

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.

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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



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



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



Established market leadership in all major markets with continued growth expected



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



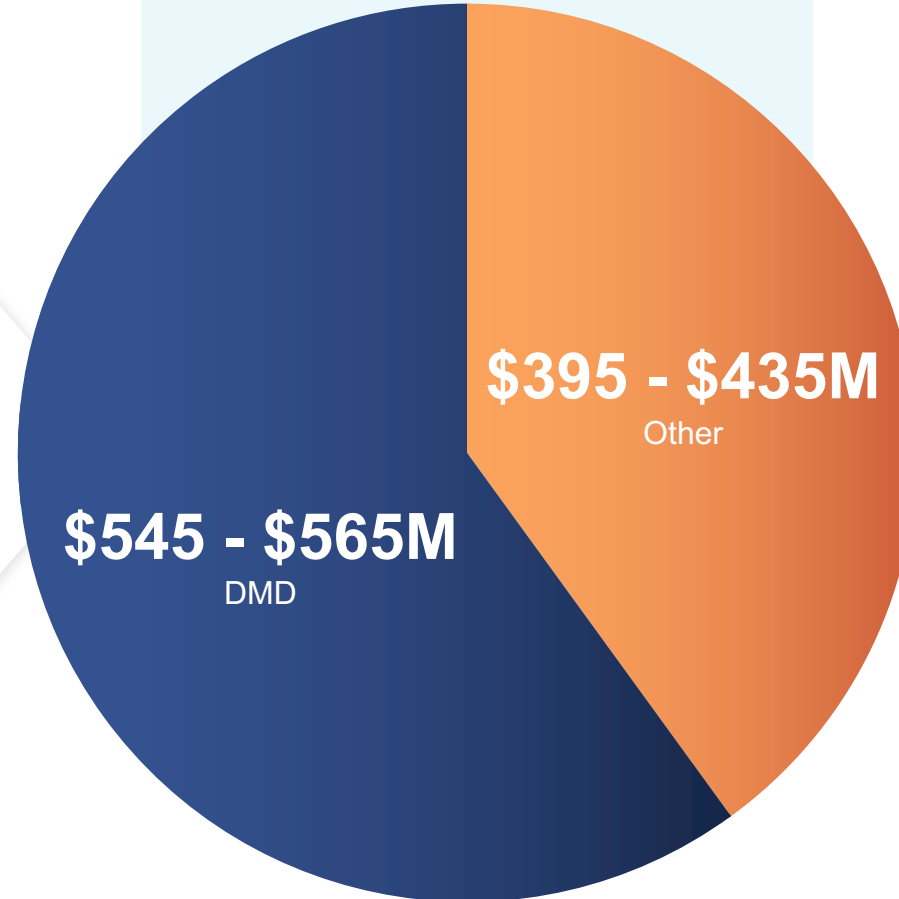
For treatment of hATTR with LATAM patients benefiting through early-access programs



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

Evrysdi®
risdiplam

Tegsedi®
(inotersen) injection
204 mg/1.5 mL

Upstaza™
(eladocagene exuparvovec)

waylivra®
(volanesorsen) injection
265 mg/1.5 mL

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

APHENITY Topline Results



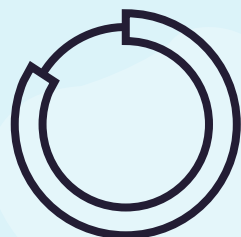
APHENITY Topline Results Demonstrate Clinical and Statistically Significant Benefit



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%)



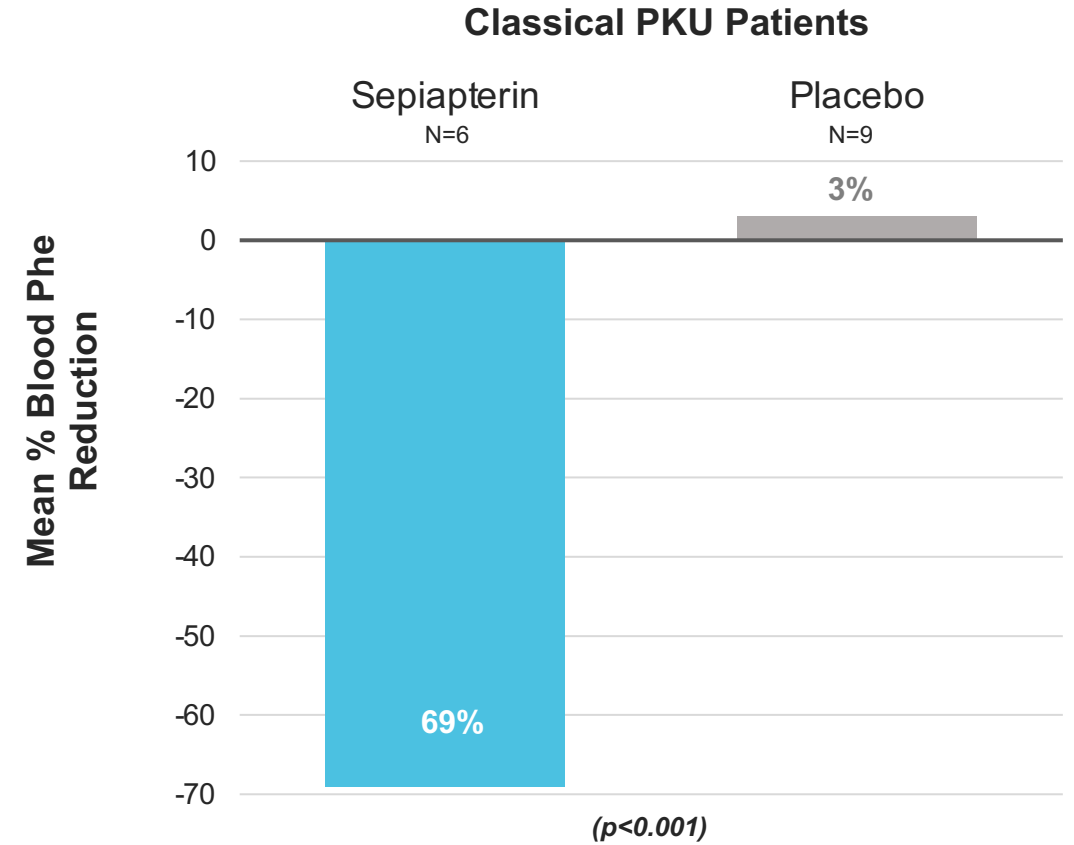
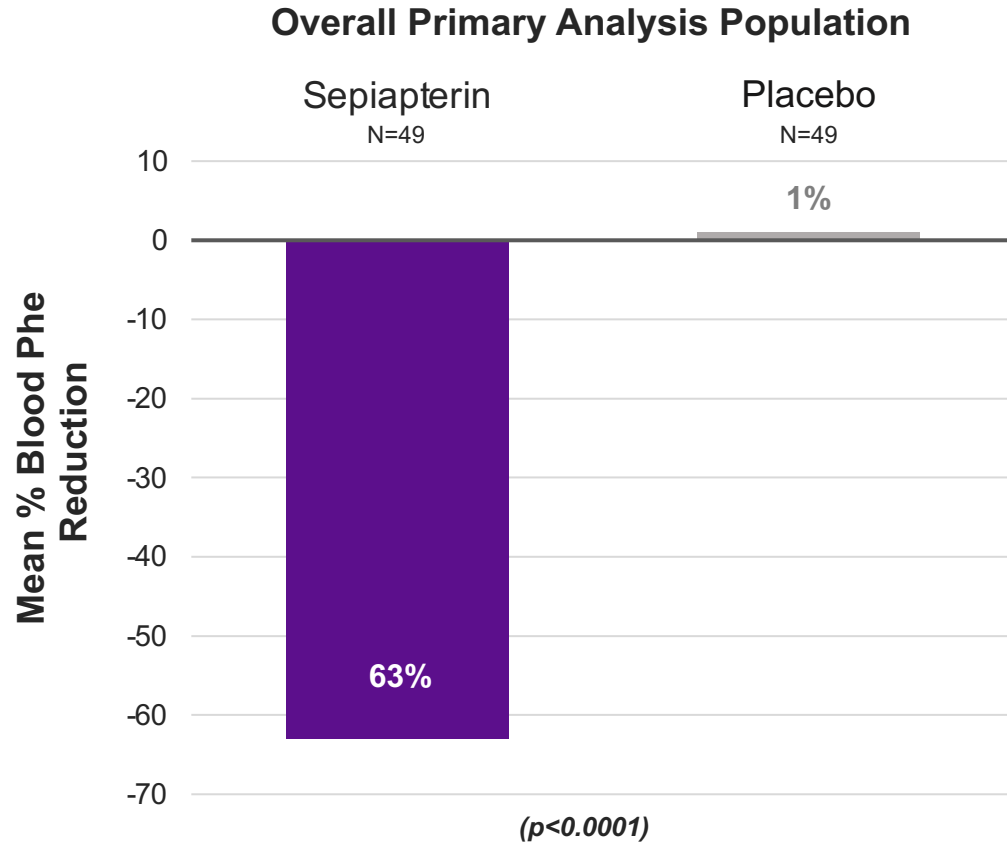
Achieved Phe reduction sufficient to bring **84% of study patients within US guidelines** for Phe reduction $< 360 \mu\text{mol/L}$



