Index of sustained Phe response and improvements in PKU clinical outcome assessments in patients receiving pegvaliase

P009

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Background

- Phenylketonuria (PKU) is an autosomal recessive disorder caused by deficiency of the enzyme phenylalanine hydroxylase, which results in phenylalanine (Phe) accumulation in the blood and brain, requiring lifelong management[1]
- Elevated Phe can result in neurological and cognitive sequelae, including symptoms of inattention and alterations in mood, which may impact an individual's quality of life[2]
- Several studies have reported improvements in neuropsychological symptoms and executive function with reductions in blood Phe[2]
  - However, study results are inconsistent as many are based on short-term interventional trials with small sample sizes, rudimentary statistical analyses, and individual coincident or concurrent Phe measurement
  - Analyses using concurrent Phe values to explore neurological and cognitive outcomes require several assumptions about the pathophysiological mechanisms underlying Phe exposure and their temporal relationships, limiting their usefulness to capture the full scope of burden of illness or the impact of treatment
- Pegvaliase is an enzyme substitution therapy approved for the management of uncontrolled blood Phe (>600 µmol/L) in adults (≥18 years in the USA; ≥16 years in the European Union)
- In the PRISM phase 3 clinical trials, pegvaliase demonstrated an unprecedented ability to substantially reduce and sustain blood Phe[3]
- Longitudinal blood Phe measures and temporal patterns of response to treatment are variable, complicating the evaluation and interpretation of the relationship between Phe response and clinical outcome assessments
- Initial work from the PRISM program reported improvements in inattention as Phe levels decreased, particularly in those with high baseline impairment and in those with the greatest reduction in blood Phe[4]
- Here we present a secondary analysis of data from the PRISM phase 3 clinical trials examining the relationship between a sustained Phe response and symptoms of impaired attention and mood disturbance

Methods

- The PRISM clinical trial program enrolled pegvaliase-naïve adult participants and monitored blood Phe at monthly, and later bimonthly, intervals
- Clinical outcome assessments were performed at baseline and at least every 8 weeks through the open-label extension study (PRISM-2, Part 4):
  - Investigator-Rated Attention Deficit Hyperactivity Disorder Rating Scale-IV Inattention (ADHD RS-IV IA) subscale[5]:
    - This is used to assess the frequency and severity of specific symptoms of inattention during the previous month
    - Lower scores correspond to fewer symptoms; scores >9 are indicative of symptoms likely to impact daily functioning in adults
  - PKU Profile of Mood States (POMS) Total Mood Disturbance (PKU-POMS TMD) score[6]:
    - POMS is a self-administered evaluation that assesses transient and variable mood states over the past week
    - PKU-POMS TMD provides an overall measure of an individual's mood by totaling scores of the 5 negative mood domains assessed (anxiety, depression, anger, tiredness, and confusion) and subtracting activity domain score (a positive mood state)
    - Scores above the median at baseline (14) were used as criteria for pretreatment deficit

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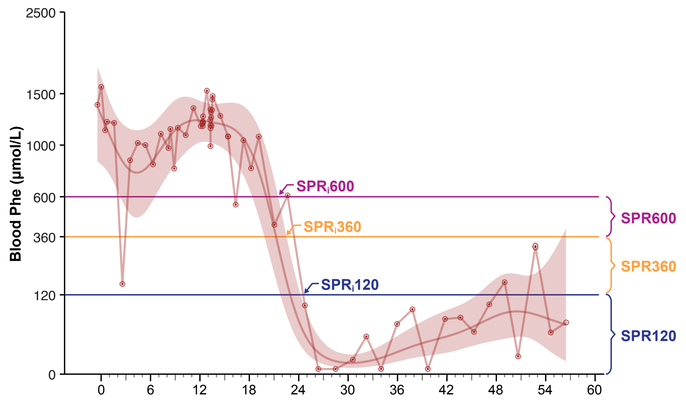
Spotlight on sustained Phe reponse (SPR)

- The longitudinal pattern of serial Phe measures for each patient, expressed as the expected value of Phe at time t (Phe_t; days since baseline), was estimated with a generalized additive model smoother function
- A 95% confidence interval (CI) for Phe_t reflects the range of plausible values for estimated Phe_t given the number of temporally proximal Phe measures and their variability
- SPR was defined as when the upper 95% CI of the longitudinally modeled pattern in estimated mean Phe_t crosses and remains below specific Phe thresholds: 600 µmol/L, 360 µmol/L, and 120 µmol/L
- To compare outcomes between different SPR thresholds, this analysis used mutually exclusive SPR categories:
  - SPR600: ≤600 µmol/L and >360 µmol/L
  - SPR360: ≤360 µmol/L and >120 µmol/L
  - SPR120: ≤120 µmol/L

