Case Study: Palynziq Rare Disease Forum

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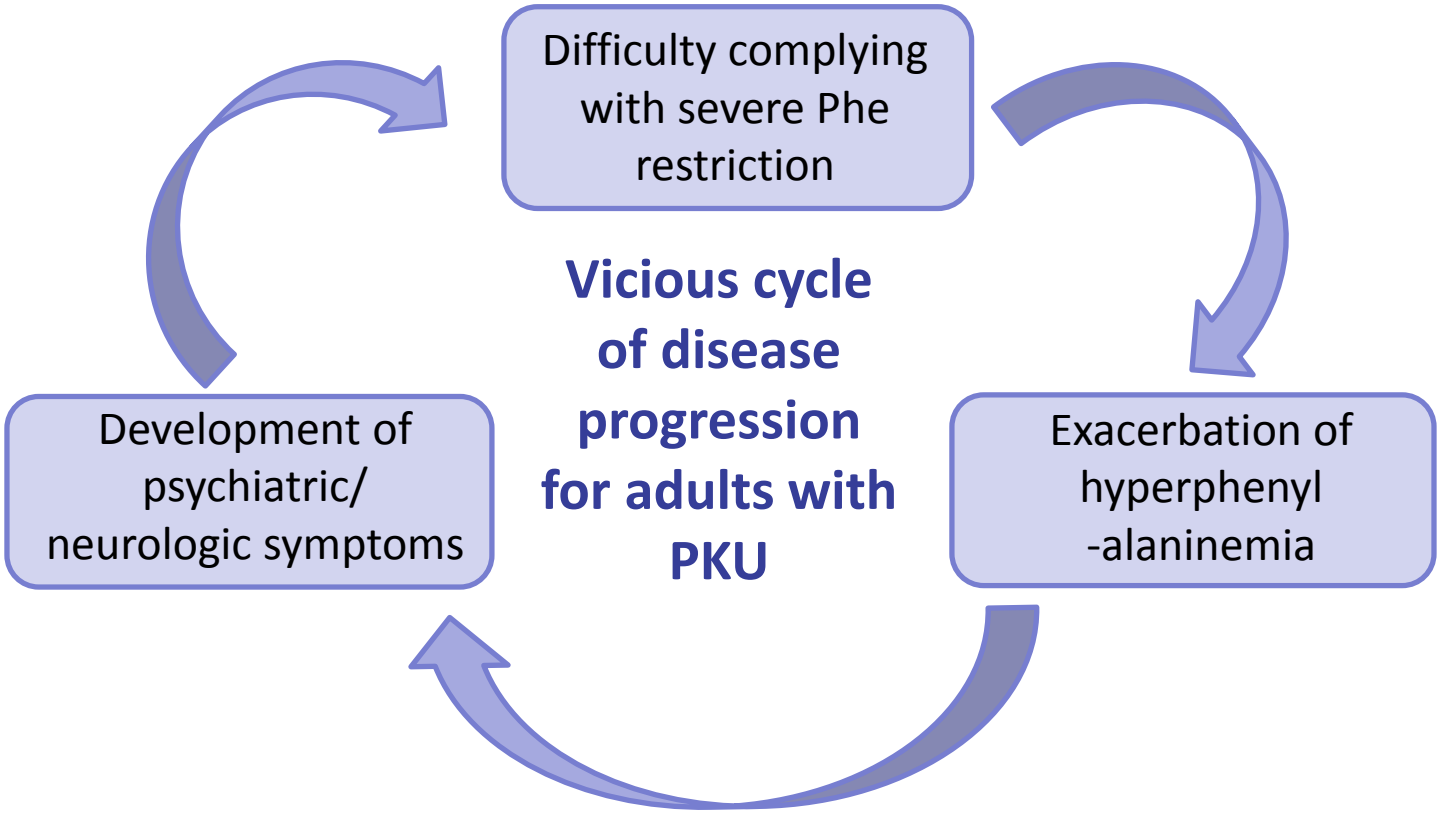
Phenylketonuria (PKU): A Rare, Serious Genetic Disease

- Caused by mutations in the phenylalanine hydroxylase (PAH) gene and results in inability to break down phenylalanine (Phe)



Overall treatment goal is reduction in blood Phe

Palynziq (pegvaliase-pqpz) Injection

- First-in-class PEGylated bacterially-derived phenylalanine ammonia lyase enzyme that substitutes for the deficient PAH enzyme activity and reduces blood Phe concentrations.