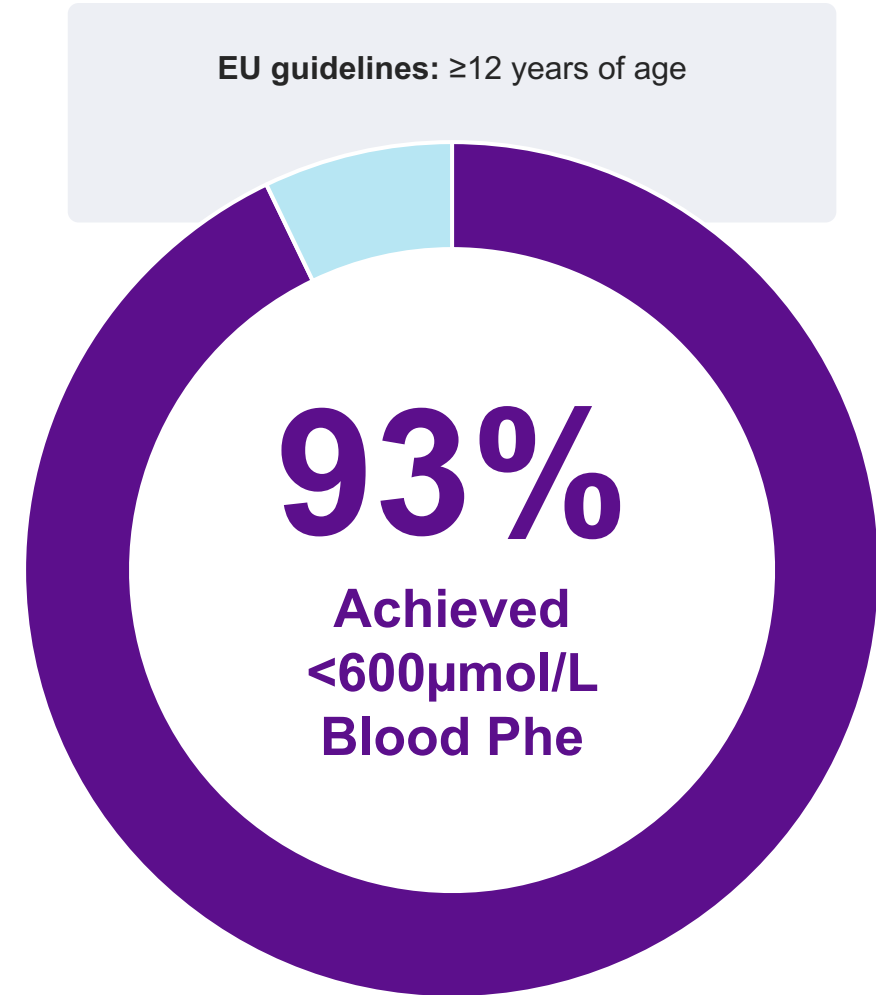
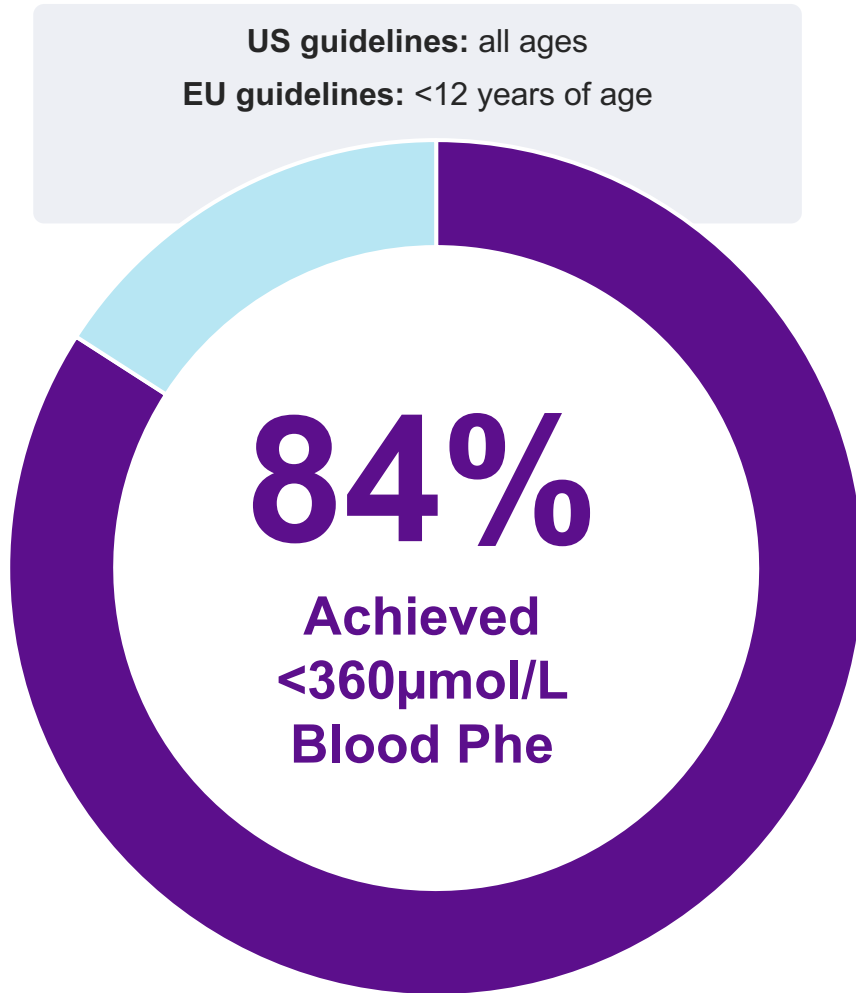
Well tolerated with no serious adverse events

