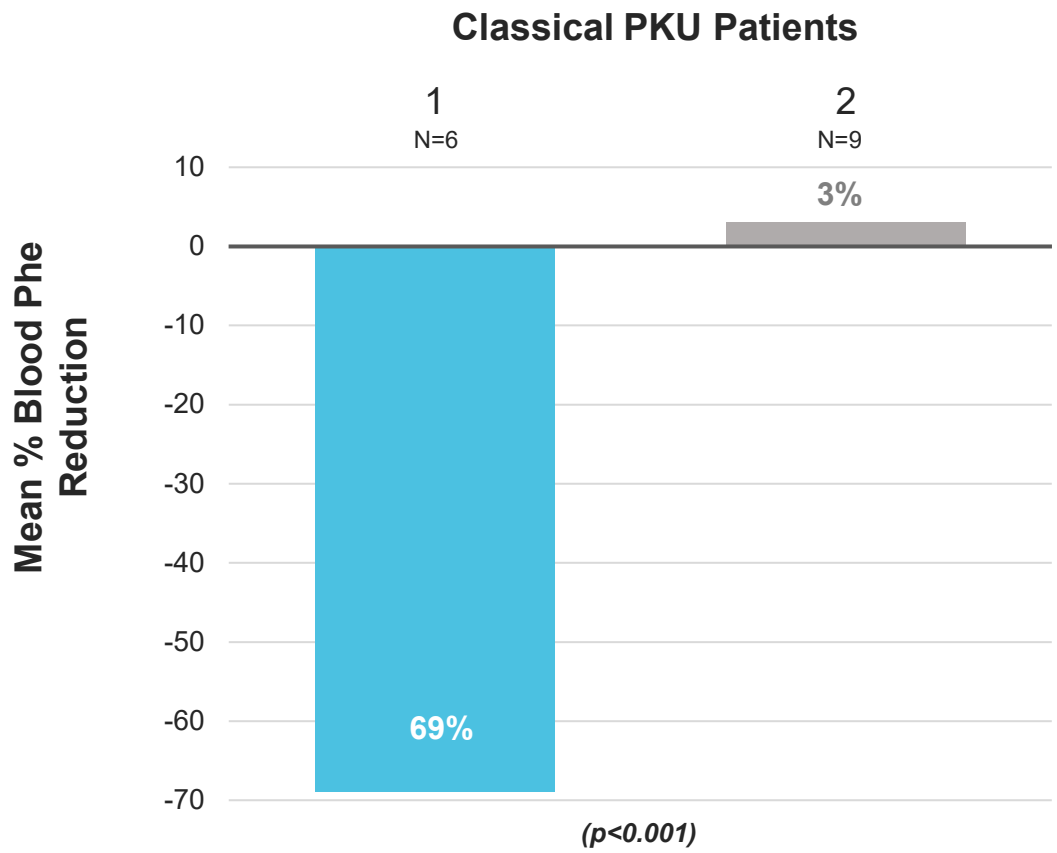
Well tolerated with no serious adverse events

PTC THERAPEUTICS

Sepiapterin Treatment Resulted in Clinically Significant Blood Phe Reduction

Mean % Blood Phe Reduction

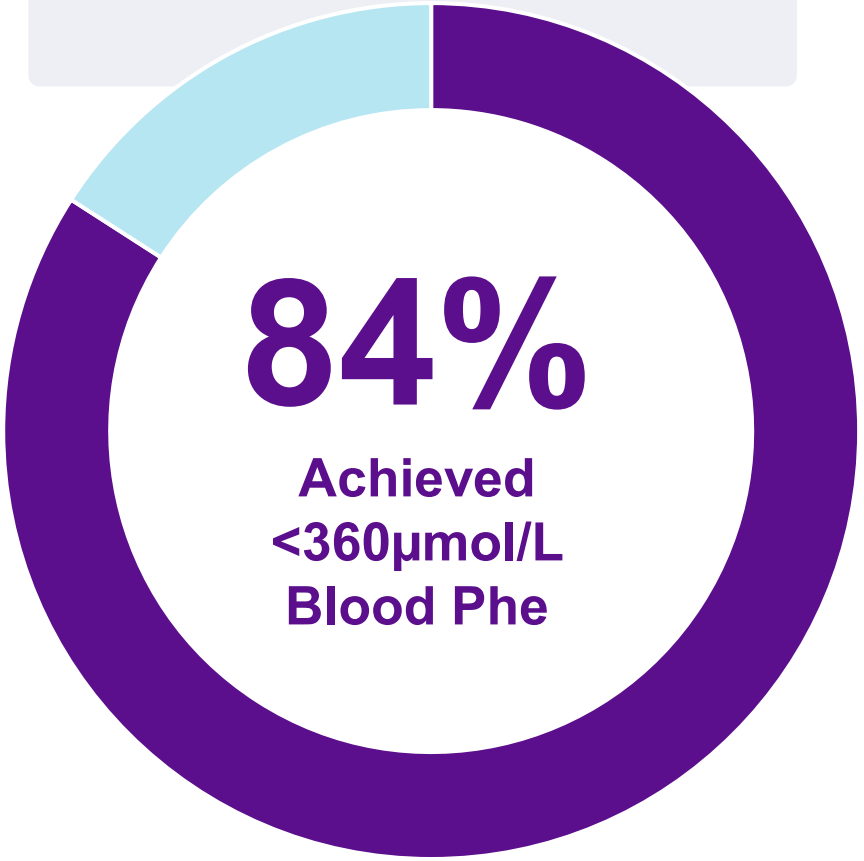




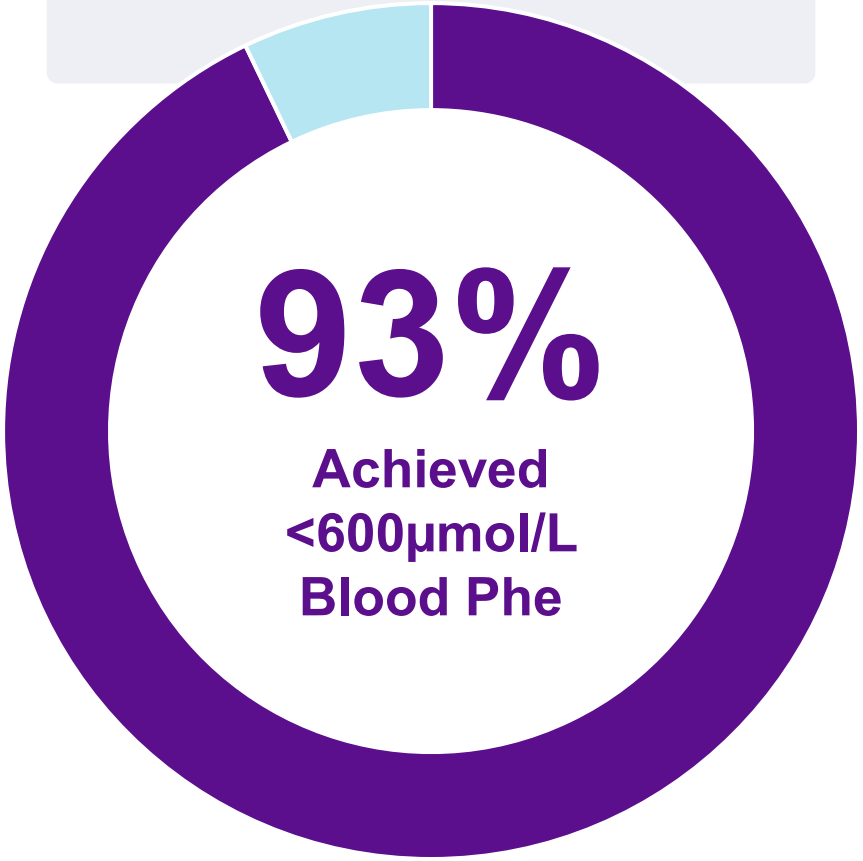
Vast Majority of Patients Achieved Guidelines Target Blood Phe Levels

