



PKU Case Study: Use of Surrogate Endpoints

Bradley J. Glasscock, PharmD

Group Vice President
Global Regulatory Affairs
BioMarin Pharmaceutical Inc.

Outline

- ❖ Introduction to BioMarin
- ❖ Case study: FDA Approval of Palynziq (pegvaliase-pqpz) for adults with PKU
 - FDA's Acceptance of Plasma Phenylalanine (Phe) as a Surrogate Endpoint Known to Predict Clinical Benefit to Support Traditional Approval
- ❖ Lessons Learned from Palynziq Review
- ❖ Recommendations for FDA's Consideration

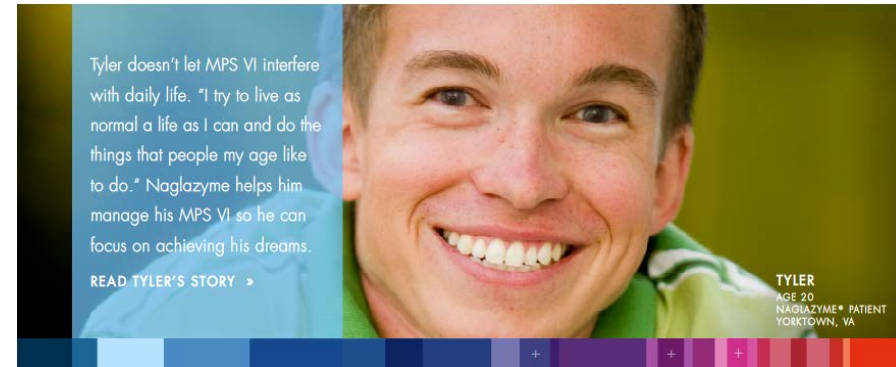
Introduction to B:OMARIN®

Focus: Rare genetic diseases,
orphan therapies



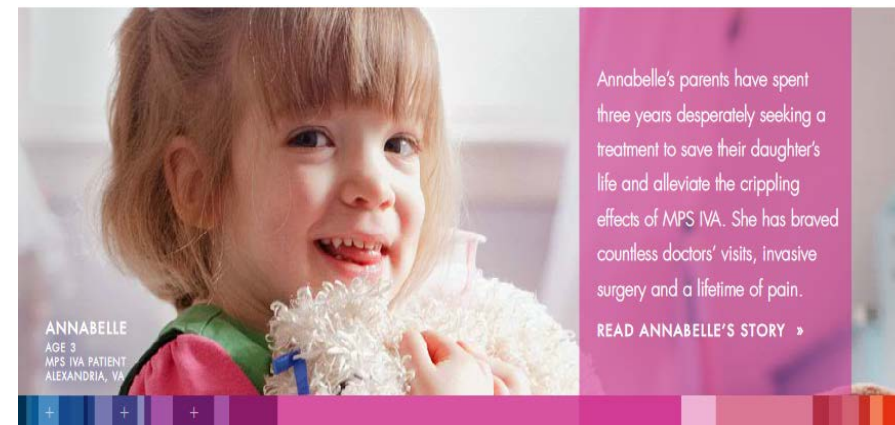
Employees:
> 2700 Worldwide

Commercial Operations:
> 70 Countries



Founded: 1997

Headquarters: Marin County, CA



6 Commercialized Products Approved in U.S.

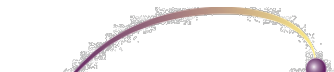
Palynziq represents the next phase of treatment options for patients with PKU