Sepiapterin Treatment Resulted in Clinically Significant Blood Phe Reduction

Mean % Blood Phe Reduction

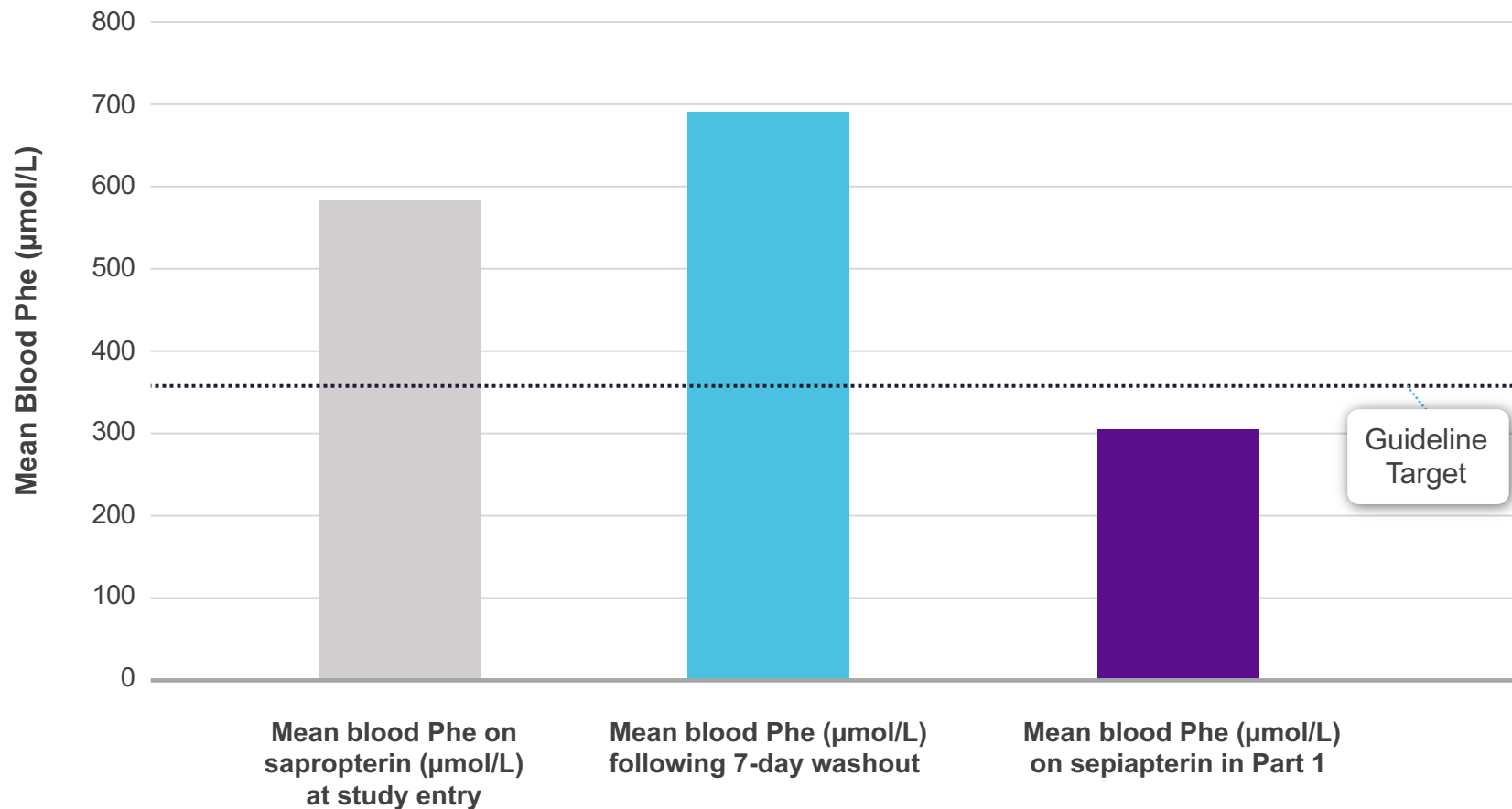


Vast Majority of Patients Achieved Guidelines Target Blood Phe Levels



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

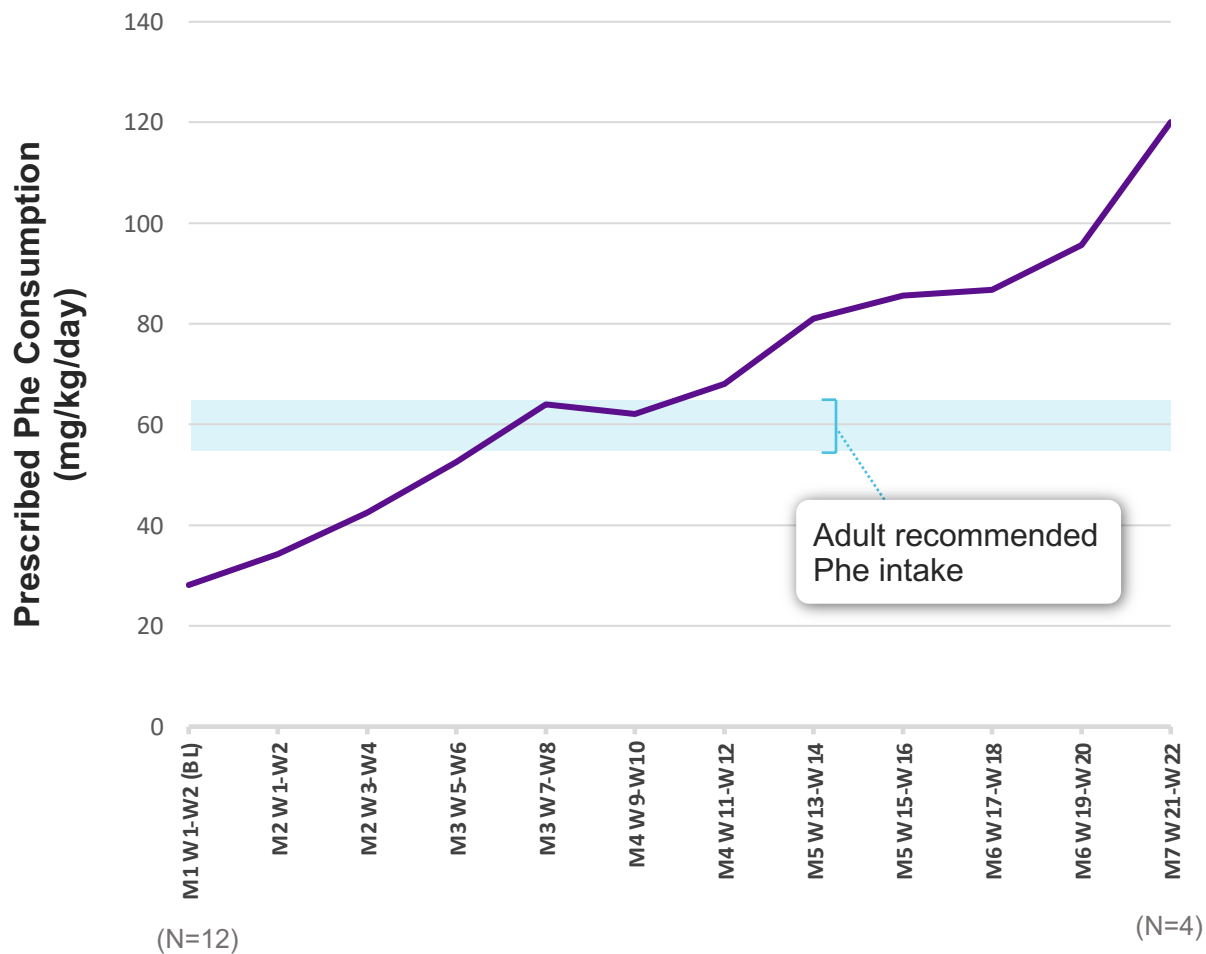
(N=27 patients)



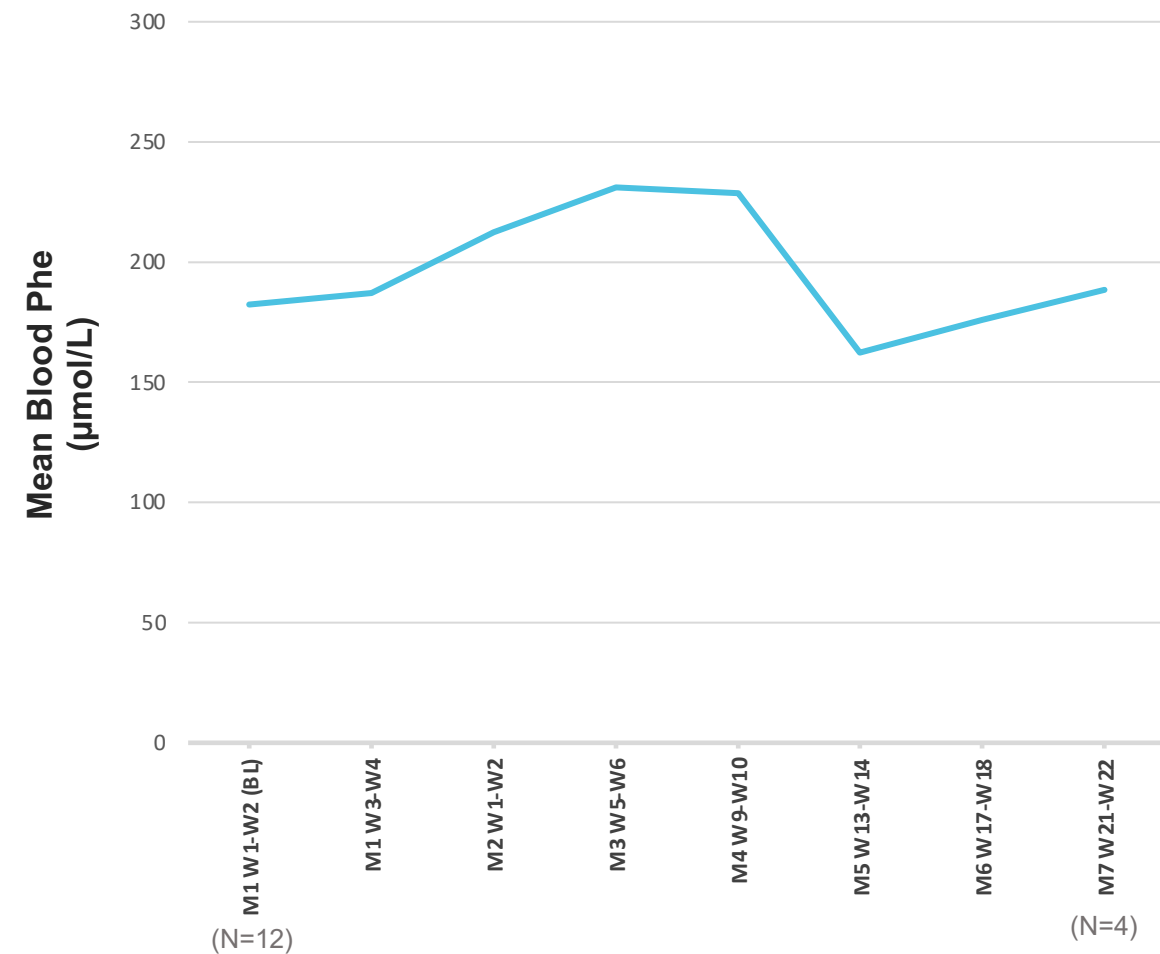
48%
lower Phe levels following sepiapterin treatment in those patients receiving sapropterin at study entry

Initial Phe Tolerance Data in Open-Label Extension

Increase in Dietary Phe Intake



Blood Phe Levels



Agenda

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 condition¹



Variants in *PAH*, the gene that encodes PAH, lead to impaired PAH function and cause PKU¹

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 disease²

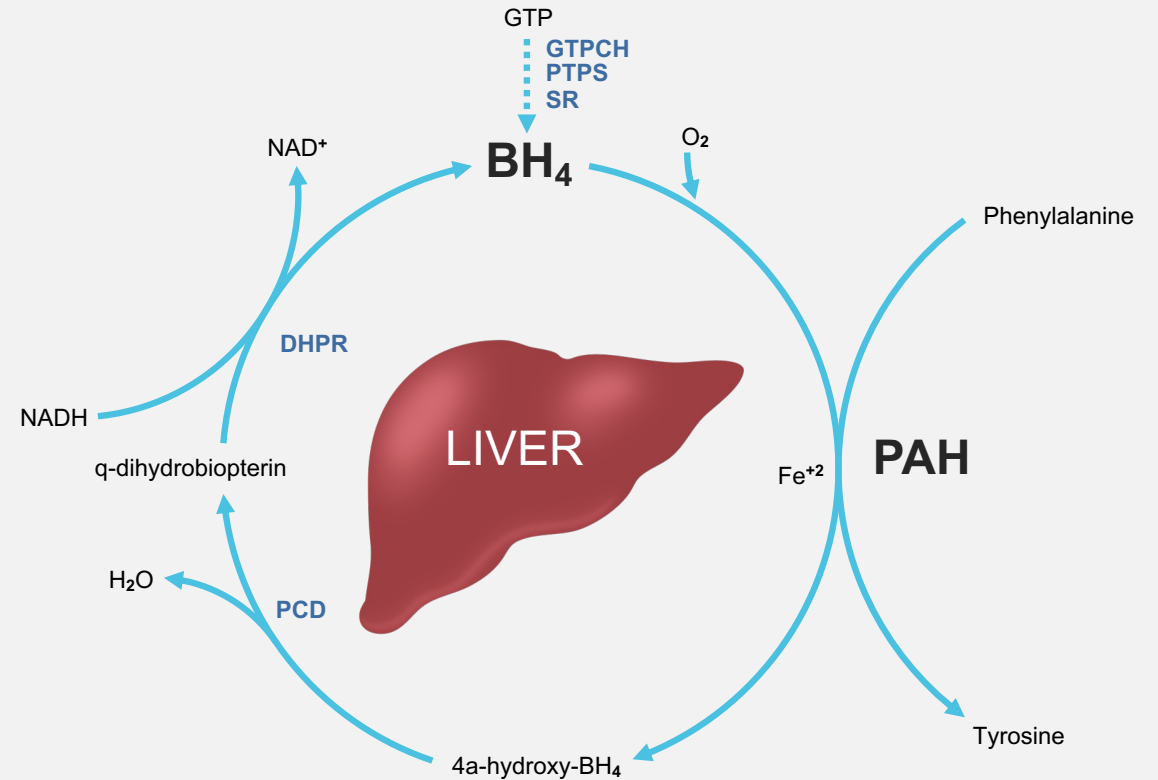
The Role of PAH in Phe Metabolic Pathway

PAH catalyzes the first and rate-limiting step in the metabolic pathway of Phe, conversion of Phe to Tyr¹

BH₄ corrects misfolding and early degradation of PAH and by this improves in-vivo PAH enzyme activity²

Impaired PAH enzymic function leads to a systemic accumulation of Phe

Phenylalanine Hydroxylating System²



Blau N, et al. 2010

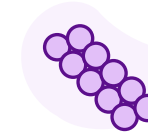
Elevated Blood Phe Interferes With Normal Production of Neurotransmitters and Leads to PKU