US guidelines: all ages

EU guidelines: <12 years of age

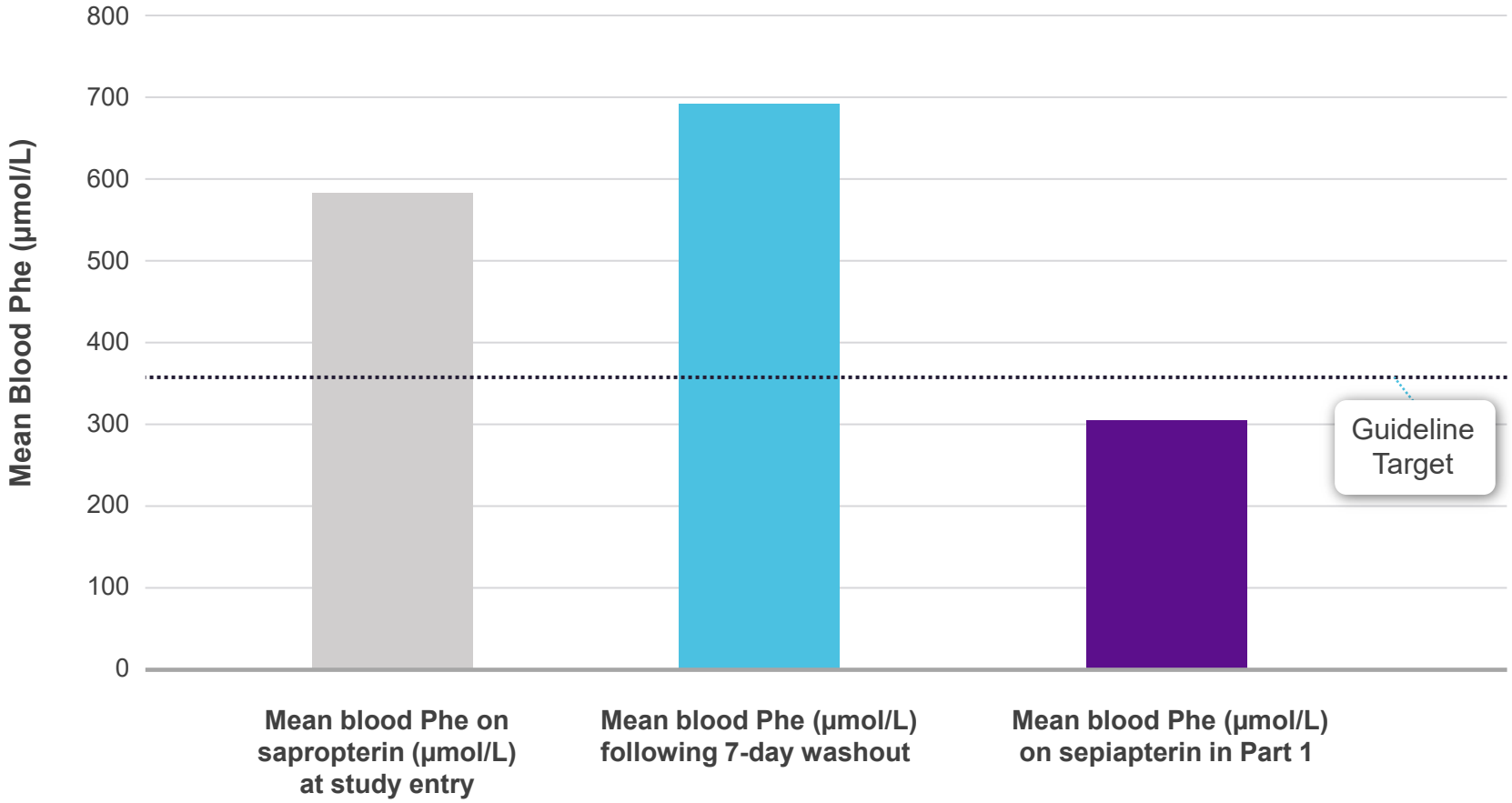


EU guidelines: ≥12 years of age



Sepiapterin Part 1 Treatment Effect in Patients Receiving Sapropterin at Study Entry

(N=27 patients)



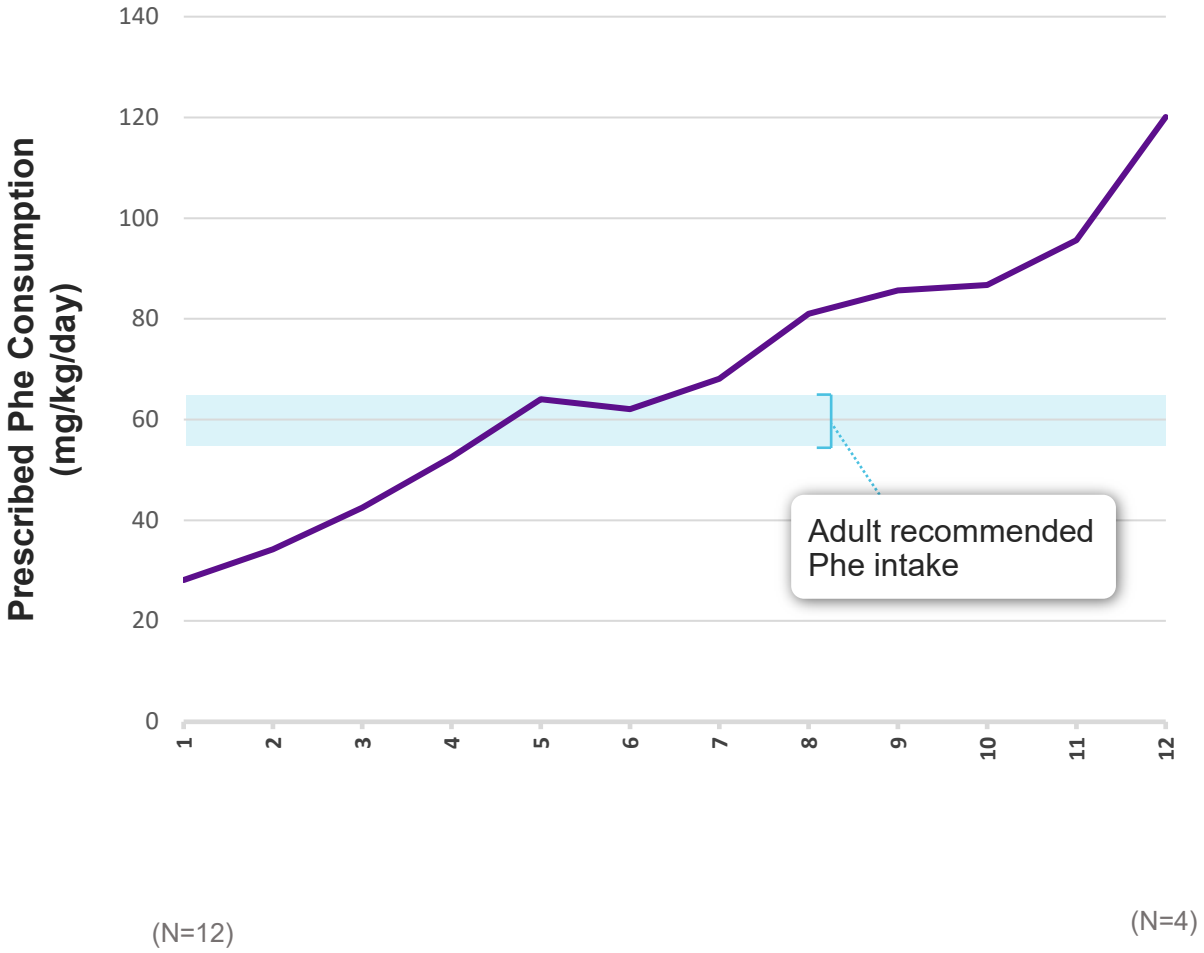
48%

lower Phe levels following sepiapterin treatment in those patients receiving sapropterin at study entry

Initial Phe Tolerance Data in Open-Label Extension

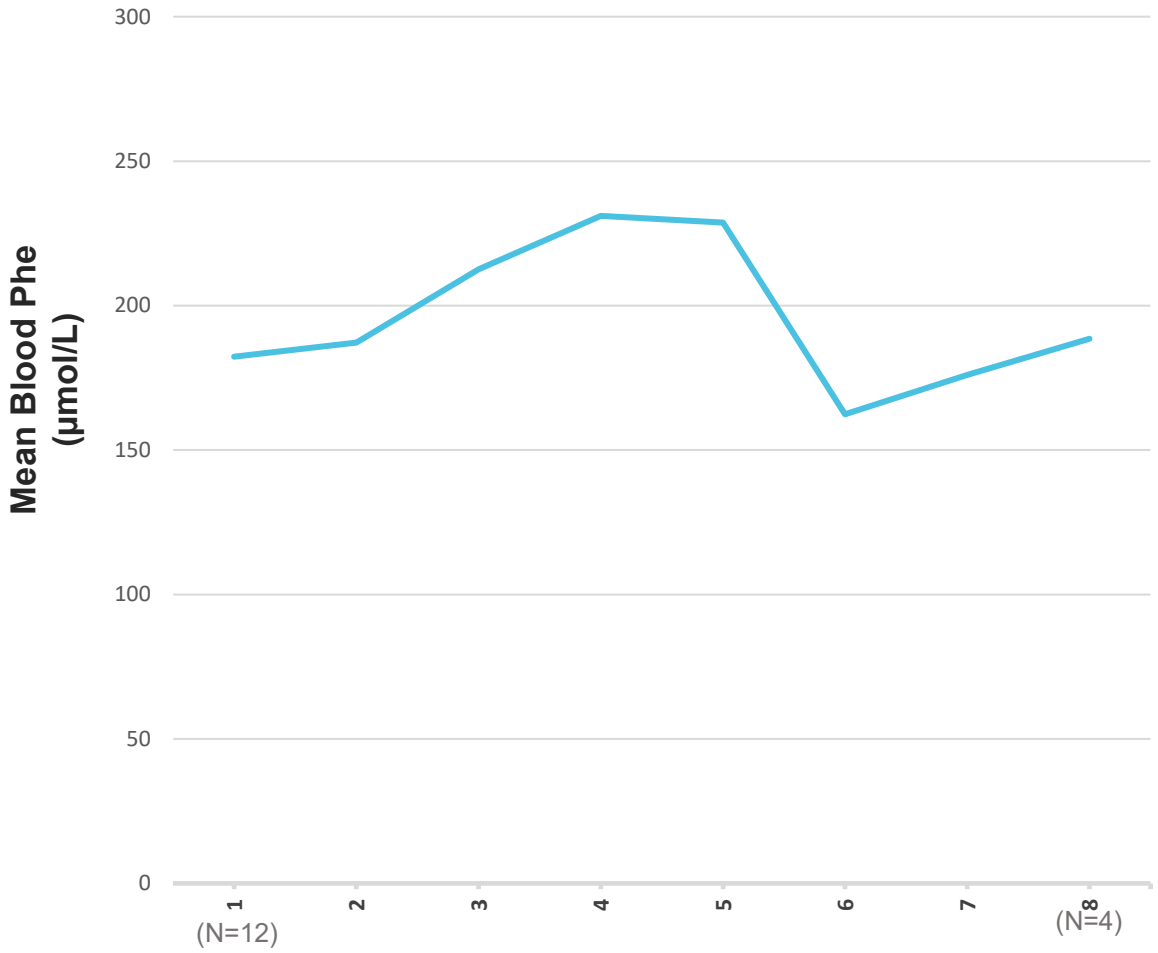
aphenity extension study

Increase in Dietary Phe Intake



(N=12) (N=4)

Blood Phe Levels



(N=12) (N=4)

PTC THERAPEUTICS

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1 Overview of PTC and Sepiapterin

2 **Clinical Practice in PKU**

3 Commercial Landscape for Sepiapterin

Overview of Phenylketonuria (PKU)

PKU is an inherited, autosomal recessive condition[1]

Variants in *PAH*, the gene that encodes PAH, lead to impaired PAH function and cause PKU [1]

More than 1,000 variants in the human *PAH* gene have been identified[1,3]

Both environment (dietary intake of Phe) and genotype are causal components of PKU

PAH genotype may not predict the clinical phenotype or be used to evaluate or treat the disease[2]

1. Blau N, et al. *The Lancet*. 2010;376:1417–1427. 2. Mitchell JJ, et al. *Genet Med*. 2011; 13:697–707. 3. Hillert, et al. *The American Journal of Human Genetics 2020*;107,1-17.