 **Brineura**[®]
(cerliponase alfa)

 **Naglazyme**[®]
(GALSULFASE)

 **KUVAN**[®]
(sapropterin dihydrochloride) Tablets

Palynziq[™]
(pegvaliase-pqpz) Injection

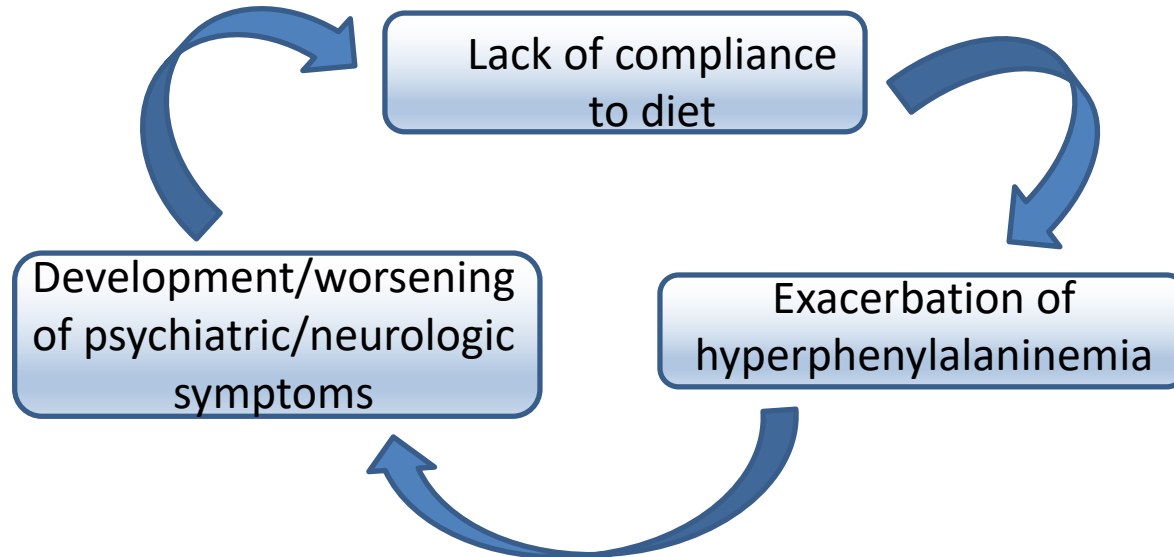
 **ALDURAZYME**[®]
(LARONIDASE)

 **VIMIZIM**[®]
(elosulfase alfa)

Phenylketonuria (PKU) – a rare and serious genetic disease

- ❖ Characterized by inability to break down phenylalanine (Phe), and is caused by mutations in the gene encoding phenylalanine hydroxylase (PAH)
- ❖ If left untreated, accumulation of Phe results in intellectual disability and psychiatric/neurologic symptoms
- ❖ Difficulty of adhering to dietary restrictions of daily Phe and protein intake
- ❖ The overall goal of treatment for PKU patients is reduction in blood Phe

**Vicious cycle of
disease progression
for adults with PKU**



Palynziq (pegvaliase-pqpz) Injection

- ❖ Pegvaliase, approved by FDA on May 24, 2018 for adults with PKU, is a PEGylated phenylalanine ammonia lyase enzyme that substitutes for the deficient PAH enzyme activity and reduces blood Phe concentrations
- ❖ *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 Pegvaliase 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 on the Phe levels, and this goal is clearly articulated in current clinical practice standards and guidelines.¹*