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



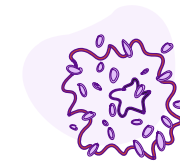
Reduced cerebral glucose metabolism



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

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 Phe¹

	Normal	Mild HPA	Mild/Moderate PKU	Severe PKU
PAH variants associated with loss of PAH function	Normal PAH function	Partially inhibited PAH function		Complete to near-complete loss of PAH function
Blood Phe level	50–110 $\mu\text{mol/L}$	120–600 $\mu\text{mol/L}$	600–1,200 $\mu\text{mol/L}$	>1,200 $\mu\text{mol/L}$
Dietary Phe tolerance		400–600 mg	350–400 mg	250–300 mg

PKU Management Guidelines

ACMG (US) TREATMENT GUIDELINES ¹	EU TREATMENT GUIDELINES ²
<p>The treatment of PKU should be initiated as early as possible.</p>	<p>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.</p>
<p>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.</p>	<p>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.</p>

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

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

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



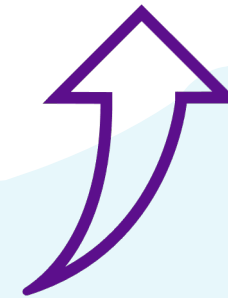
Adults

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

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



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

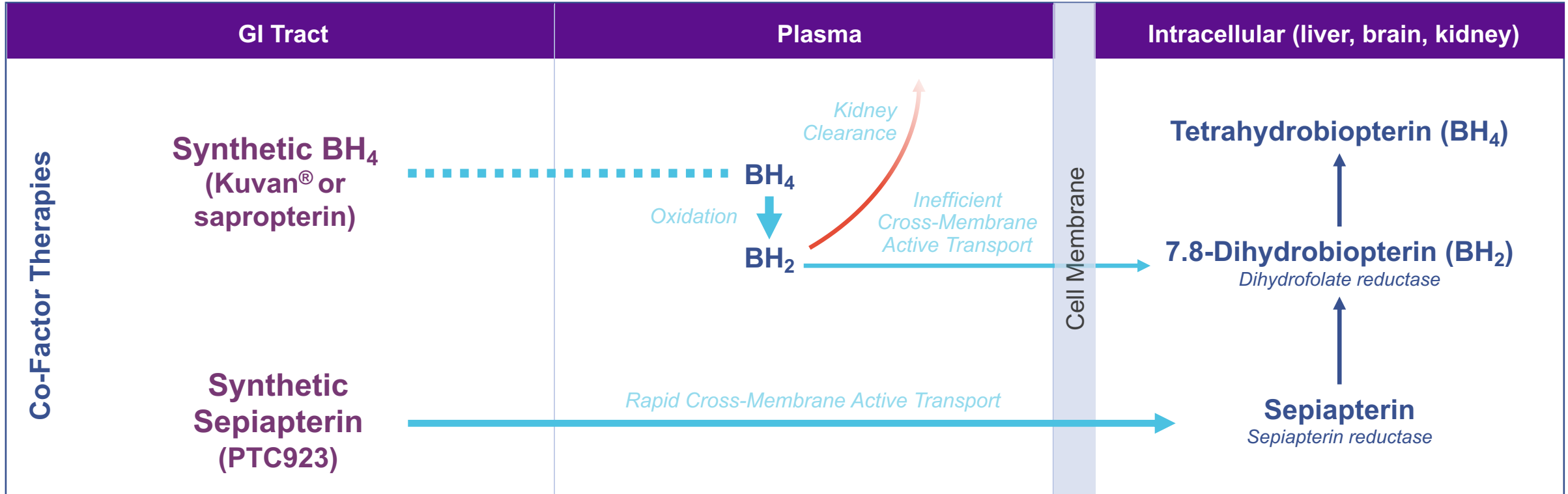


Indication: Adults who have uncontrolled blood Phe ($>600 \mu\text{mol/L}$) on existing management

Clinician Reported Challenges^{1,2}

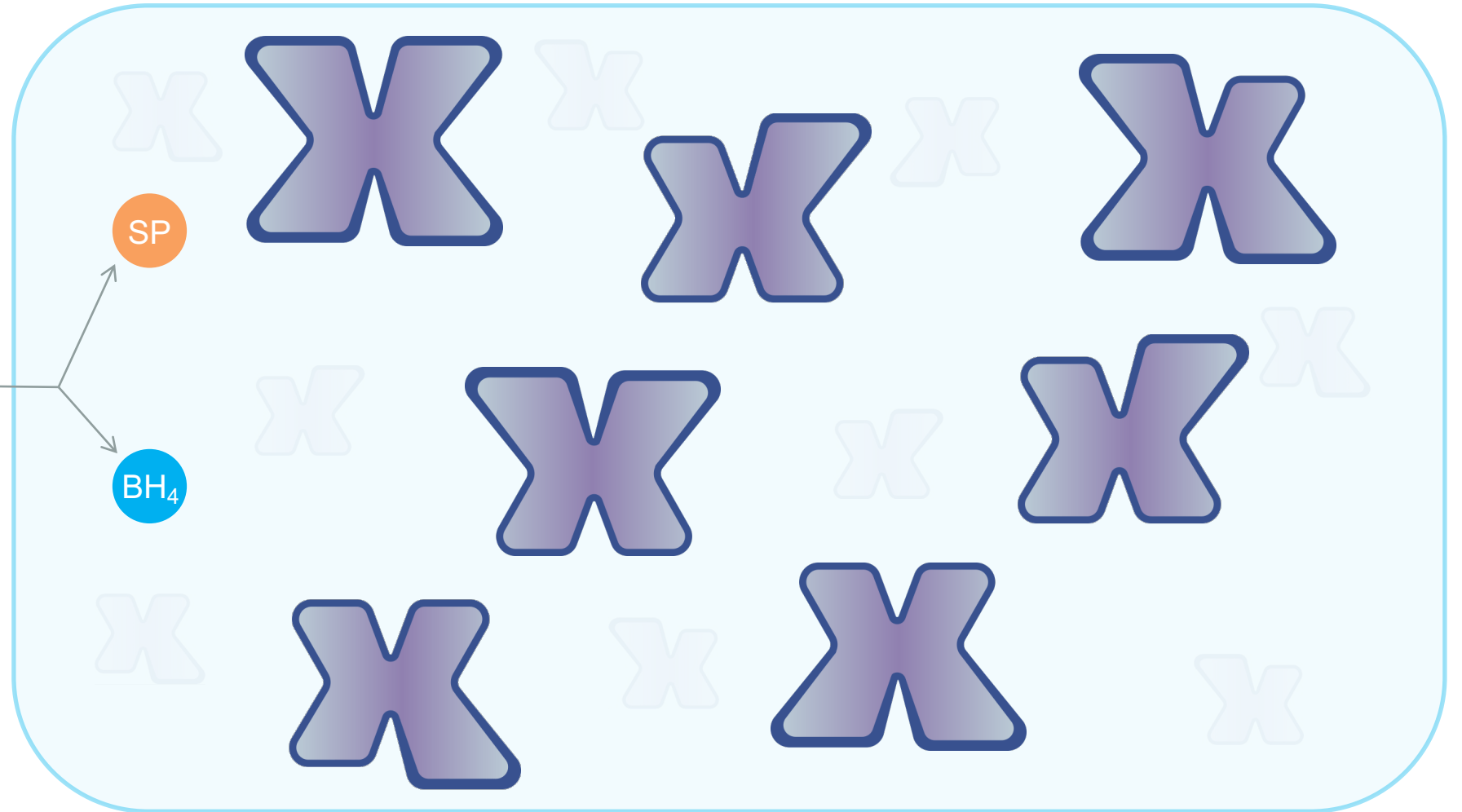
- Palynziq is indicated only for adults
- Demonstrated safety issues, including anaphylaxis
- Inconvenient injectable administration, and lengthy titration process

Mechanistic Advantages of Sepiapterin Over Sapropterin



Additive Effects of Sepiapterin

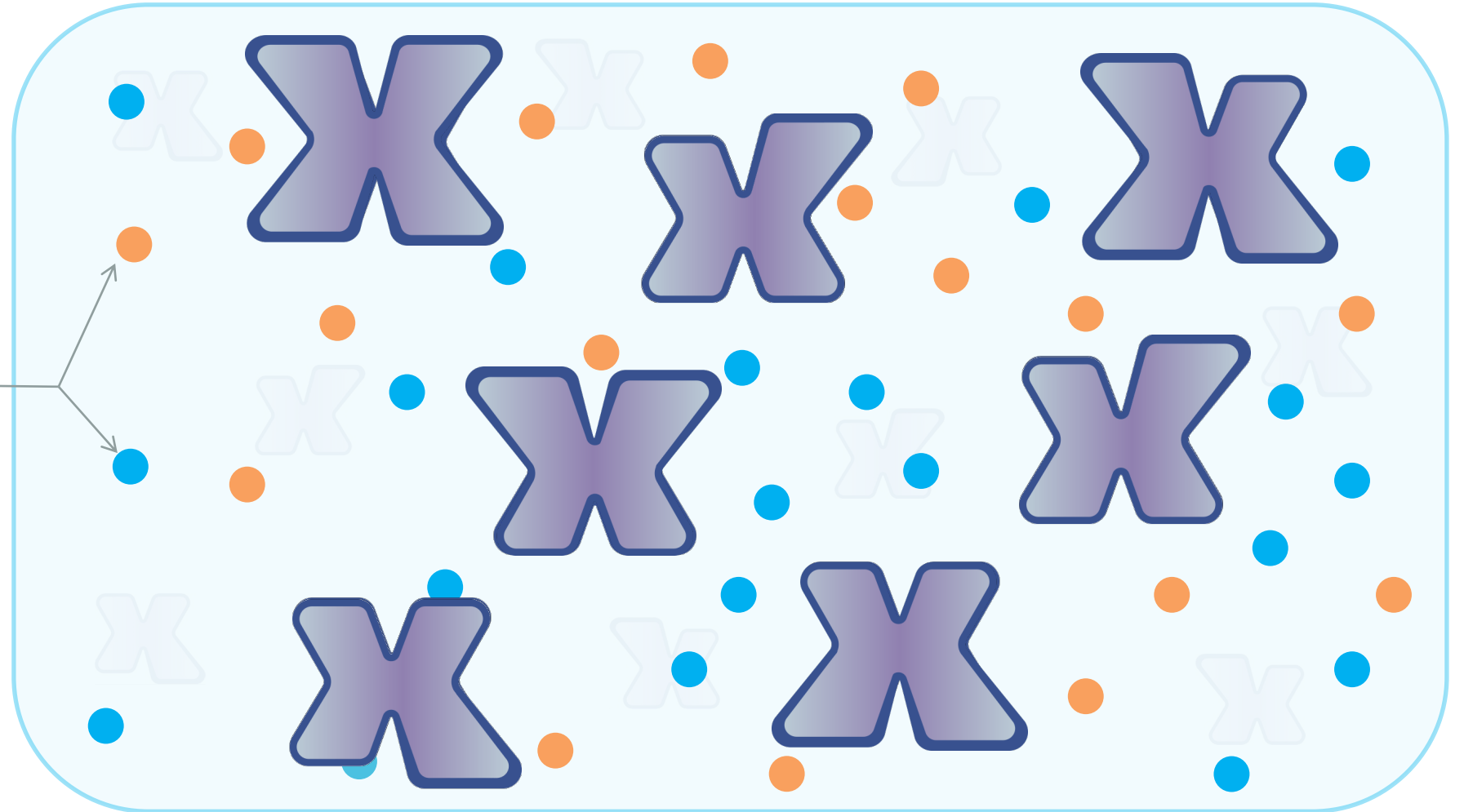
Sepiapterin is actively transported to misfolded variant PAH tetramers inside a cell and converted to BH₄ in pharmacologic concentrations