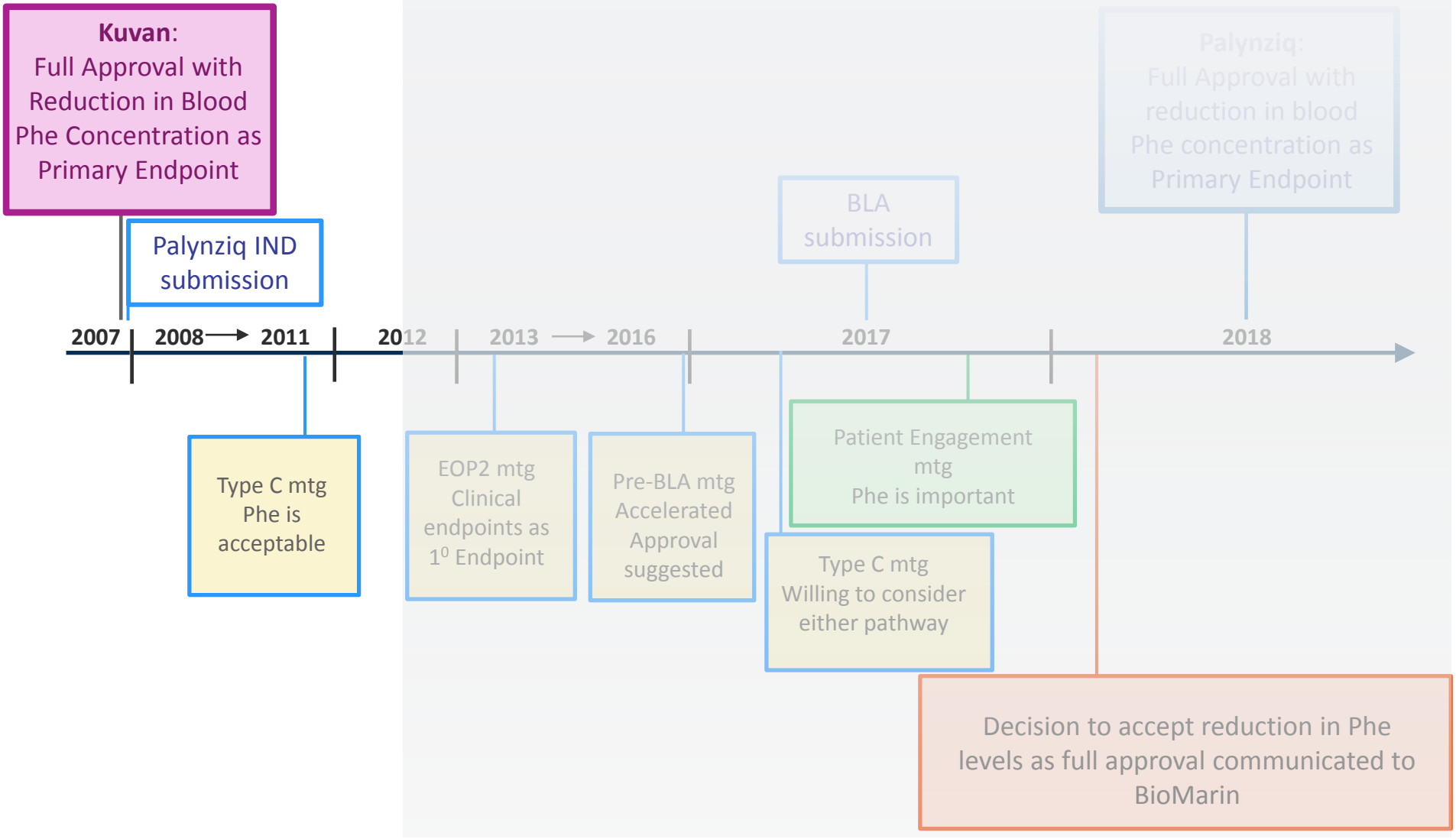
- Approved by FDA on May 24, 2018 for adults with PKU