PTC THERAPEUTICS

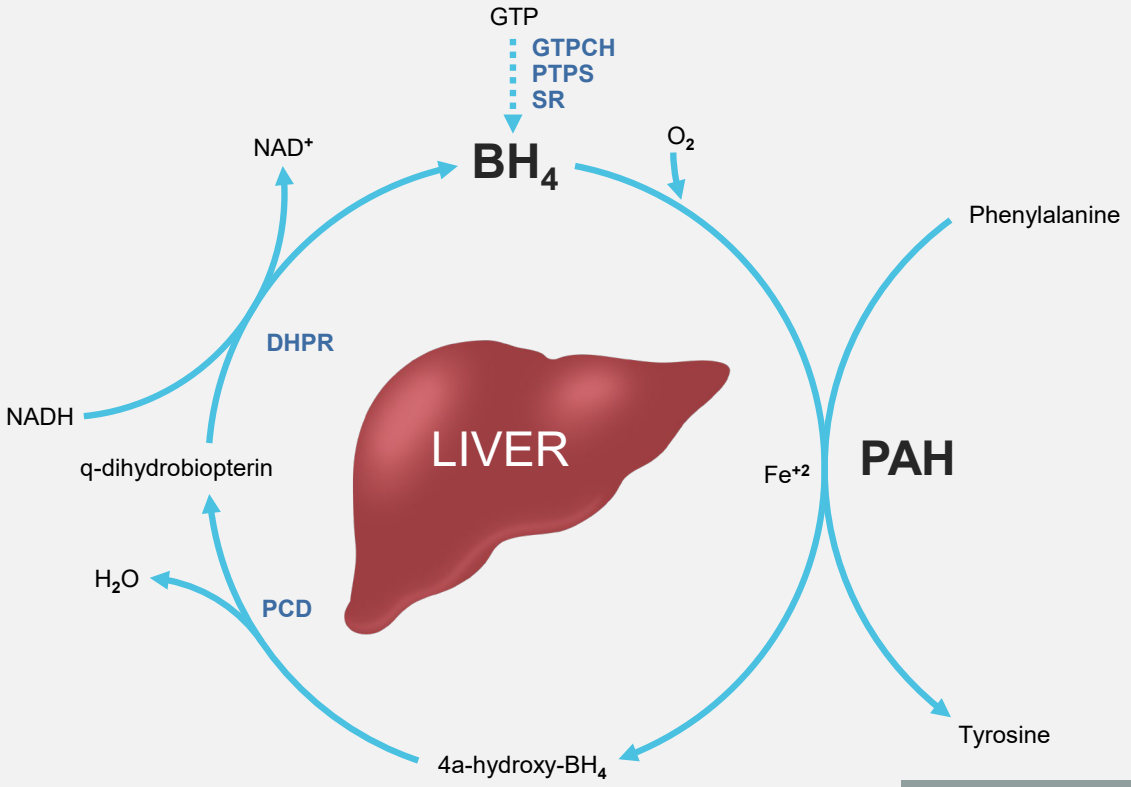
The Role of PAH in Phe Metabolic Pathway

PAH catalyzes the first and rate-limiting step in the metabolic pathway of Phe, conversion of Phe to Tyr[1]

BH_4 corrects misfolding and early degradation of PAH and by this improves in-vivo PAH enzyme activity[2]

Impaired PAH enzymic function leads to a systemic accumulation of Phe

Phenylalanine Hydroxylating System[2]



Blau N, et al. 2010

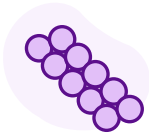
DHPR, dihydropteridine; GTP, guanosine triphosphate; GTPCH, GTP cyclohydrolase; HPA, hyperphenylalaninemia; PAH, phenylalanine hydroxylase; PCD, carbinolamie-4a-dydropterin; Phe, phenylalanine; PTPS, 6-pyruvoyl-tetra-hydopterin synthase. 1. Flydal MI, Martinez A. IUBMB Life. 2013;65:341-349. 2. Blau N, et al. The Lancet. 2010;376:1417-1427.

Elevated Blood Phe Interferes With Normal Production of Neurotransmitters and Leads to PKU

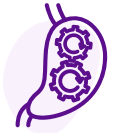
Elevated blood Phe level and accumulation of Phe in the brain is toxic to the central nervous system and impairs neurological functions

Excessive Phe Impact

White matter lesion and reduced myelin production



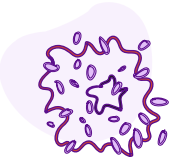
Formation of amyloid-like Phe aggregates



Reduced cerebral glucose metabolism

Alteration of methylation pattern of a panel of genes

LNAA deficiency due to Phe-mediated competition for LAT1



Oxidative stress

Neurotransmitter deficiency

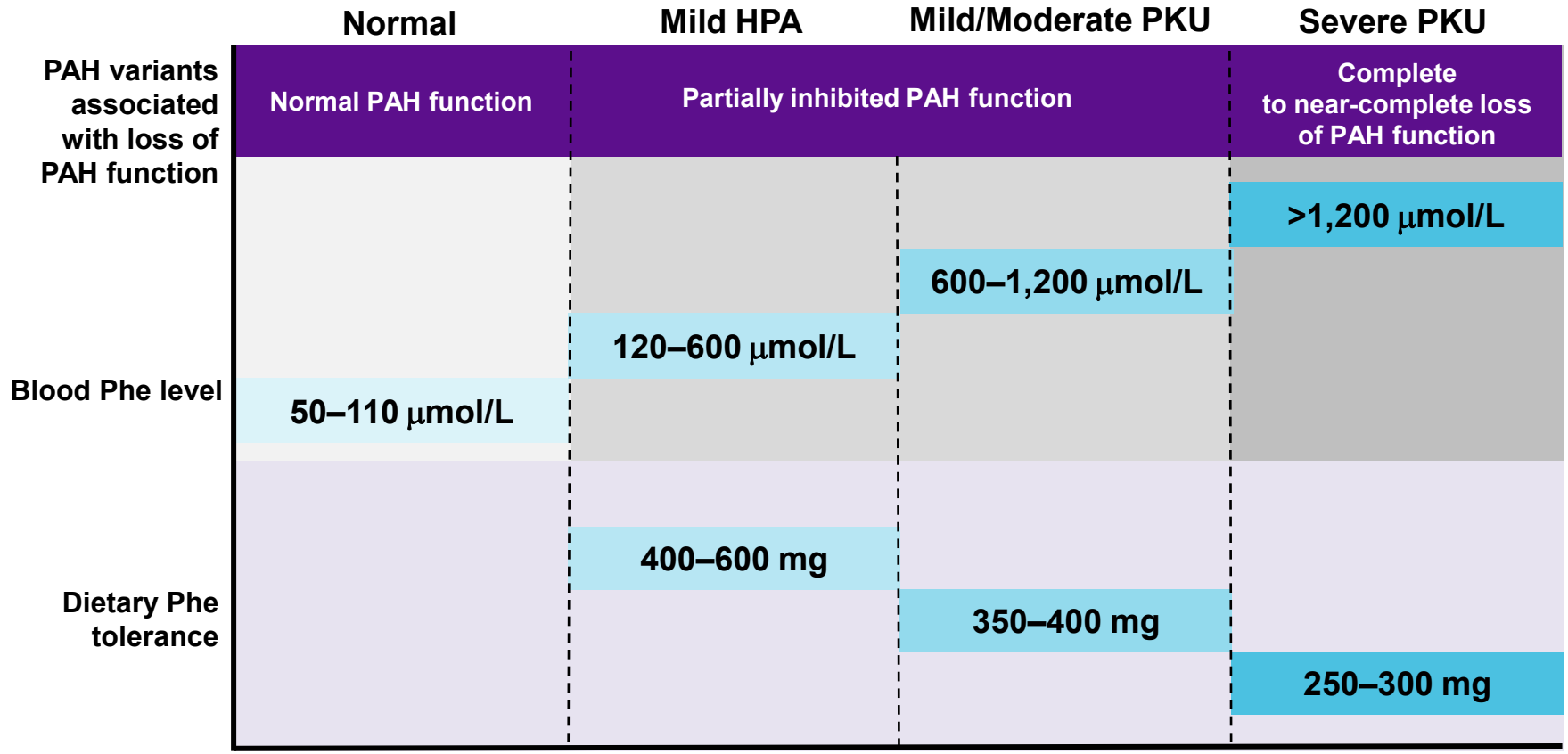
Cardiovascular and renal effects

Phe, phenylalanine; PKU, phenylketonuria.

van Spronsen FJ, et al. Nat Rev Dis Primers. 2021;7:36.

PKU Severity Is Associated With Higher Blood Phe Levels and Decreasing Phe Tolerance

- Patients with PKU are intolerant of dietary intake of the essential amino acid Phe[1]



HPA, hyperphenylalaninemia; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, PKU, phenylketonuria.

Blau N, et al. The Lancet. 2010;376:1417-1427.

PKU Management Guidelines

ACMG (US) TREATMENT GUIDELINES[1]	EU TREATMENT GUIDELINES [2]
The treatment of PKU should be initiated as early as possible.	No intervention is required if the blood phenylalanine concentration is less than 360 µmol/L. Treatment is recommended up to the age of 12 years if the phenylalanine blood concentration is between 360 µmol/L and 600 µmol/L, and lifelong treatment is recommended if the concentration is more than 600 µmol/L.
Treatment is lifelong with a goal of maintaining blood phe levels in the range of 120-360 µmol/l (2-6 mg/dl) in patients of all ages.	Treatment target concentrations are as follows: 120–360 µmol/L for individuals aged 0–12 years and for maternal PKU, and 120–600 µmol/L for non-pregnant individuals older than 12 years.