- Sepiapterin (SP)
- Tetrahydrobiopterin (BH₄)
- ✕ Misfolded PAH
- ✕ Functional PAH

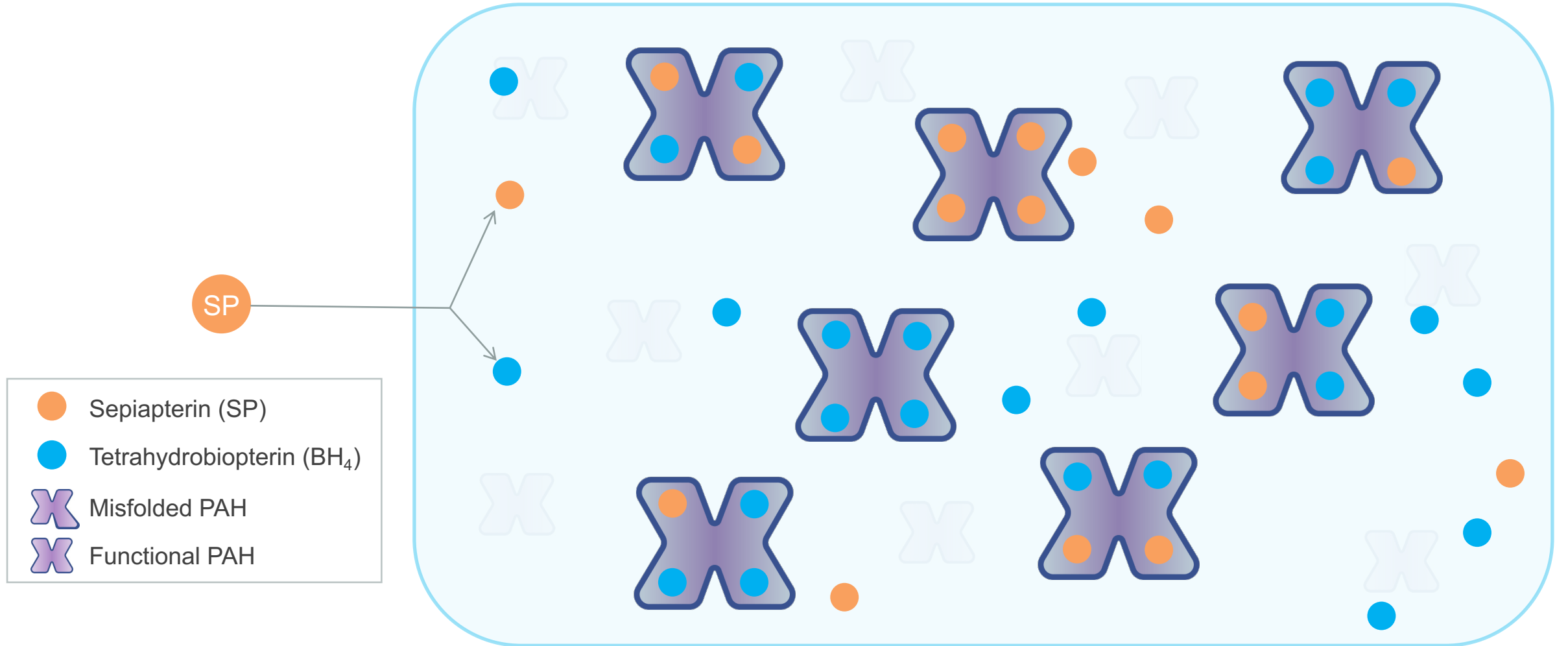
Additive Effects of Sepiapterin

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



- Sepiapterin (SP)
- Tetrahydrobiopterin (BH₄)
- ✕ Misfolded PAH
- ✕ Functional PAH

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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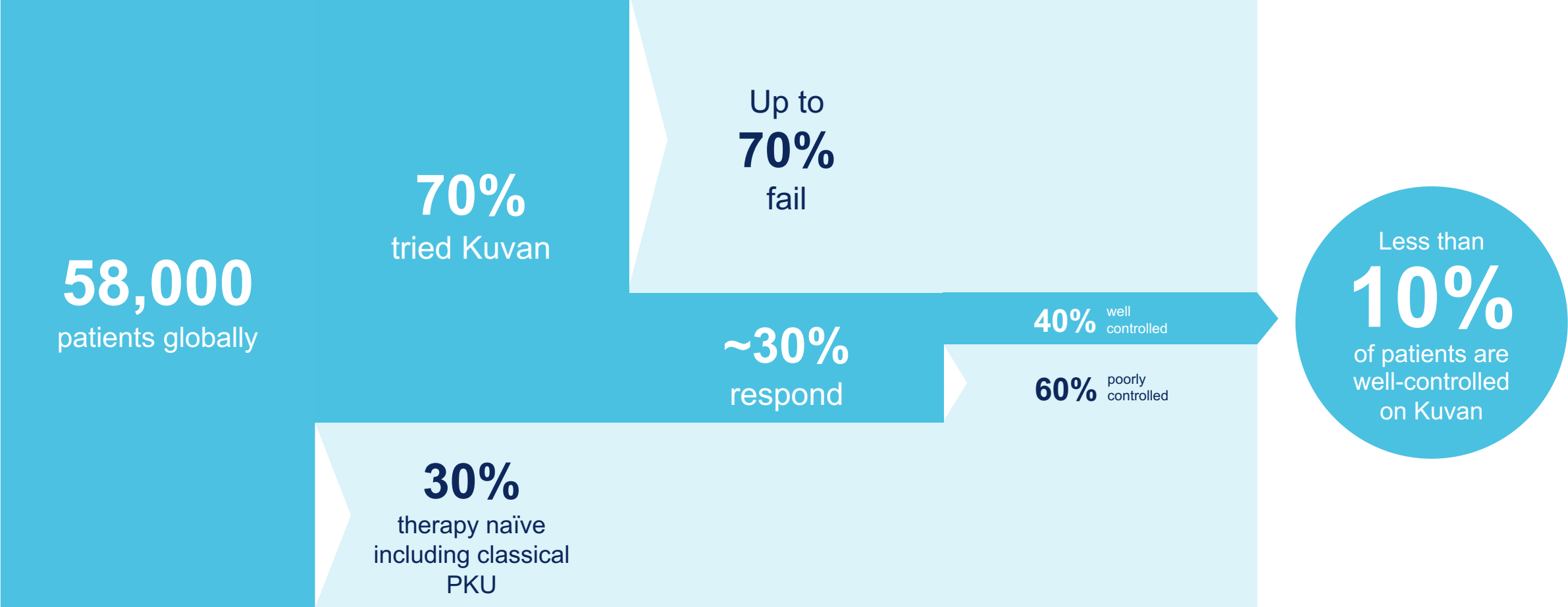
Commercial Landscape for Sepiapterin