The blood Phe reductions *demonstrated in the clinical trials of Palynziq observed in association with an unrestricted diet represent a major therapeutic advance in the treatment of adult PKU patients.*[1]

Although the Palynziq clinical program did not evaluate formally or extensively the benefit on neuropsychiatric endpoints, one also needs to acknowledge that ***in PKU, the standard of care and goal of treatment is metabolic control measured by reduction of Phe levels****, and this goal is clearly articulated in current clinical practice standards and guidelines.*[1]

[1]Language from FDA's Summary Basis of Approval

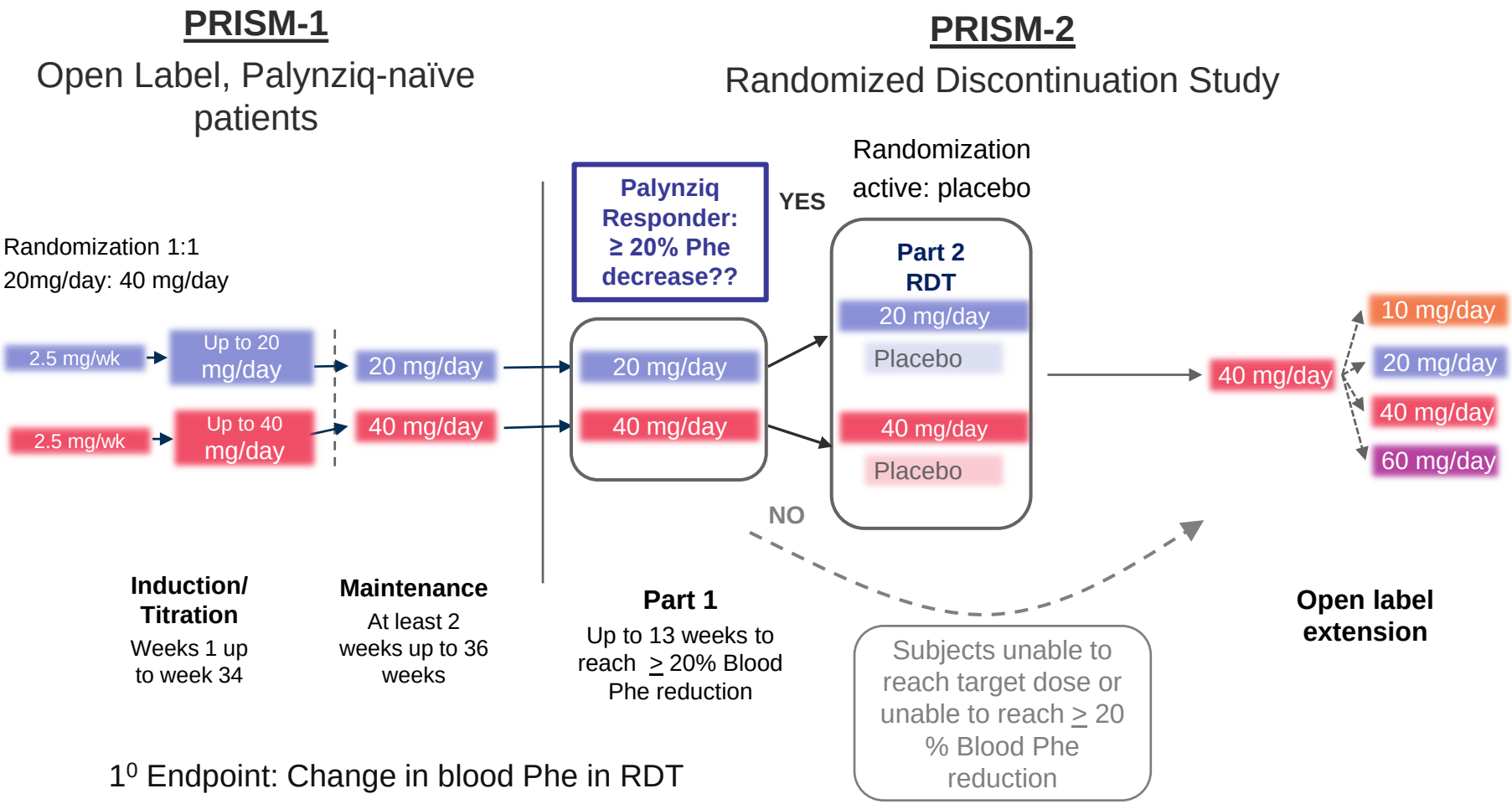
What Study Design to Use for Phase 3?