- Guidelines focus on Phe levels that are 10x normal levels

[1]Vockley, Andersson, Antshel et al, Phenylalanine hydroxylase deficiency: diagnosis and management guideline, Genetics in Medicine, 2014, doi:10-1038/gim.2013.57 and Singh, Rohr, Frazier, etc al, Recommendations for the nutrition management of phenylalanine hydroxylase deficiency, Genetics in Medicine, 2014, doi:10- 1038/gim.2013.179. [2]van Wegberg AMJ, MacDonald A, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, Burlina A, Campistol J, Feillet F, Giżewska M, Huijbregts SC, Kearney S, Leuzzi V, Maillot F, Muntau AC, van Rijn M, Trefz F, Walter JH, van Spronsen FJ. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis. 2017 Oct 12;12(1):162.

Lifelong Diet Restrictions Remain a Key Requirement for PKU Patients

Types of Dietary Treatment

Low-protein diet

Phe-free medicinal foods

Modified low-protein products

Glycomacropeptide

High concentration of LNAA

Barriers to Long-Term Continuation

Palatability, lack of variety of PKU diet

Prohibitive costs of medicinal foods

Risk of malnutrition

Increased GI issues from microbiome

Social barriers

Potential lack of insurance coverage

LNAA, large neutral amino acid; Phe, phenylalanine, PKU, phenylketonuria.
Lowe TB, et al. Orphanet J Rare Dis. 2020;15:266.

Diet Restrictions Alone Result in Suboptimal Outcomes

Despite early and continuous management of diet alone, PKU patients may experience cognitive symptoms as well as emotional and behavioral problems

Suboptimal Outcomes in PKU Treated With Dietary Treatment Alone

Children and Adolescents

- Poor academic performance due to PKU-related suboptimal learning capability
- Executive function abnormalities
- Reduced processing speeds
- Impaired bone formation

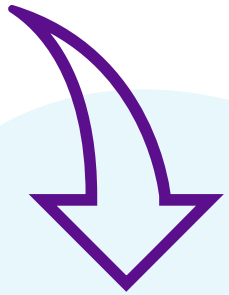
Adults

- Depressed mood
- Generalized anxiety
- Phobias
- Decreased positive emotions
- Social maturity deficit
- Social isolation
- Low bone density

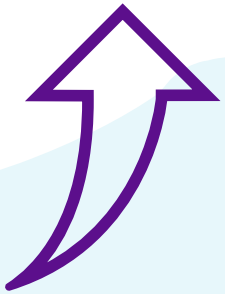
PKU, phenylketonuria.

Enns GM, et al. Mol Genet Metab. 2010;101:99--109.

Two Main Goals of Therapy for PKU Patients



Decreased Blood Phe Levels



Increased Dietary Protein Intake (Phe Tolerance)

Clinician-Reported Challenges With Two Currently Approved Treatments for PKU

KUVAN®
(sapropterin dihydrochloride)
Tablets or Powder for Oral Solution

Indication: For adult and pediatric patients ≥1 month

Clinician Reported Challenges

- Sapropterin has a limited response rate and Phe reduction, both initially and over time
- Classical PKU patients receive little to no Phe reduction from sapropterin

Palynziq®
(pegvaliase-pqpz) Injection

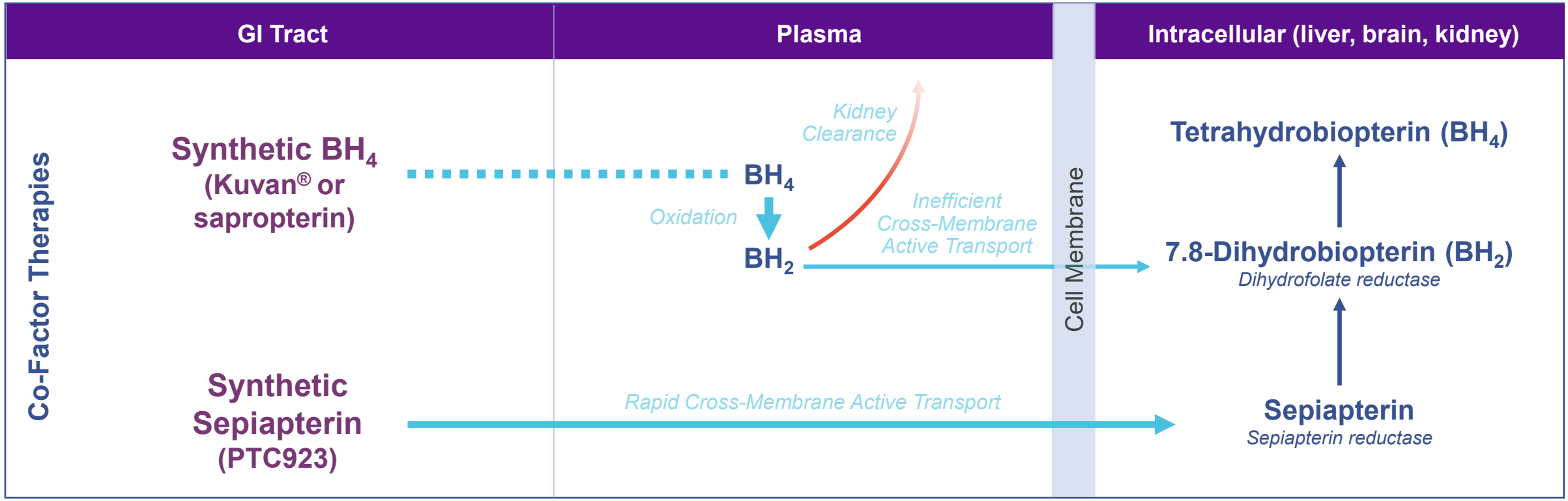
Indication: Adults who have uncontrolled blood Phe (>600 μmol/L) on existing management

Clinician Reported Challenges[1,2]

- Palynziq is indicated only for adults
- Demonstrated safety issues, including anaphylaxis
- Inconvenient injectable administration, and lengthy titration process

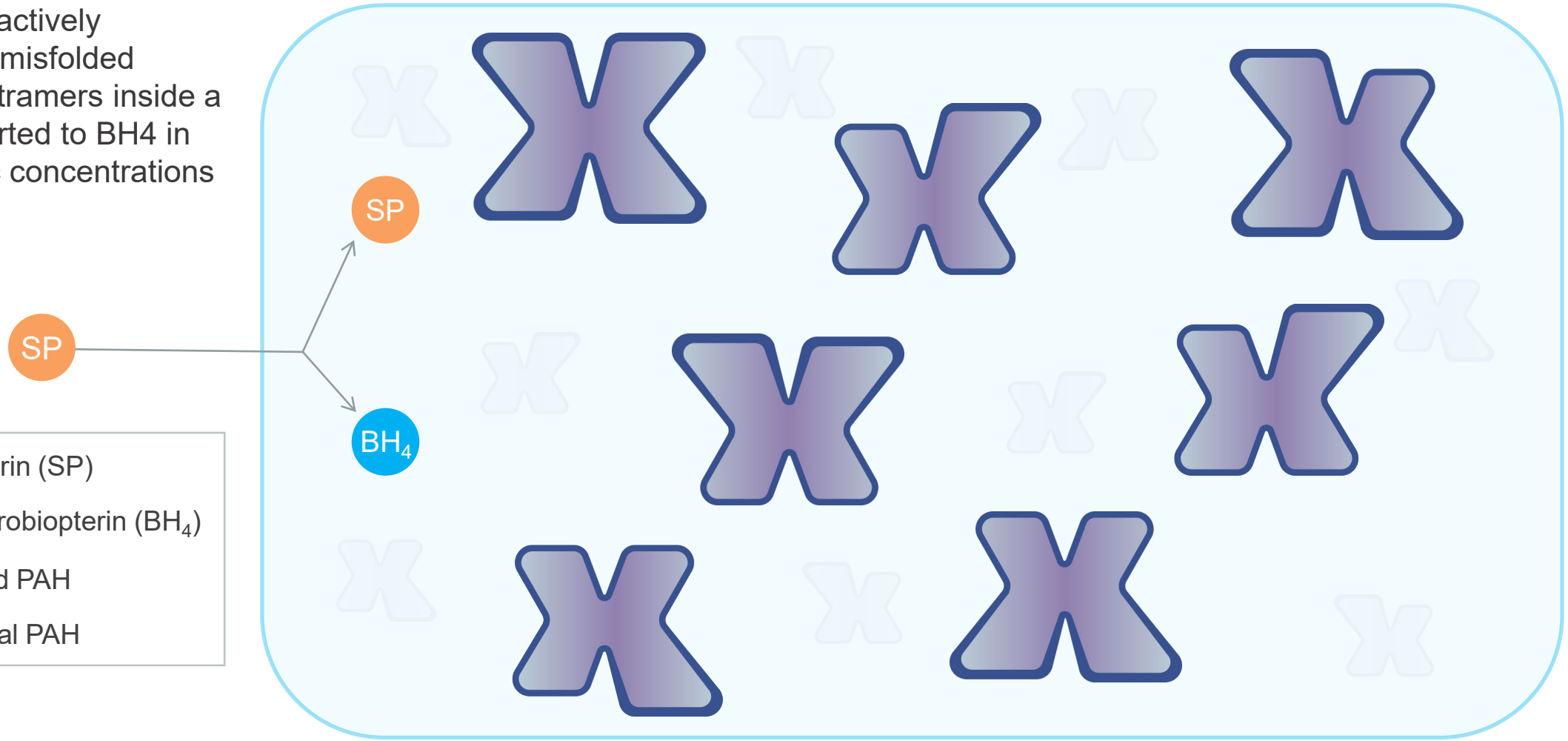
[2]PALYNZIQ label (pegvaliase-pqpz) – Accessdata.fda.gov, [3]Kramer, J. et al. Mol Genet Metab 2023; 139: 1-9