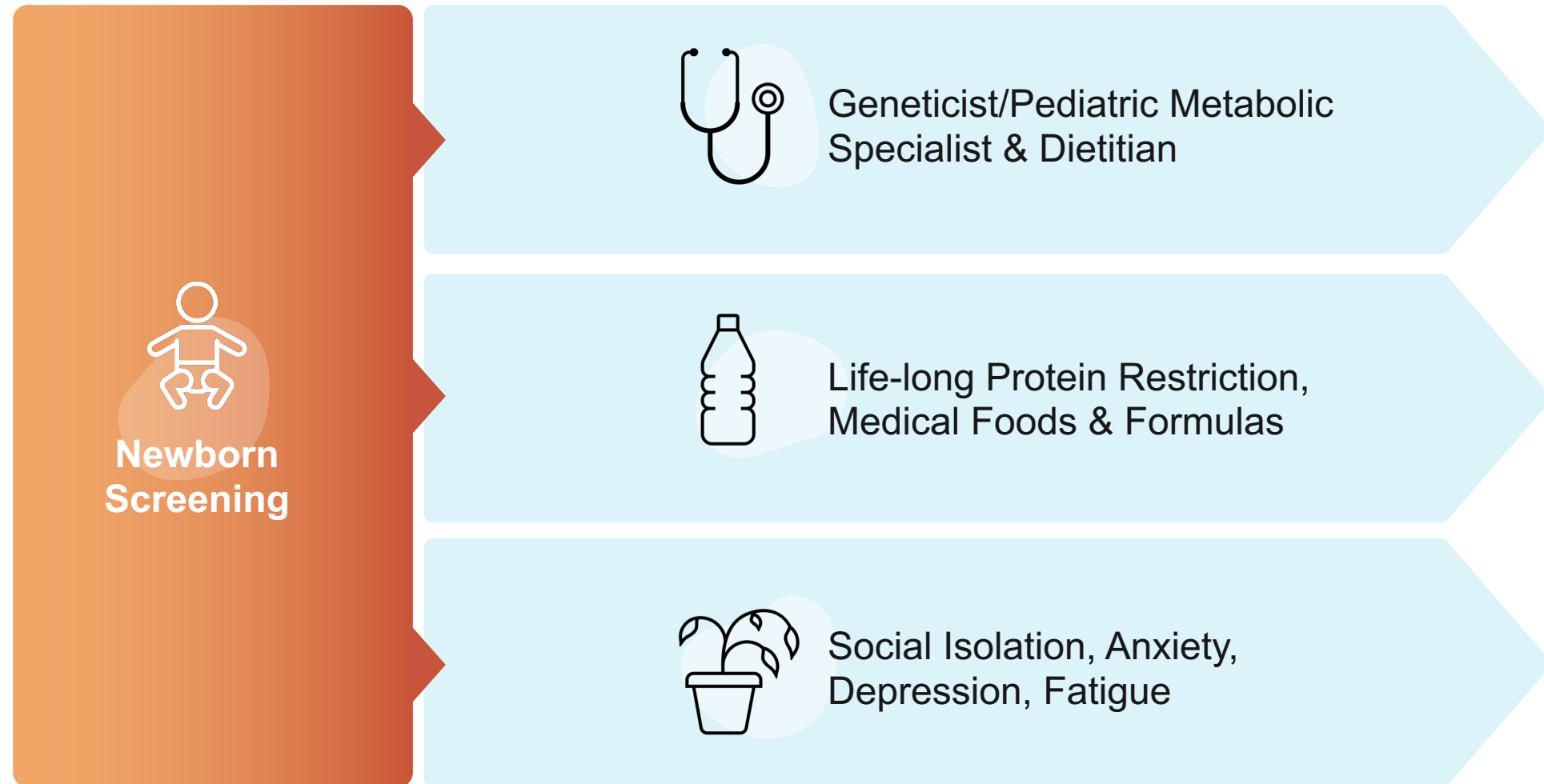
Unmet Need in PKU



Large Unmet Need Remains in PKU



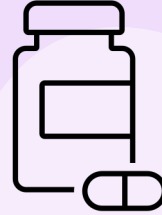
The PKU Patient Journey Begins at Birth and Continues Throughout Life



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

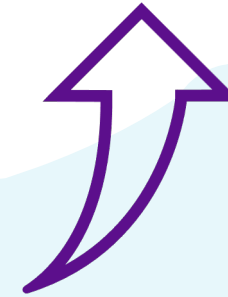


The consequences of lack of effective Phe control can be devastating to the quality of life for these patients and irreversible in terms of intellectual disability

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

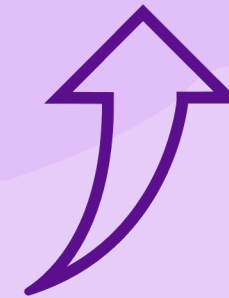
Correlations between Phe level and intelligence quotient (IQ) were extracted from 40 studies and confirmed a significant correlation between blood Phe level and IQ¹

Each **100 $\mu\text{mol/l}$** increase in Phe predicted a
1.9 to 4.1
point reduction in IQ

Two Main Goals of Therapy for PKU Patients



**Decreased Blood
Levels Phe**



**Increased Dietary
Protein Intake
(Phe Tolerance)**

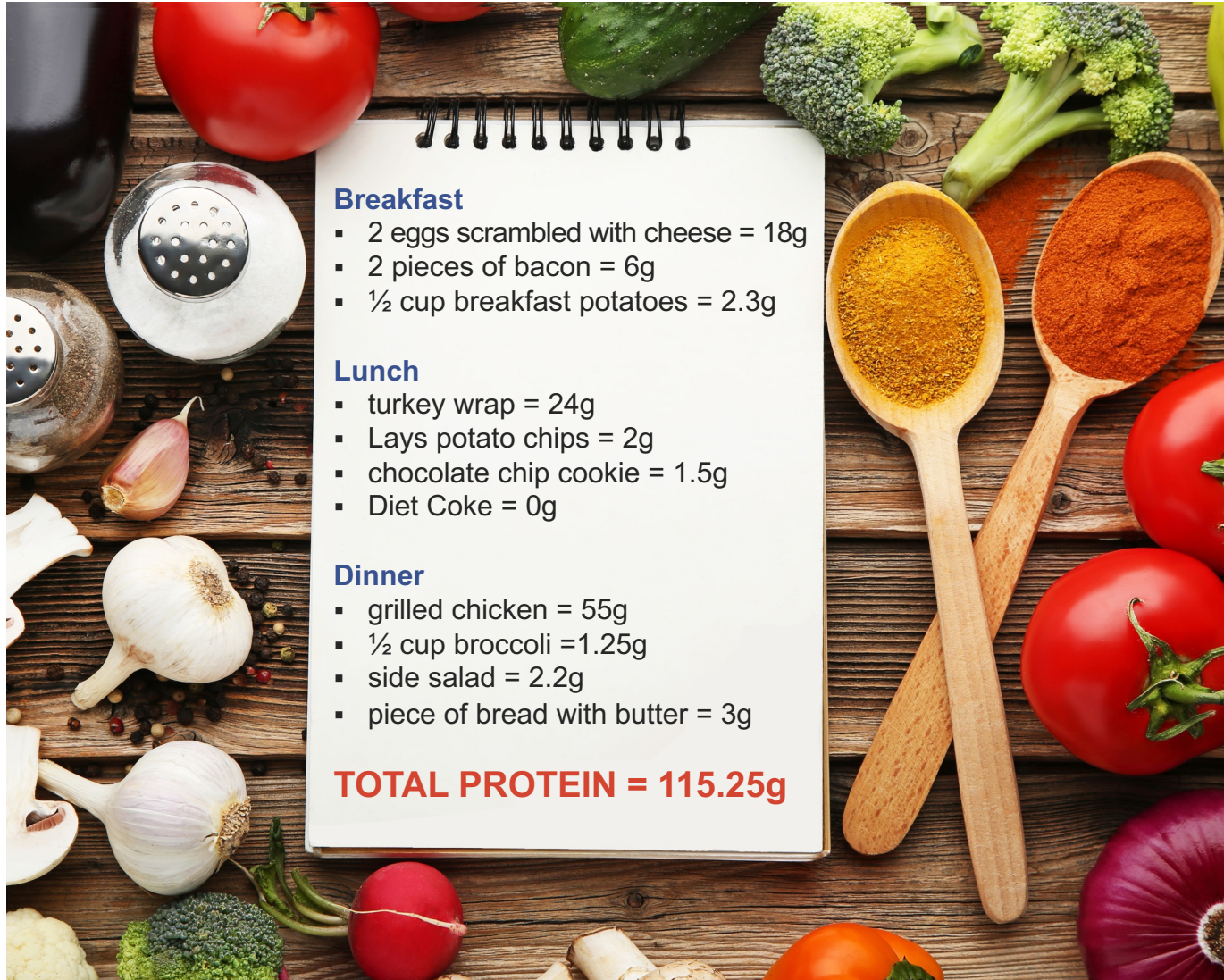
Keeping a Strict Diet Is the Largest Burden and Makes Patients Constantly Feel Frustrated and Extremely Limited

Controlled
Stressed
Limited
Frustrated
Annoyed Concerned
Anxious
Disappointed

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*

Diet for Non PKU Patient



Breakfast

- 2 eggs scrambled with cheese = 18g
- 2 pieces of bacon = 6g
- ½ cup breakfast potatoes = 2.3g

Lunch

- turkey wrap = 24g
- Lays potato chips = 2g
- chocolate chip cookie = 1.5g
- Diet Coke = 0g

Dinner

- grilled chicken = 55g
- ½ cup broccoli = 1.25g
- side salad = 2.2g
- piece of bread with butter = 3g

TOTAL PROTEIN = 115.25g

Diet for PKU Patient



The Burden of a PKU Diet is Substantial

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



2g of protein



1-2g of protein

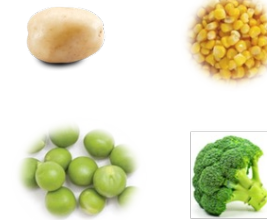


6g of protein

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



ABIGAIL

“

I know that a lot of children and myself included, like in teenage years tend to struggle with staying on diet. It can be a little bit tricky when you're trying to deal with peer pressure and just growing up in the community where everyone's different from you. You're definitely a minority and it's a condition that not a lot of people are familiar with.

”

SAM

“

So that's why it's really important when you're younger, when your brain is developing, to have such a strict diet because that's when your brain is, is developing. And now it's still important because when I have high blood levels, I have bad memory. My hands get shaky. I have brain fog. My mood is all over the place.

”

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**

Physician Perspective



Dr. Drago Bratkovic

Head of Metabolic Unit

Metabolic Clinic

Women's and Children's Hospital, Australia

“

There is very much a massive unmet need in PKU. The diet on its own, whilst you can get good Phe levels with it, takes a lot of work and we do need other therapies that are easier to undertake and also maintain throughout the lifespan of a patient. You or I could probably do the diet for a few weeks. Patients with PKU have to do the diet for their whole life and it's very exhausting. So we need to have new therapies to come along to help patients maintain their levels, the phenylalanine levels, at the level that maintains their quality of life and their ability to function and work.

”

Prof. Nicola Longo

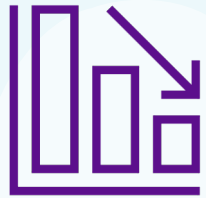
Chief of Medical Genetics/Pediatrics
University of Utah, USA

“

There is an unmet need for PKU patients in finding some oral medication that can really control better phenylalanine level to allow a little bit more diet liberalisation. Having the capacity to eat normal food for them is very important and any step that we can take in this direction will help them achieve their full potential.