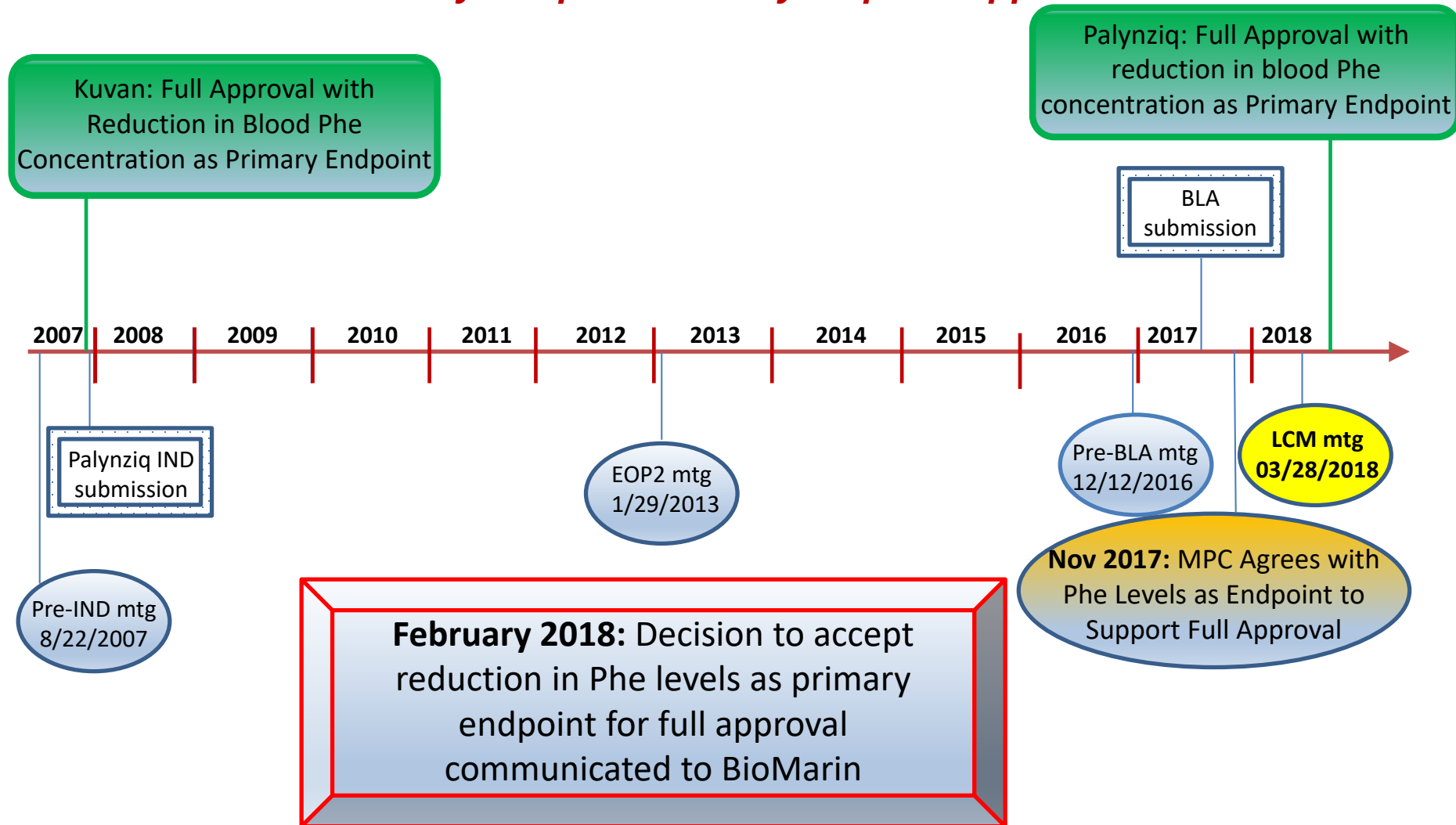
¹Language from FDA's Summary Basis of Approval

Strong support for Phe as established surrogate endpoint known to predict clinical benefit

- ❖ Well characterized pathophysiology and mechanism of action
 - MOA corrects the underlying metabolic deficiency
 - Clinical data provide strong substantiation of clinical effect with clear, statistically compelling evidence of restoration of the missing physiologic activity
- ❖ Current treatment guidelines and Literature
 - Metabolic control measured by reduction of Phe levels is the standard of care and this goal is clearly articulated in current clinical practice standards and guidelines
 - Significant body of evidence from literature shows that uncontrolled blood Phe in adulthood is associated with executive dysfunction, depression, and a variety of behavioral and psychiatric problems
- ❖ Regulatory precedent
 - FDA acceptance of Phe lowering as a clinical efficacy endpoint supporting traditional approval for Kuvan in 2007 for both pediatrics and adults
- ❖ Consideration of challenges to endpoint identification and validation and lack of validated disease-specific PRO tools in the PKU population