What Study Design to Use for Phase 3?

- FDA recommended a placebo-controlled Phase 3 study
- Randomization at the treatment onset could potentially unblind due to the presence of hypersensitivity adverse events (HAEs) in Palynziq treated group
  - Treatment with a bacterially derived enzyme like Palynziq causes HAEs
  - HAEs were more frequent during initial treatment and rates then decreased with maturation of the immune response

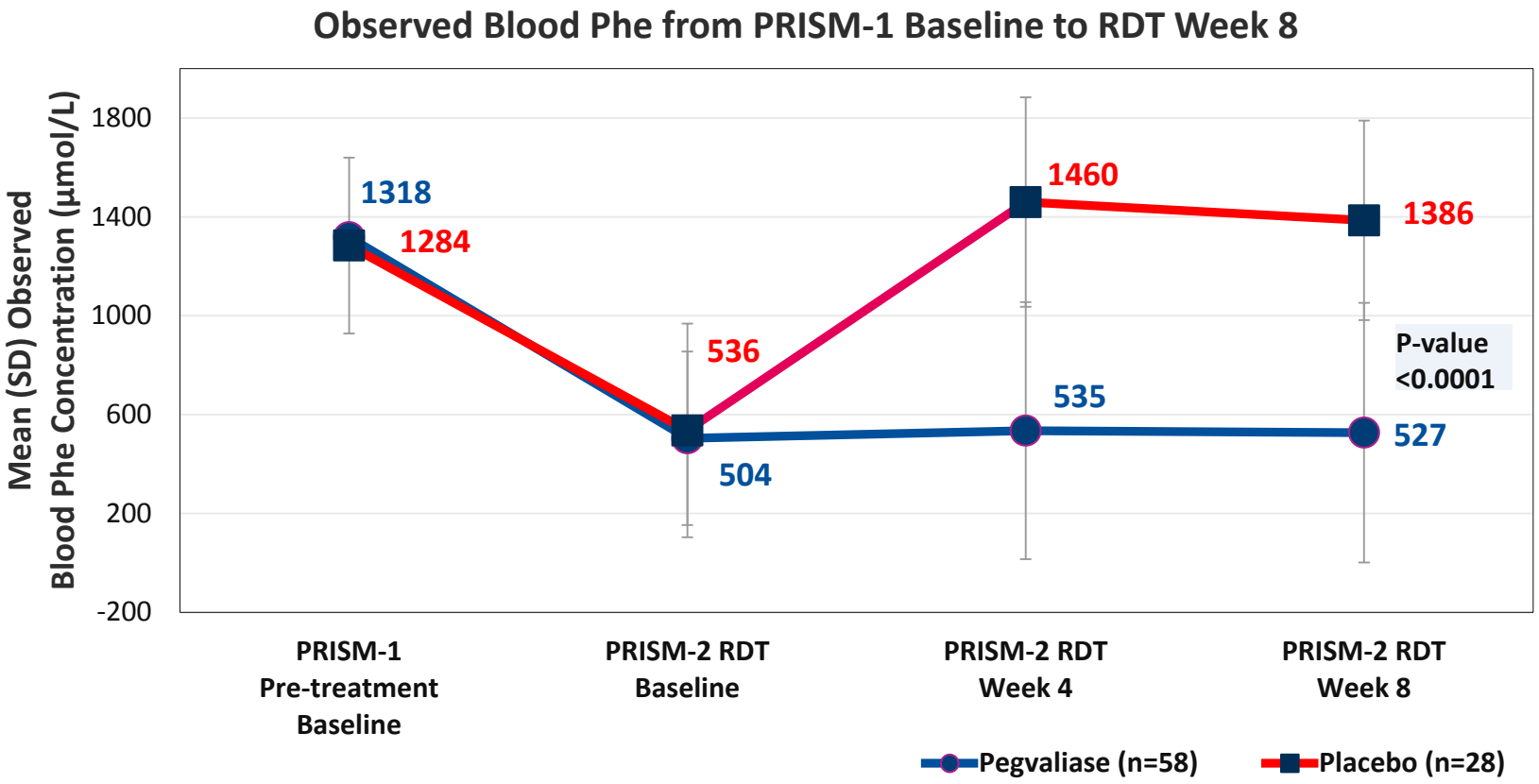
Demonstrating Phe Effect via Randomized Discontinuation (RDT) Study with Enrichment