”

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 (120-360 μ M/L)



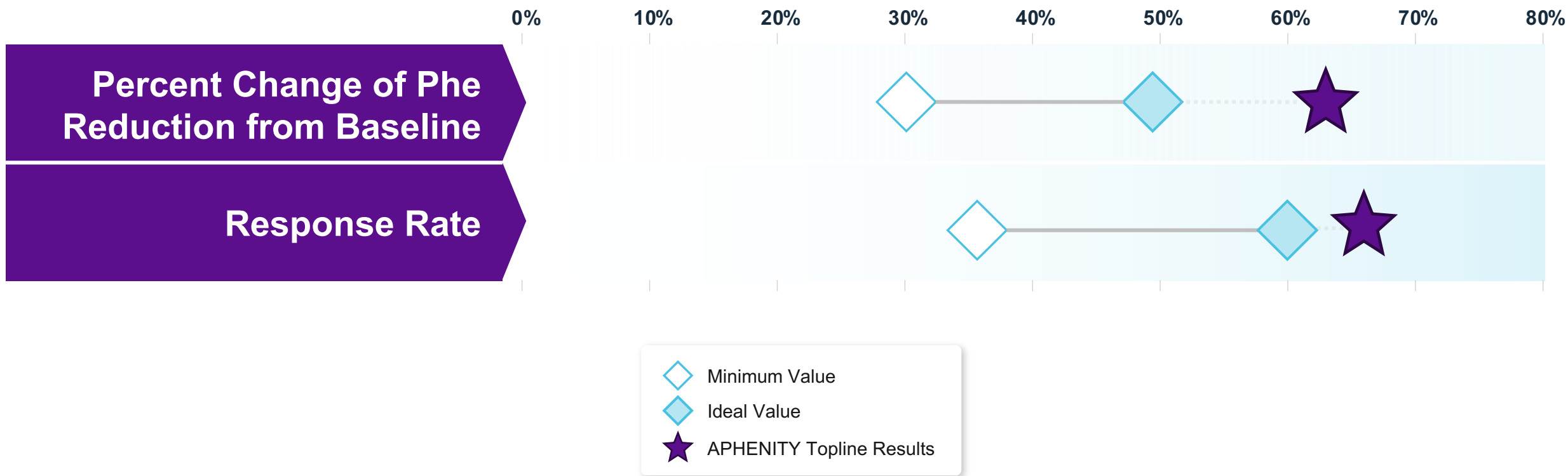
Phe Tolerance

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



Quality of Life

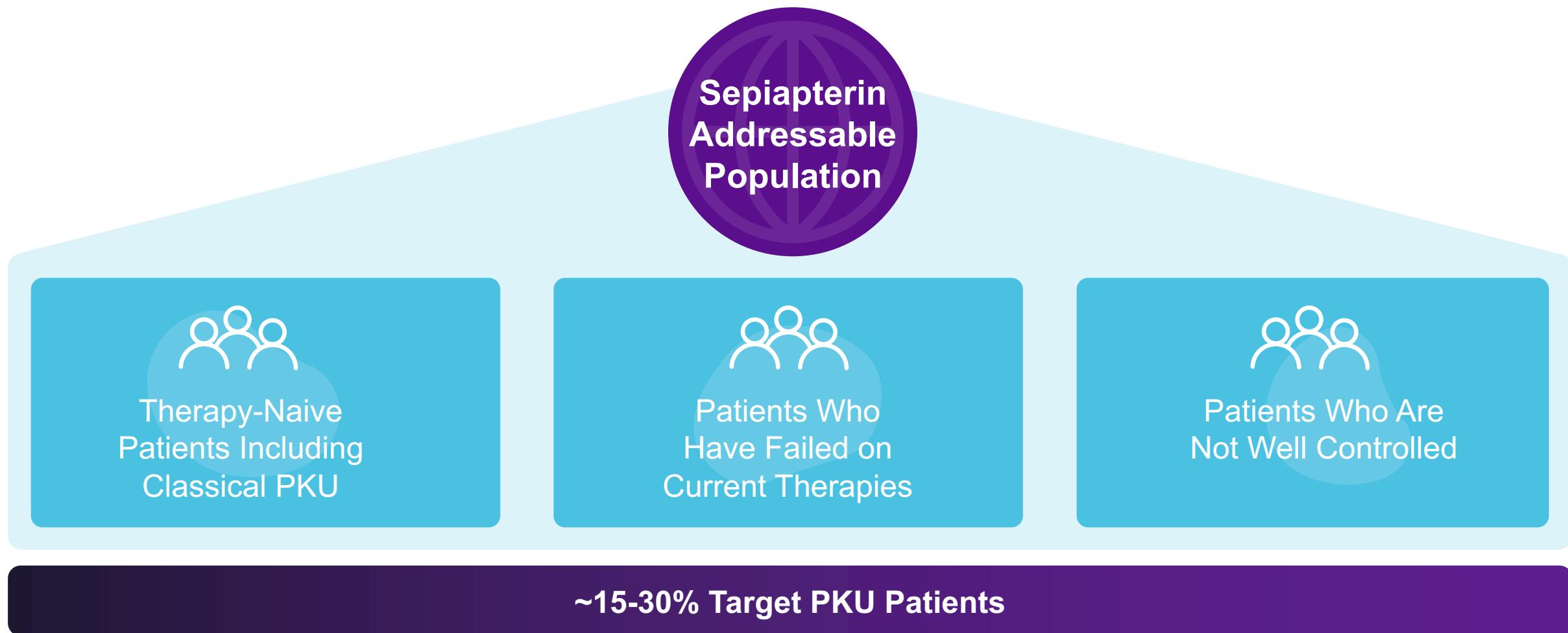
Physicians Expect 30%-50% Phe Reduction from Baseline for a First-Line PKU Therapy



Commercial Launch Strategy



APHENITY Results Support Potential for Sepsiapterin 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