Regulatory Timeline

Uncertainty Regarding Acceptability of Reduction in Blood Phe Concentration as Primary Endpoint for Palynziq Full Approval



Lessons Learned from Palynziq Review

❖ Importance of and need for effective FDA communication with Sponsor

- Early/timely decision making and communication
- Transparency



Potential impact of earlier decision-making and communication of decision to accept Phe lowering as an endpoint to support approval:

- *trials may have been simpler*
- *development program may have been expedited and streamlined*
- *Treatment may have been available to patients sooner*

If Phe Lowering was accepted as an endpoint for traditional approval for PKU in 2007, why was this not accepted for pegvaliase until Feb 2018 (3 months prior to approval)?

Lessons Learned from Palynziq Review

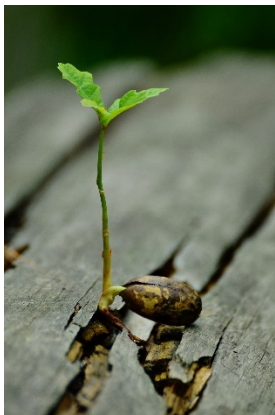
❖ Multi-stakeholder Collaboration: FDA – Sponsor – Patients

- Patient voice is key– patient meetings with FDA and sponsor are important
- Patient participation can be valuable throughout drug development
- Patient engagement during the actual BLA review may be too late to influence some aspects of development that could have benefitted from the patient perspective



Patient experience data (PED) is important to understand burden, what is meaningful to patients, and what level of risk patients are willing to accept for benefit

Encouraging Developments: Recent FDA actions signal pragmatic science-based regulatory flexibility



- ❖ FDA's July 2018 draft guidance "Human Gene Therapy for Rare Diseases" notes that "[s]ome biomarkers or endpoints are very closely linked to the underlying pathophysiology of the disease (e.g., a missing metabolite in a critical biosynthetic pathway). In this case, total or substantial restoration of the biosynthetic metabolic pathway may generally be expected to confer clinical benefit. Changes in such biomarkers could be used during drug development... as an early demonstration of drug activity."
- ❖ FDA's July 2018 draft guidance "Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies" notes that "[w]hen the pathophysiology of a disease is well understood and the mechanism of action of the drug/biologic is well characterized, specific drug-induced substrate reduction in relevant tissue(s) can have a reasonable likelihood of predicting clinical effectiveness."
- ❖ FDA's surrogate endpoint table released in July fulfills a 21st Century Cures Act requirement to publish a list of "surrogate endpoints which were the basis of approval or licensure (as applicable) of a drug or a biological product" under both accelerated and traditional approval pathways.

Recommendations for FDA's Consideration

❖ Consistency

- Consistent application of regulatory principles for rare disease drug development across review disciplines, FDA Centers, Review Divisions, and products
- Leverage the anticipated OND reorganization in CDER, but carefully consider placement or re-allocation of applications to review divisions
- Consider a dedicated rare disease review division
- Cross-center collaboration for consistency in regulatory flexibility and decision-making across modalities where appropriate, e.g., endpoints acceptable for other drugs in CDER should be acceptable for gene therapy and emerging biotherapeutics when supported by the science and the underlying disease pathophysiology
- Acceptability of surrogate endpoints, e.g., when there is good understanding of pathophysiology and MOA of the drug and/or applicable regulatory precedent

❖ Communication

- Effective, timely, transparent

❖ Patient Voice

- Incorporation of the Patient Voice is valuable throughout drug development in regulatory decision making; don't wait until NDA/BLA review
- FDA should share learnings from patient engagement as it relates to products they regulate. Transparency will help advance multi-stakeholder learning

THANK YOU

BIOMARIN®