1^0 Endpoint: Change in blood Phe in RDT

2^0 Endpoint: Change in attention and mood scores

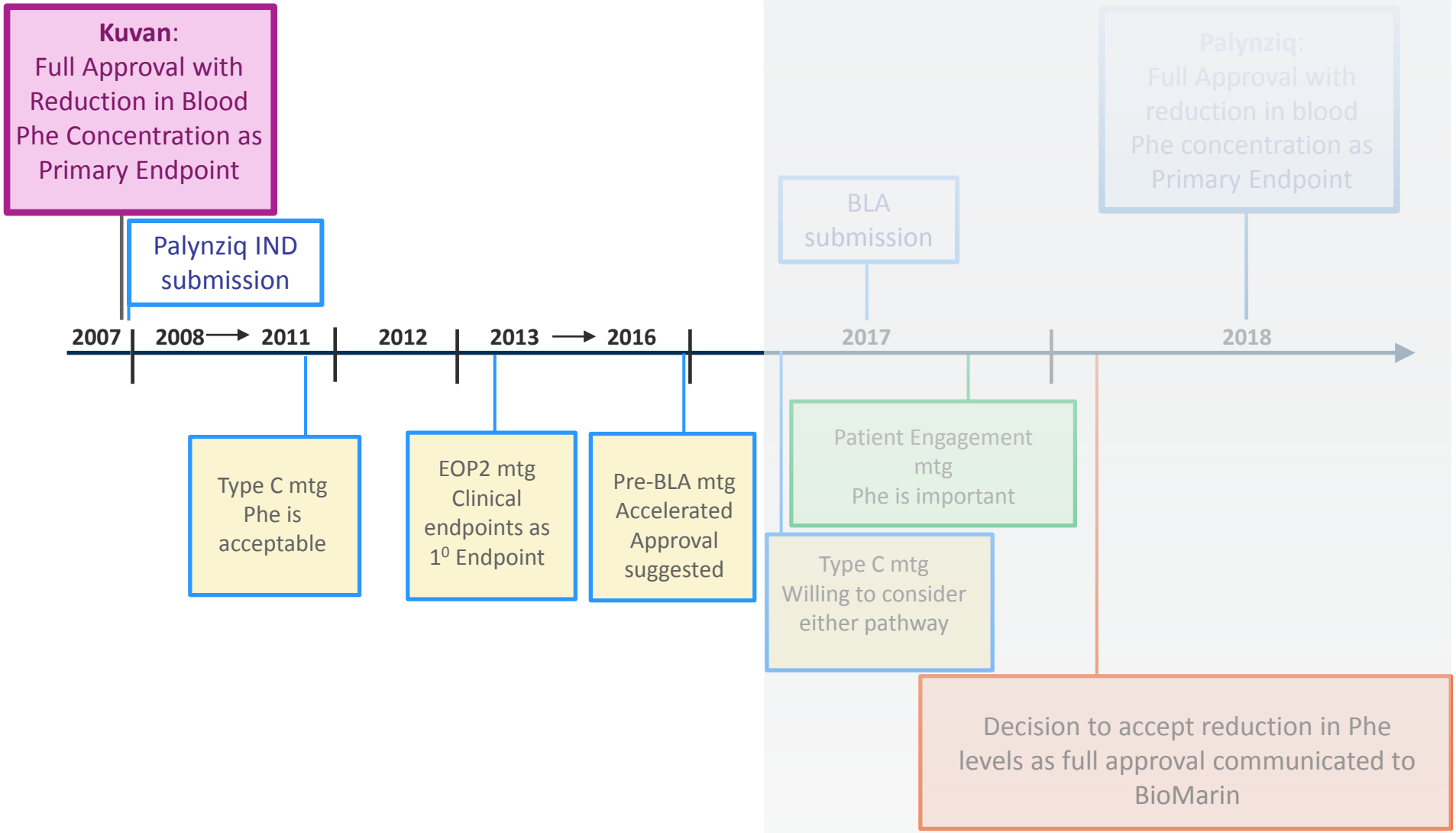
Mean Blood Phe in Enriched Subjects in RDT