Mechanistic Advantages of Sepiapterin Over Sapropterin



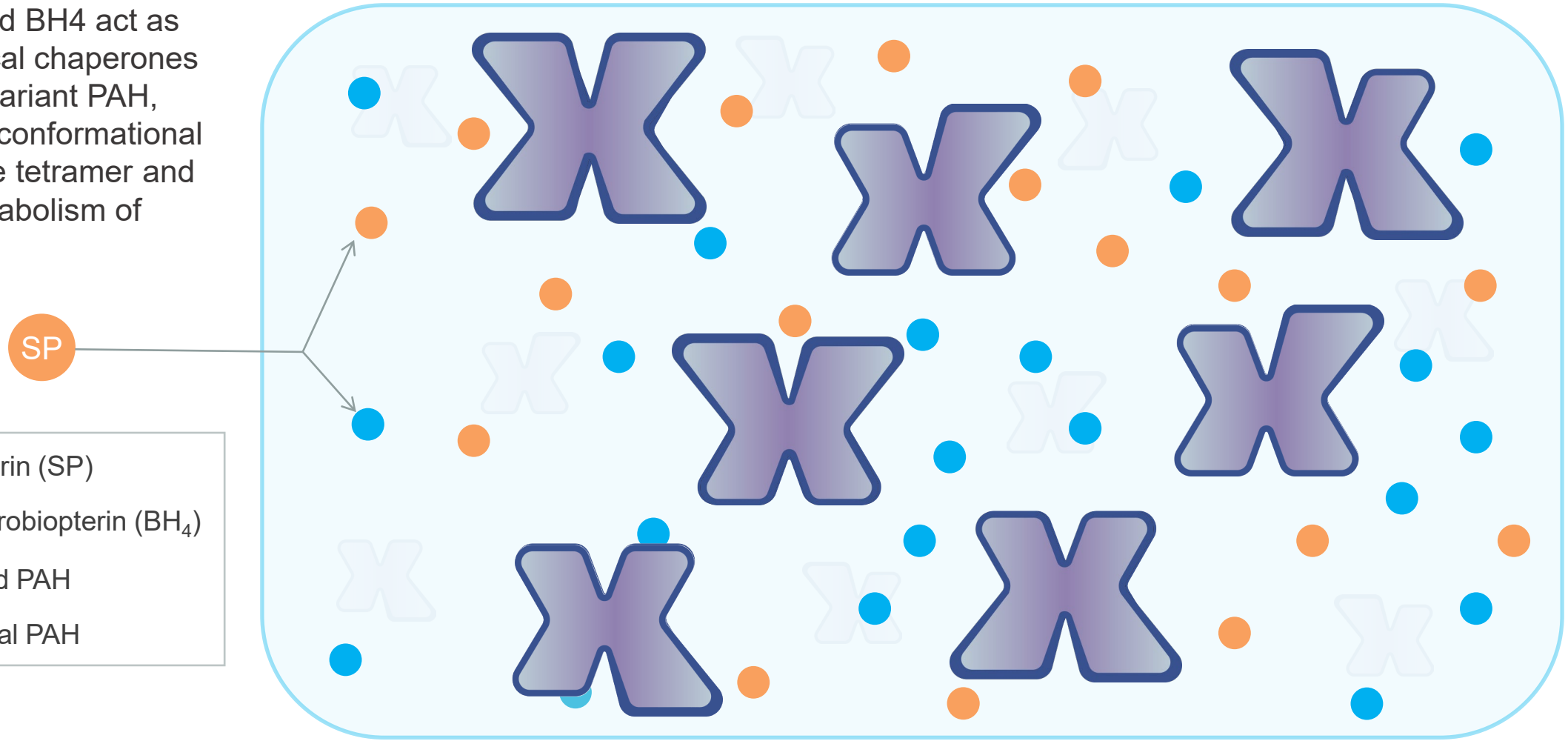
Additive Effects of Sepiapterin

Sepiapterin is actively transported to misfolded variant PAH tetramers inside a cell and converted to BH4 in pharmacologic concentrations

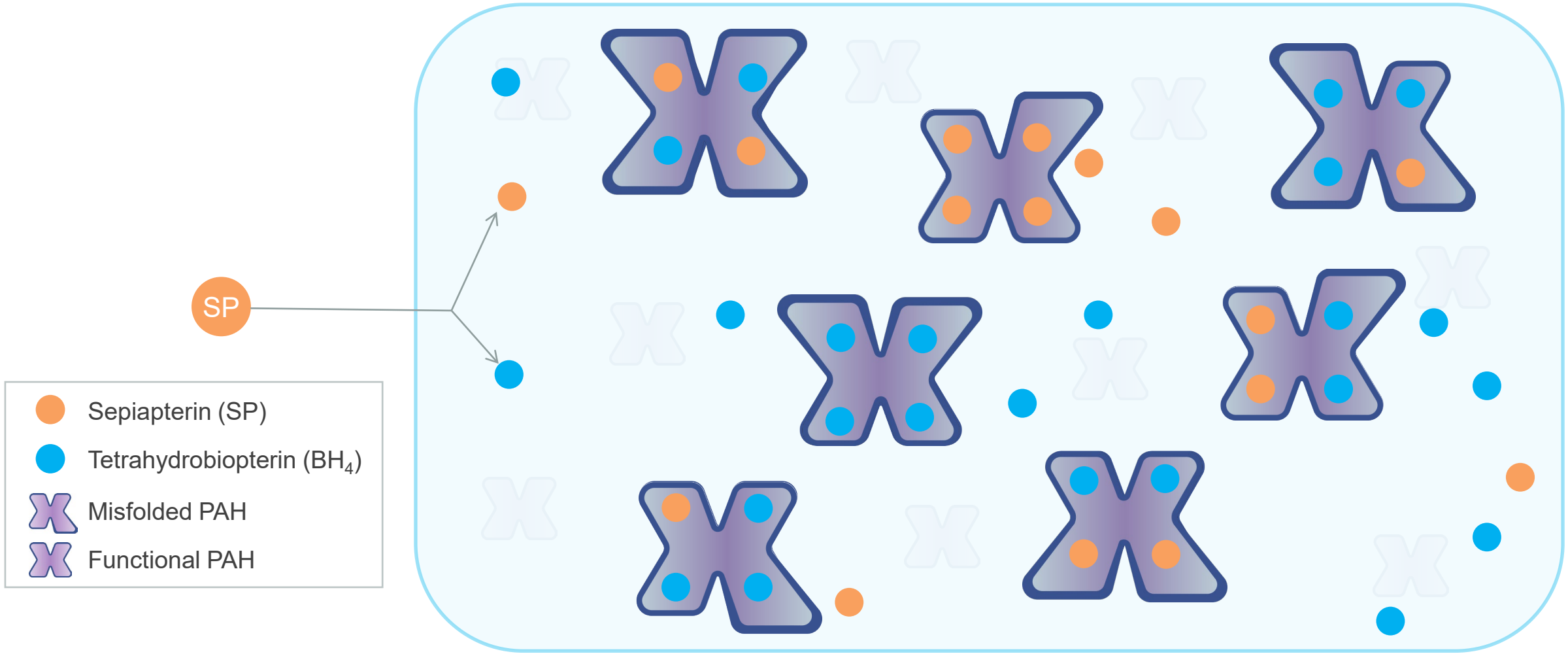


Additive Effects of Sepiapterin

Sepiapterin and BH4 act as pharmacological chaperones by binding to variant PAH, correcting the conformational structure of the tetramer and promoting metabolism of Phe to Tyr



Additive Effects of Sepiapterin



Potential for Sepiapterin to Address Majority of PKU Patients

Sepiapterin Patient Segments

- Therapy-Naive Patients Including Classical PKU
- Patients Who Have Failed on Current Therapies
- Patients Who Are Not Well Controlled

Unmet Need Remains in PKU That Can Potentially Be Addressed by Sepiapterin

PKU leads to a toxic accumulation of Phe in the brain and must be treated from birth

Current therapies are not suitable for all PKU patients, and a large unmet need remains

Sepiapterin has potential advantages over both sapropterin and Palynziq and can potentially treat a broader range of PKU patients

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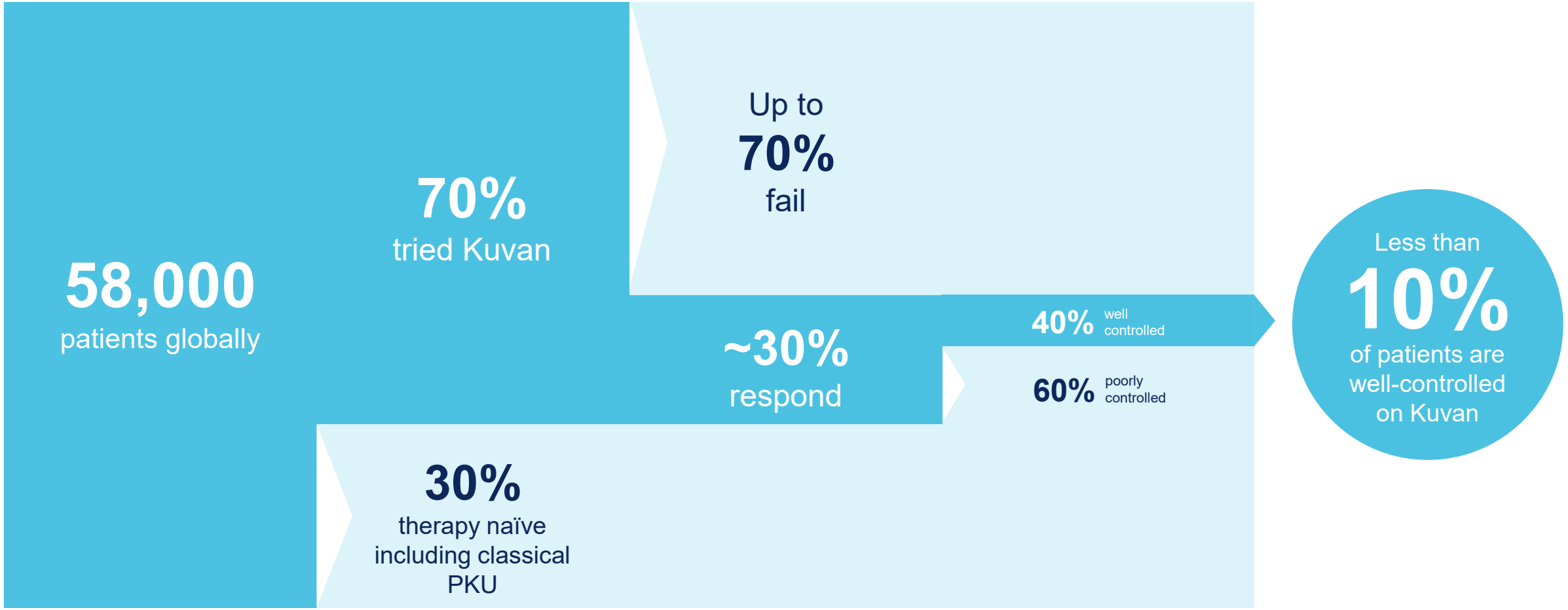
2 Clinical Practice in PKU