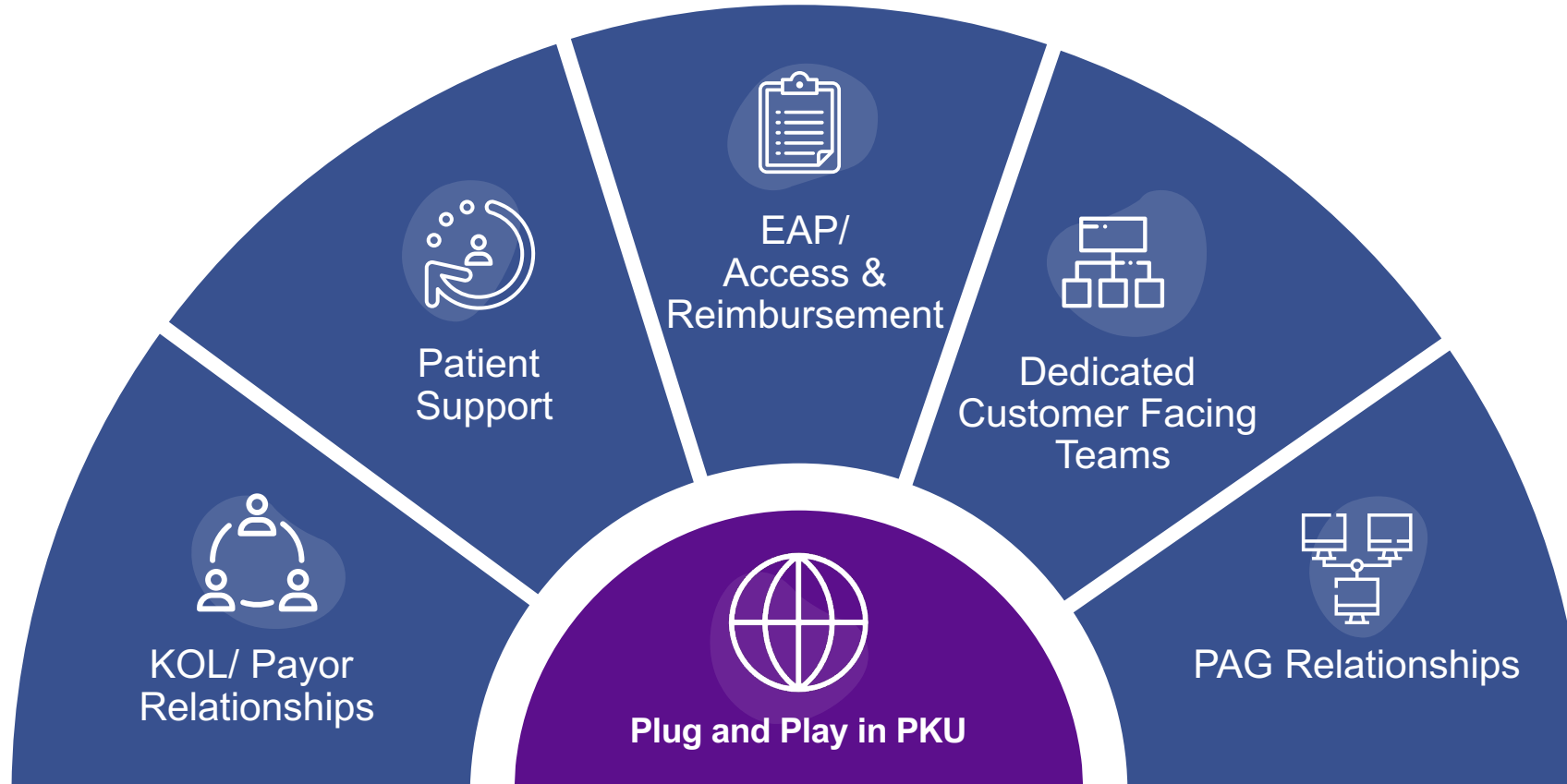


Disease pathology
well understood
and documented

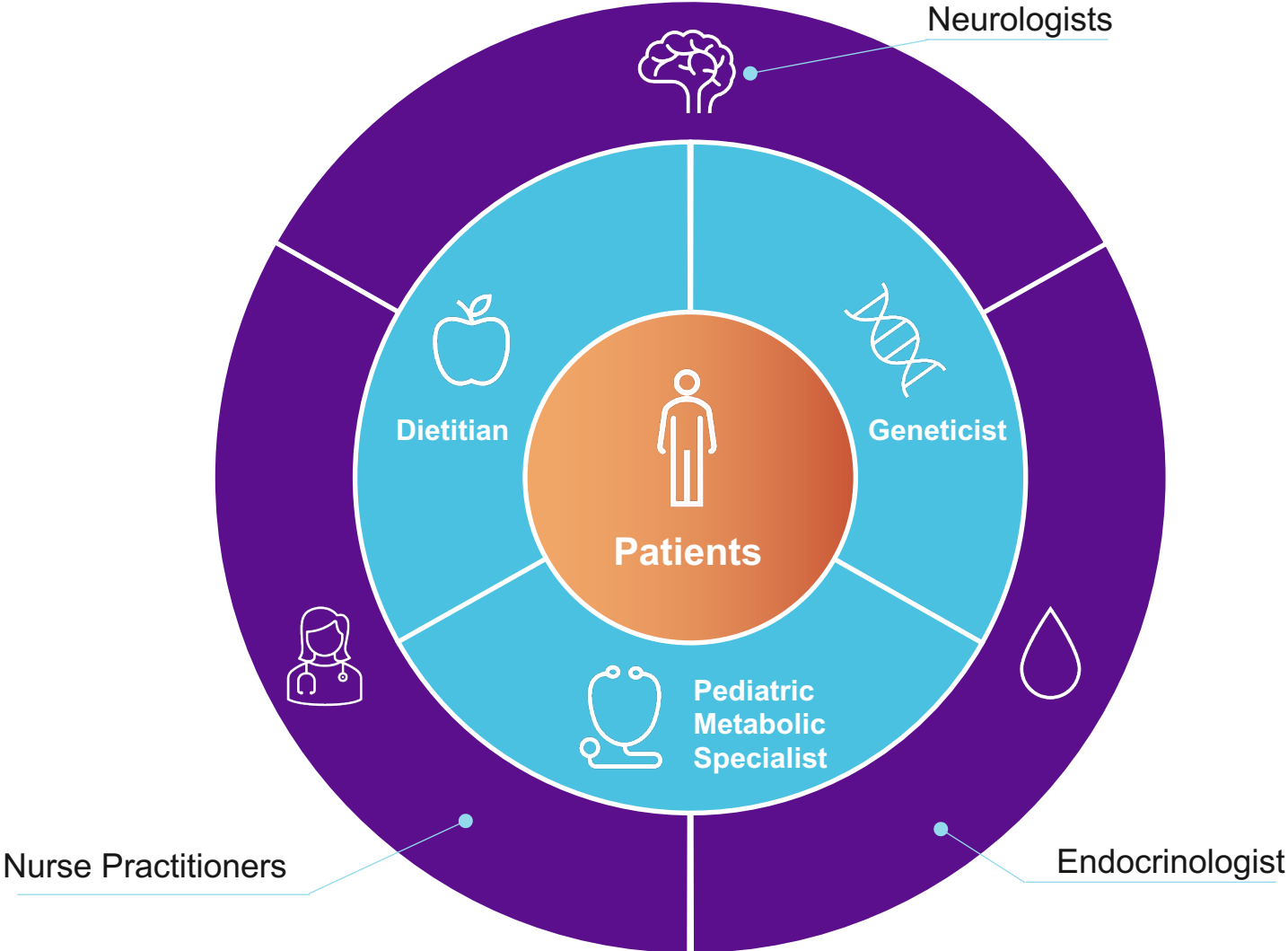


Connected and
coordinated
patient advocacy
community

PTC Global Commercial Infrastructure Will Allow for Rapid Worldwide Launch



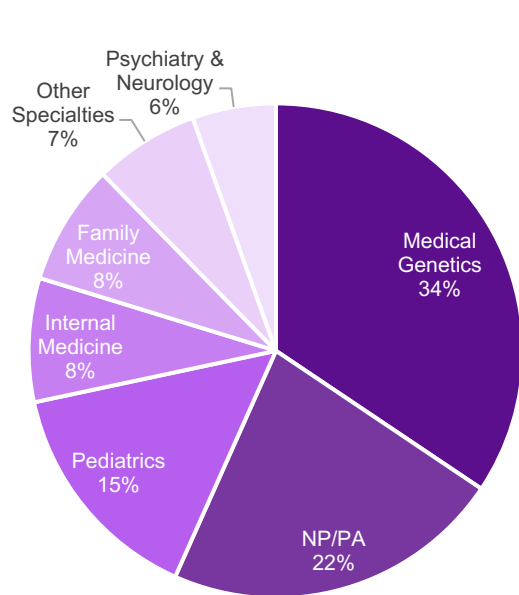
Understanding the Cross-Functional Team at PKU Clinics



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

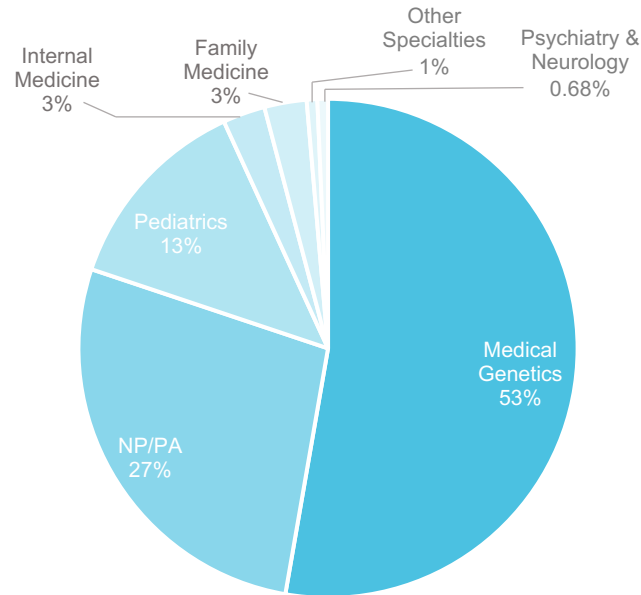
~500 HCPs Kuvan Writers

Treating ~3,000 PKU patients



~150 HCPs Palyngiq Writers

Treating ~1,000 PKU patients



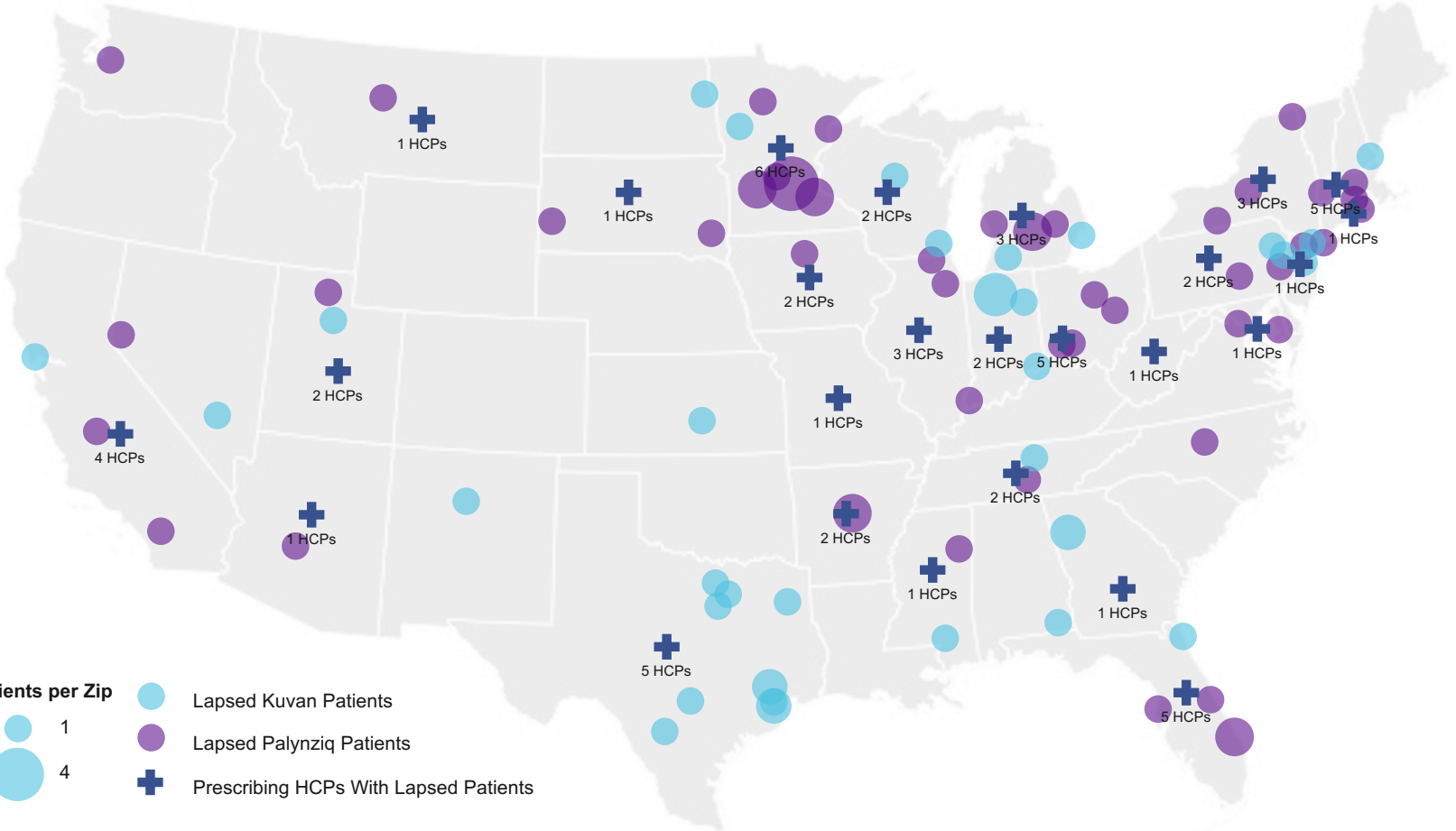
For each US HCP we have visibility into:

- 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

Overlap exists between KUVAN and PALYNZIQ writers

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

Key Professional Associations & Patient Advocacy Groups

Scientific Medical Associations:



Dietitian/Nutritionist Associations:



Patient Advocacy Groups:



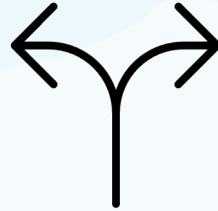
Setting the Launch Strategy for an Effective PKU Treatment That Works for More Patients



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



Ensuring Access

to the broadest range of PKU patients

- Pricing/reimbursement strategy
- Early access programs

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



Pre-Submission
Meetings



Regulatory
Submissions



Initiate Launch
Preparation