Compared to pre-treatment blood Phe, Palynziq group maintained low Phe and placebo group returned to pre-treatment Phe (p<0.0001)

Figure bars represent SD. LS, least square; MMRM, Mixed-Effect Model Repeated Measure.
Primary efficacy endpoint with MMRM analysis is difference in LS mean (95% Confidence Interval) of change in blood Phe from RDT baseline to Week 8 between pegvaliase and placebo treatment groups: 20.0 (-80.1, 120.0) and 849.2 (705.1, 993.4), P-value <0.0001.

Is Blood Phe Alone Sufficient for Full Approval?



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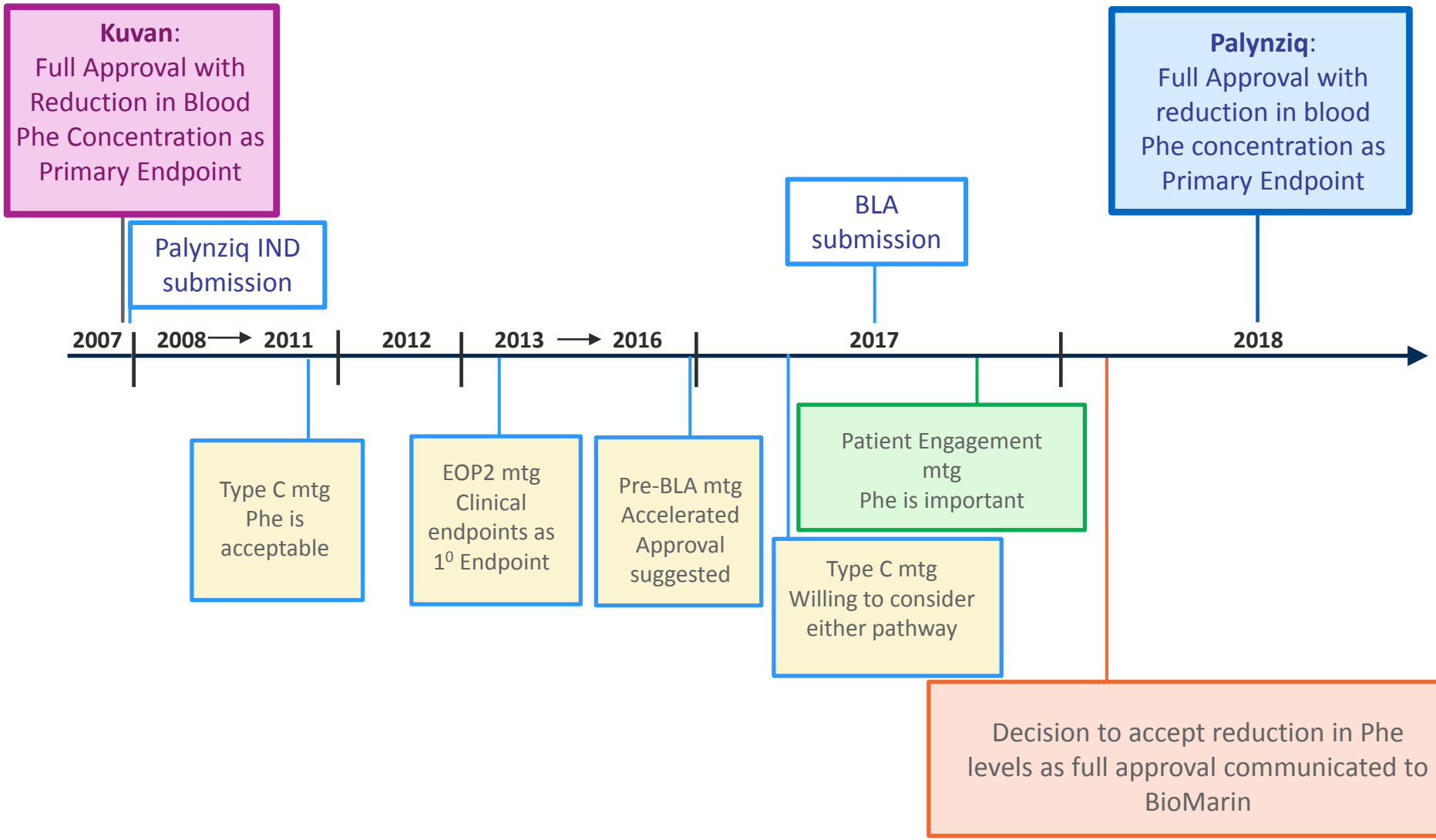


Safety of Palynziq and Overall Benefit Risk

Challenge	Solution
Hypersensitivity Adverse Events (including Anaphylaxis) ✓ **What is the mechanism?** ✓ **How to mitigate?**	▪ Mechanism of action evaluated through immune complex (IC)-related AE's, circulating ICs, complement levels and drug-specific IgE ▪ HAEs are Type III hypersensitivity ▪ Critical evaluation of value of risk mitigations ▪ Safety meeting to share concerns and proposal ▪ Risk evaluation and mitigation strategies + ETASU to mitigate

Benefit Risk	▪ Patient survey data on willingness to take a drug like Palynziq
	▪ FDA sought patients' and clinicians' views on:
	  ▪ Unmet need
	  ▪ Willingness to accept benefits & risk of Palynziq

What Has Worked

Palynziq™ (pegvaliase-pqpz) Injection

Frequent and Open Communication

- Led to better understanding of critical issues and ability to identify solutions
- Agreements made prior to BLA about data package needed to evaluate safety
- Effective orientation meeting and throughout process to discuss key data and view the benefit risk profile