3 **Commercial Landscape for Sepiapterin**

Unmet Need in PKU

Large Unmet Need Remains in PKU



1. BioMarin first quarter 2021 presentation 1Q 2021. 2. Third party reports prepared for PTC

The PKU Patient Journey Begins at Birth and Continues Throughout Life

Newborn Screening

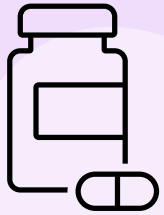
Geneticist/Pediatric Metabolic Specialist & Dietitian

Life-long Protein Restriction, Medical Foods & Formulas

Social Isolation, Anxiety, Depression, Fatigue

Key Issues in PKU Management

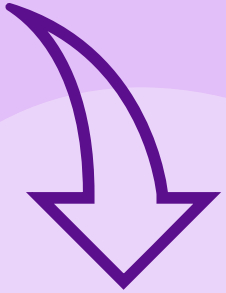
The majority of PKU patients on diet alone do not achieve effective Phe control by early adulthood due to difficulty staying on the unpalatable, expensive foods and medical formulas required



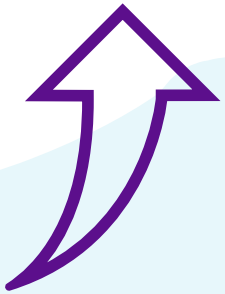
A large majority of PKU patients are not well-controlled on any approved treatment or combination of treatments

The consequences of lack of effective Phe control can be devastating to the quality of life for these patients and irreversible in terms of intellectual disability

Two Main Goals of Therapy for PKU Patients



Decreased Blood Phe Levels



Increased Dietary Protein Intake (Phe Tolerance)

Significant Correlation Between Blood Phe Level and IQ

Correlations between Phe level and intelligence quotient (IQ) were extracted from 40 studies and confirmed a significant correlation between blood Phe level and IQ[1]

Each **100 µmol/l** increase in Phe predicted a

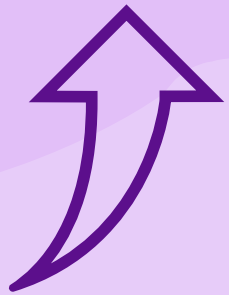
1.9 to 4.1

point reduction in IQ

[1] Waisbren et al. Mol Genet Metab (2007) Sep-Oct;92(1-2):63-70

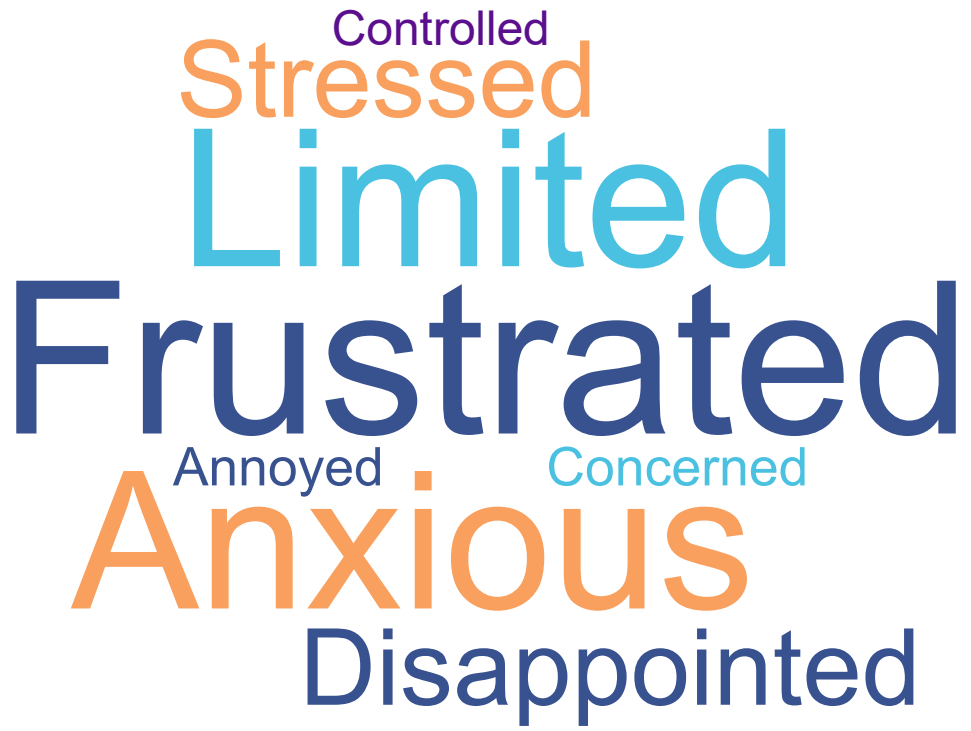
Two Main Goals of Therapy for PKU Patients

Decreased Blood Levels Phe



Increased Dietary Protein Intake (Phe Tolerance)

Keeping a Strict Diet Is the Largest Burden and Makes Patients Constantly Feel Frustrated and Extremely Limited



Patients were asked their current feelings about their dietary restrictions

- *Patients currently feel **limited, frustrated, and anxious** regarding their current PKU situation*
- *The **inability to eat the same foods as their friends** and having **limited options at restaurants and school cafeterias** heighten these unpleasant emotions*
- ***Easing diet restriction is the primary driver** for patients to seek more therapeutic options*

TRINITY US Qualitative Interviews (N=20 HCPs; N=10 PKU Patients)

Diet for Non PKU Patient

Diet for PKU Patient

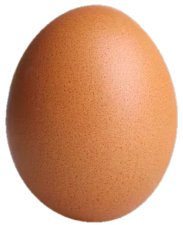
PTC THERAPEUTICS

The Burden of a PKU Diet is Substantial

What is in 5-10g of protein **a day?**

2g of protein

1-2g of protein



6g of protein

Avoid all high protein foods

Limited natural protein: under 10g/day

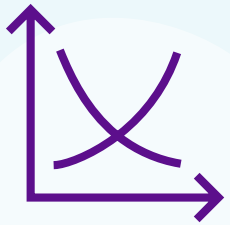
Very low protein foods allowed

Special low protein prescription foods

Protein substitute – must be taken at least 3 times daily

Patient Perspective

Patients Want a Treatment That Allows Them to Liberalize Their Diet While Decreasing the Inconveniences of Some Side Effects

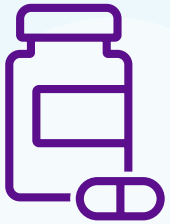


Efficacy

- Patients want a treatment that will reduce the Phe levels significantly
    1. Allow them to eat more protein and **liberalize their diet**
    2. **Improve their cognitive fog and focus**

Safety

- Patients are concerned about **potential side effects**, especially those that are **serious and/or persistent**



Ease of Use

- Patients mentioned that **ease of use includes route of administration, dosing options, and easy storage**

TRINITY US Qualitative Interviews (N=20 HCPs; N=10 PKU Patients)

Physician Perspective

Blood Phe Reduction and Phe Tolerance Are the Most Important Drivers for HCPs

Blood Phe Reduction

The goal of PKU treatment is to get patient's Phe levels into a target range (120-360μM/L)

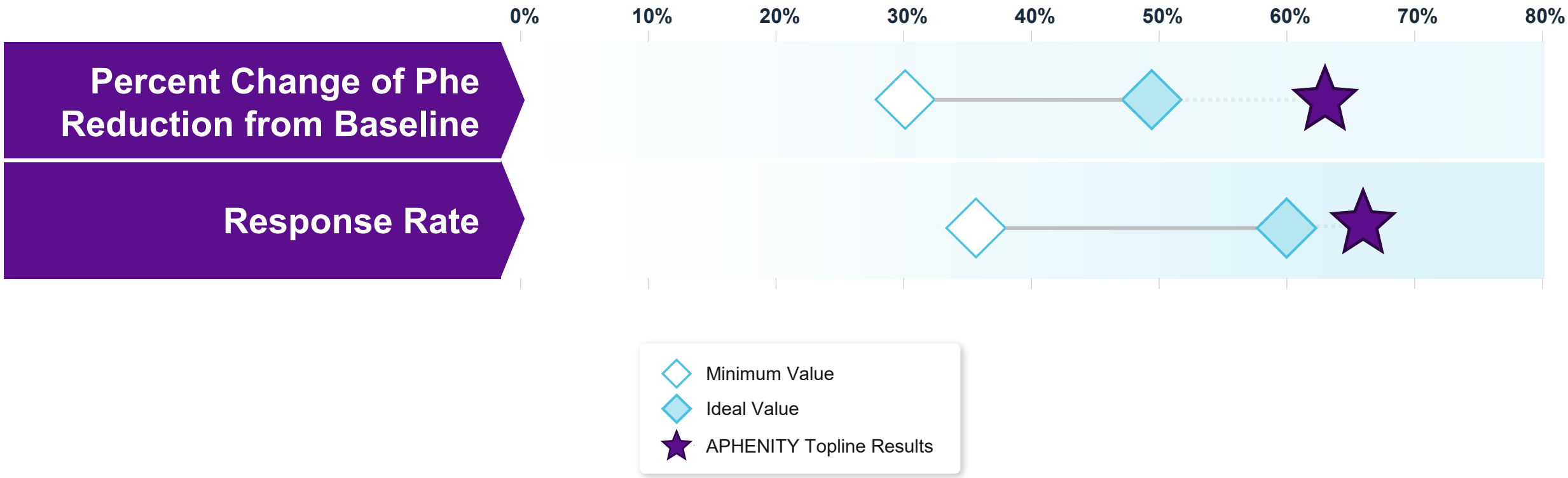
Phe Tolerance

Physicians place high importance on Phe tolerance due to issues with outcomes from diet alone

Quality of Life

TRINITY US Qualitative Interviews (N=20 HCPs; N=10 PKU Patients)