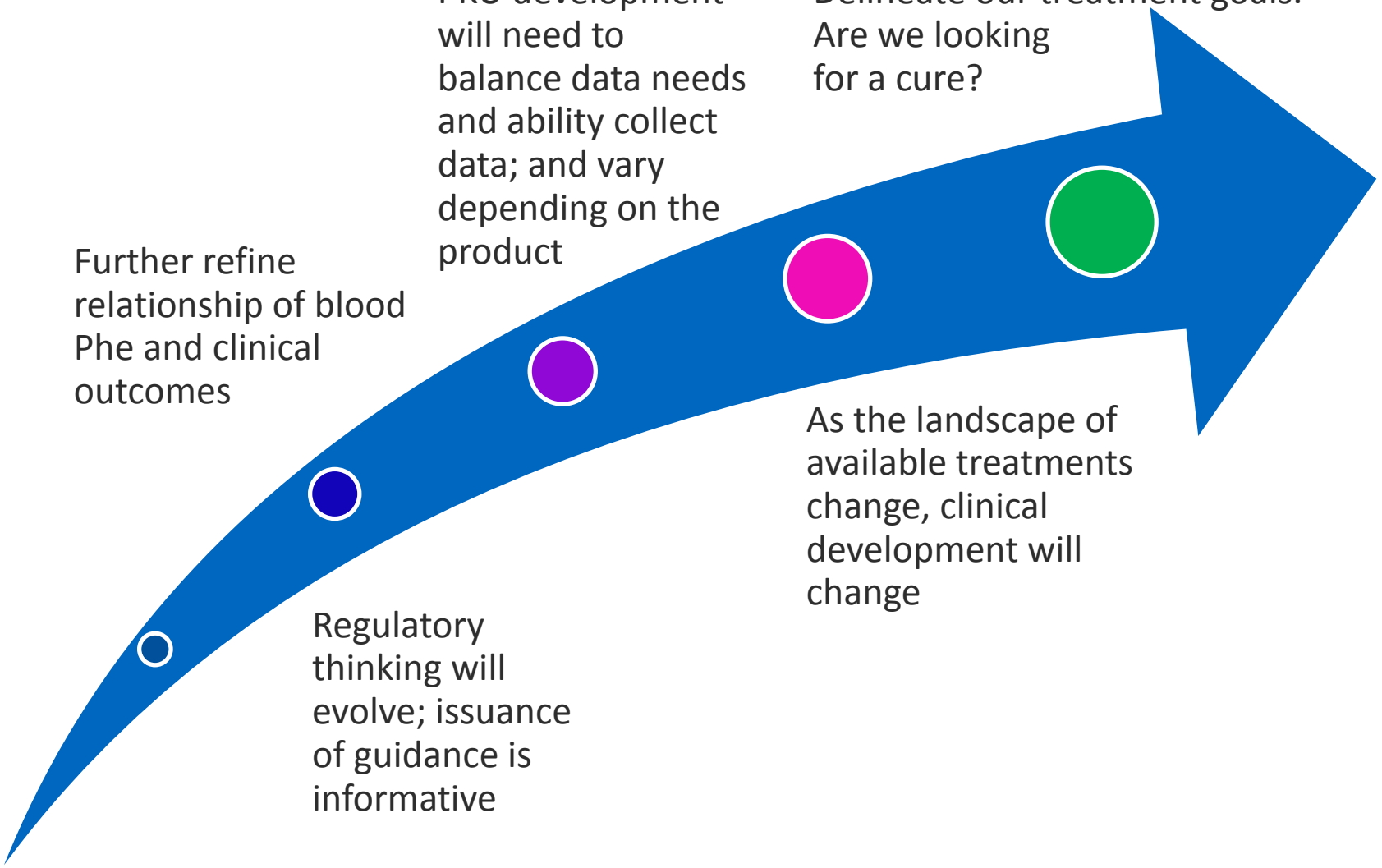
Commitment to Collaboration

- Patient, clinician, and patient advocacy voice on unmet medical need and importance of Phe control to minimize symptoms
- FDA input to shape program tailored to product

Flexibility

- Not 1 size fits all
- Willingness to consider different approval pathways as part of review

Future Challenges



Conclusion

- Given limited data in rare diseases like PKU, there's critical need for innovative and flexible approaches
- Keys to success were early and frequent communication and joint commitment to finding the best path forward for patients
- We would like to thank the dedication and collaboration from:
  - Patients and patient advocacy
  - Physicians and other clinical site personnel
  - FDA
  - BioMarin team

"Alone we can do so little; together we can do so much."

– Helen Keller