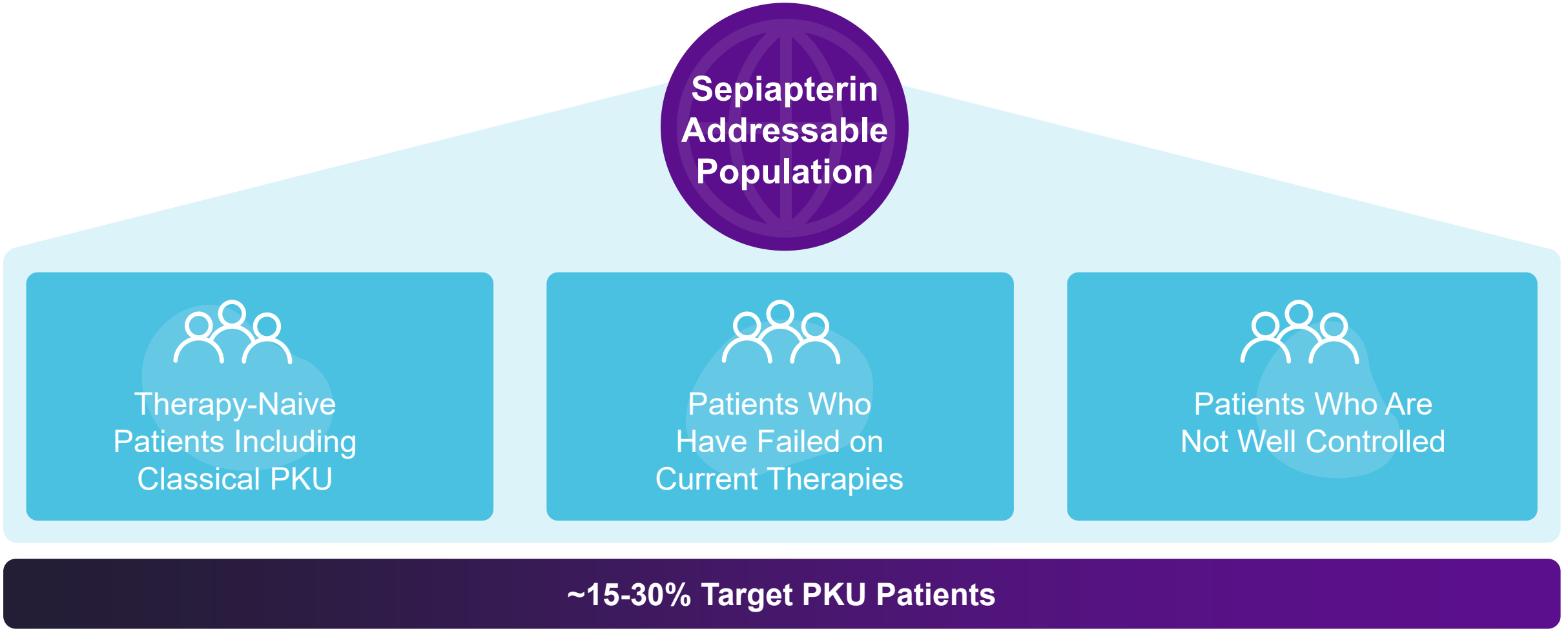
Physicians Expect 30%-50% Phe Reduction from Baseline for a First-Line PKU Therapy



TRINITY US Qualitative Interviews (N=20 HCPs; N=10 PKU Patients) (Data on File)

Commercial Launch Strategy

APHENITY Results Support Potential for Sepiapterin to Address Majority of PKU Segments



Commercial Pillars for Success Already Established

Newborn screening with ~58,000 patients worldwide[1,2,3]

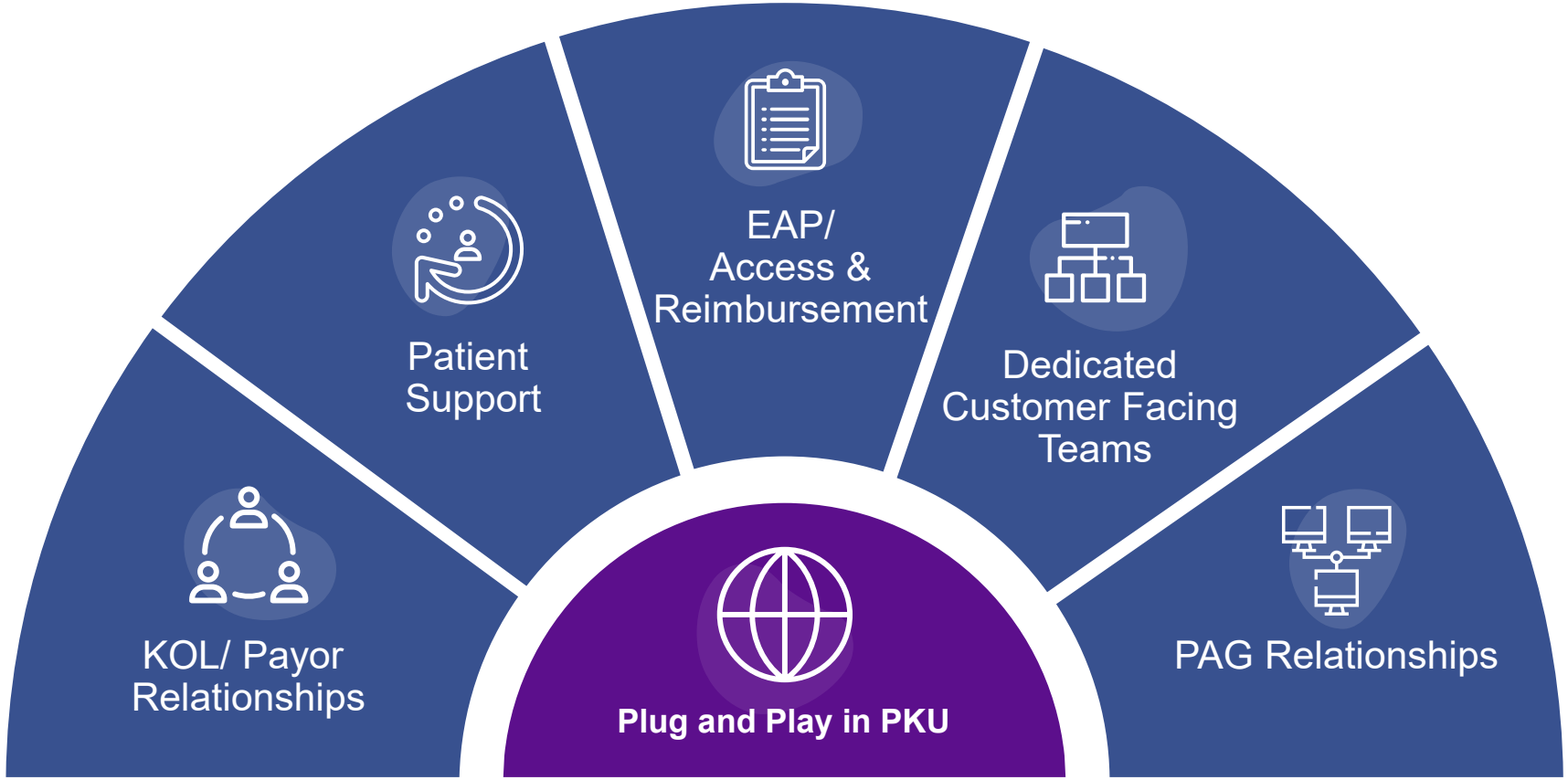
Well-known metabolic centers of excellence worldwide

Disease pathology well understood and documented

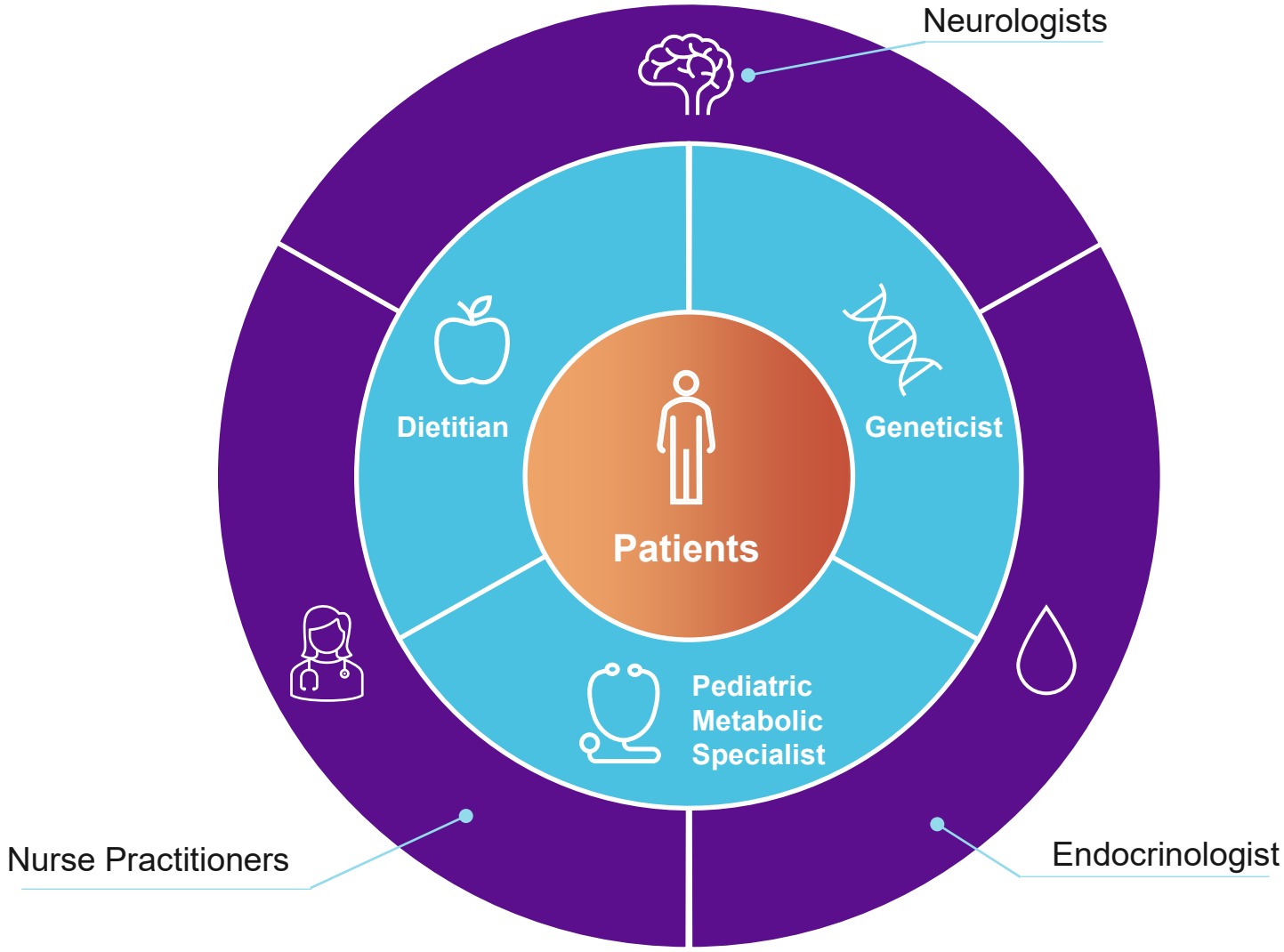
Connected and coordinated patient advocacy community

1. NPKUA; https://www.npkua.org/, 2. Shoraka et. Al, Clin Exp Pediatr. 2020; 63(2): 34–43., 3. Borrajo G., Acta Ped Mex. 2012; 33(6): 279-287.

PTC Global Commercial Infrastructure Will Allow for Rapid Worldwide Launch



Understanding the Cross-Functional Team at PKU Clinics

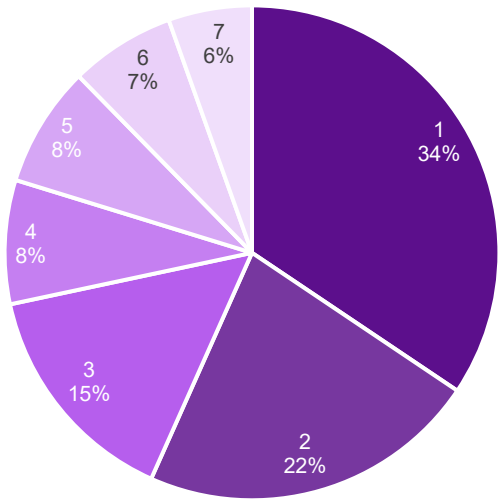


We Have a Deep Understanding of US PKU Treaters and How to Reach Them

~500 HCPs

Kuvan Writers

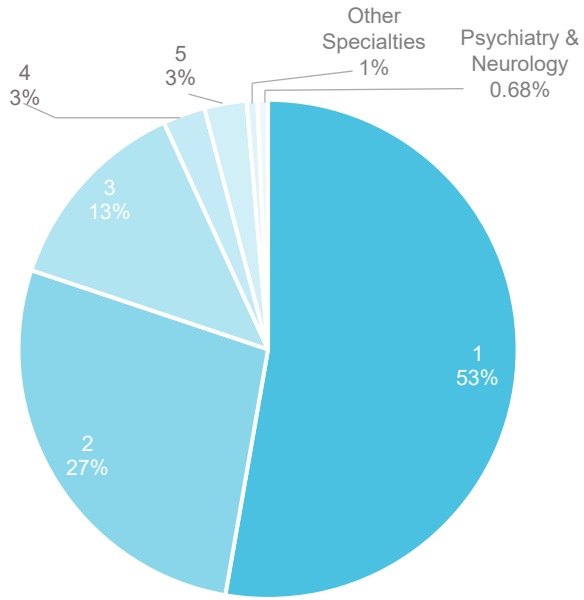
Treating ~3,000 PKU patients



~150 HCPs

Palynziq Writers

Treating ~1,000 PKU patients



Overlap exists between KUVAN and PALYNZIQ writers

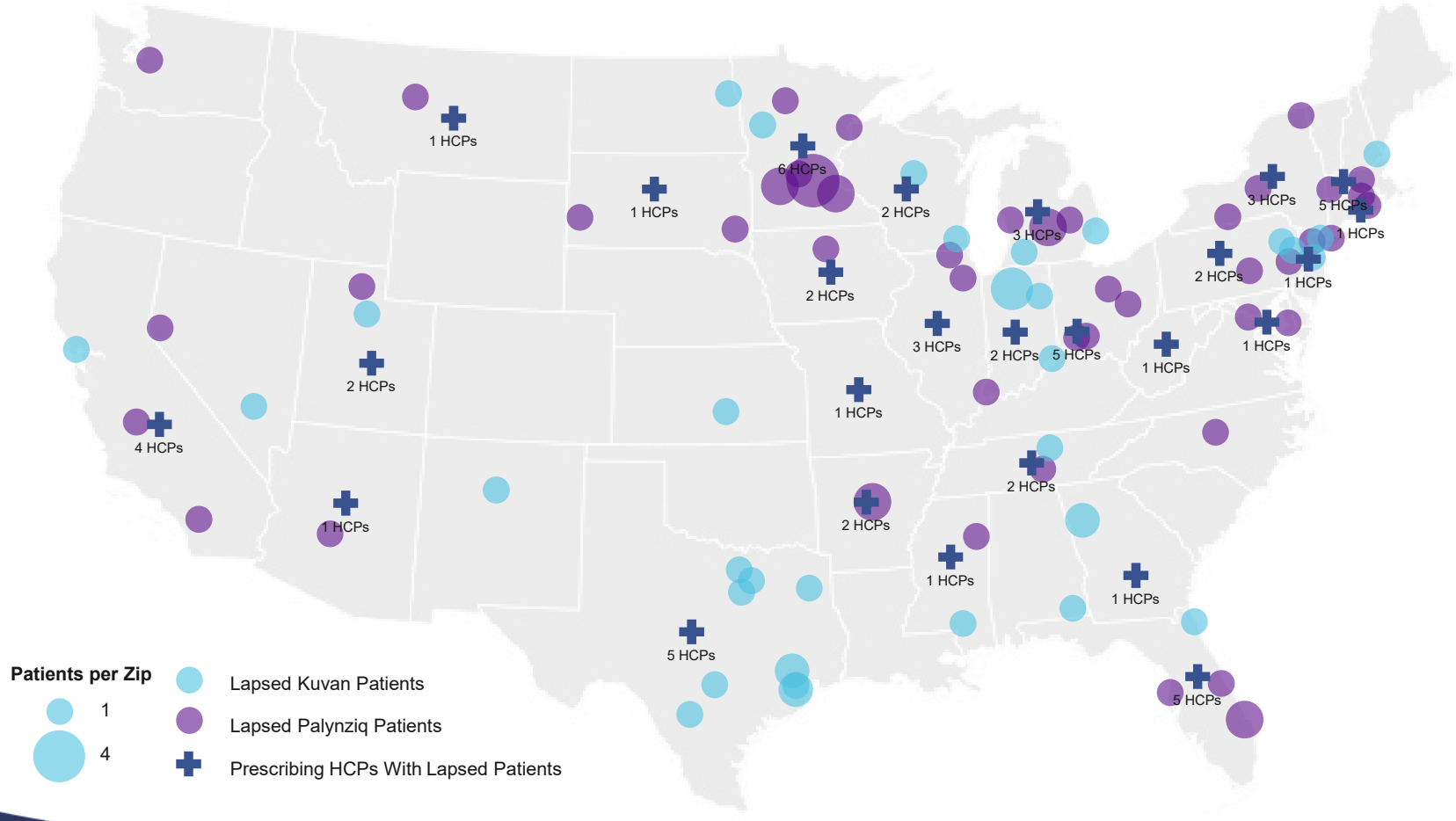
For each US HCP we have visibility into:

- First/Last Name
- Provider taxonomies and demographics
- Affiliation Hierarchy
- Institutional vs Professional claim types, with differentiation of treatment settings
- Line-item charge details for visit types, procedures, and prescriptions
- Patient makeup and volume
- Professional practice address
- Email
- NPI number, which is used for one-to-one media targeting and sales call planning

Lucid Connected Intelligence Real-World Claims Data

Initial Areas for New Treatment Consideration Have Been Identified

Real-world data reveals a valuable opportunity among clinicians with lapsed Kuvan & Palynziq users



~60 HCPs

Kuvan and/or Palynziq Writers With Lapsed Patients

Lucid Connected Intelligence Real-World Claims Data

Key Professional Associations & Patient Advocacy Groups

Scientific Medical Associations:

ACMG American College of Medical Genetics and Genomics

SIMD Society for Inherited Metabolic Disorders

SSIEM

ICIEM 2021 21-23 NOVEMBER 2021, SYDNEY, AUSTRALIA 14TH INTERNATIONAL CONGRESS OF INBORN ERRORS OF METABOLISM

Dietitian/Nutritionist Associations:

GMDI Genetic Metabolic Dietitians International

SSIEM DIETITIANS GROUP

Patient Advocacy Groups:

National PKU Alliance

E.S.PKU

Canadian PKU and Allied Disorders Inc

Metabolic Dietary Disorders Association

gap Global Association for PKU — Bridging the gap for PKU worldwide

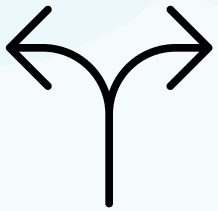
PTC Therapeutics

Setting the Launch Strategy for an Effective PKU Treatment That Works for More Patients

Build Confidence

in the efficacy and safety of sepiapterin at launch

- Amplify strong clinical data and MOA
- Physician and Patient Education Programs

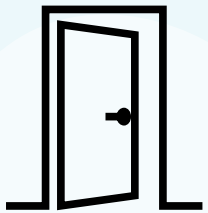


Establish Differentiation

through the clinical body of evidence

- Leverage advocates
- Provide superior patient support

PTC Cares™



Ensuring Access

to the broadest range of PKU patients

- Pricing/reimbursement strategy
- Early access programs

PTC THERAPEUTICS

APHENITY Results Support Next Steps in the Regulatory Process and Commercial Planning

aphenity

Pre-Submission Meetings

Regulatory Submissions

Initiate Launch Preparation

PTC THERAPEUTICS

PTC Therapeutics PKU Deep Dive

July 19, 2023

Patient Living with PKU