Example of individual SPR plot



Phe, phenylalanine; SPR, sustained Phe response; SPR_i, initiation of sustained Phe response

Modeling

- A Bayesian multilevel ordinal regression model estimated the monotonic effects[7-10] of SPR on ADHD RS-IV IA and PKU-POMS
  - Conditioning on patient, with varying intercepts and varying effects
  - SPR fitted as a 4-level ordinal predictor (Not in SPR vs SPR600, SPR360, and SPR120)

Results

Demographics

- Demographics of participants included in the 2 models were broadly similar to the overall PRISM population, although with a slightly higher percentage of female participants in the PKU-POMS TMD model

	Overall PRISM (n=261)		ADHD RS-IV IA* (score >9; n=91)	PKU-POMS TMD* (score >14; n=69)
Age at first dose				
Mean (SD)	29.7 (8.8)		32.2 (9.3)	31.2 (9.1)
Median	28.1		30.4	29.1
Sex, % female	49.8		48.4	56.5
Baseline blood Phe	(n=253)			
Mean (SD)	1226 (383.8)		1296 (366.7)	1243 (400.6)
Median	1210.0		1271.0	1260.0
Baseline score	**ADHD RS-IV IA (n=251)**	**PKU-POMS TMD (n=169)**		
Mean (SD)	9.8 (6.1)	16.0 (13.3)	15.4 (3.9)	27.1 (9.1)
Median	9.0	14.0	15.0	25.0

*n values for model results include patients with ADHD RS-IV IA >9 or PKU-POMS TMD >14 *and* concurrent SPR level not missing
ADHD RS-IV IA, Attention Deficit Hyperactivity Disorder Rating Scale-IV Inattention; Phe, phenylalanine; PKU, phenylketonuria; PKU-POMS TMD, PKU Profile of Mood States Total Mood Disturbance; SD, standard deviation; SPR, sustained Phe response

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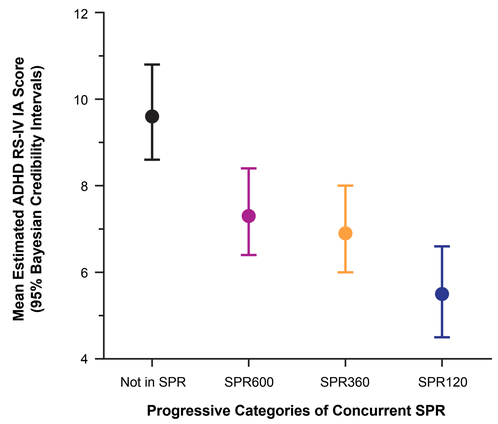
Disclosures

All authors are/were employees and shareholders of BioMarin Pharmaceutical Inc. at the time of this analysis.

Estimated ADHD RS-IV IA scores in distinct SPR categories

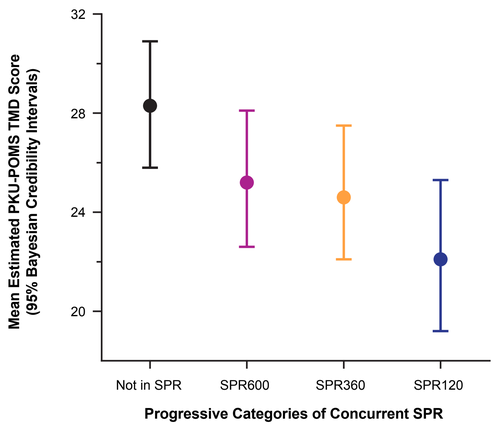
- In the regression model for participants with ADHD RS-IV IA score >9 (n=91), estimated inattention scores were lower for each of the successive SPR categories SPR600, SPR360, and SPR120 vs "Not in SPR" (Bayesian posterior probability, BPPr>0 = 0.99)
- Similar patterns were observed in additional models:
  - Including the overall population without restriction on baseline score; and
  - For ADHD RS-IV total score



ADHD RS-IV IA, Attention Deficit Hyperactivity Disorder Rating Scale-IV Inattention; Phe, phenylalanine; SPR, sustained Phe response

Estimated PKU-POMS TMD scores in distinct SPR categories

- In the regression model for participants with PKU-POMS TMD baseline score >14 (n=69), estimated mood scores were lower for each of the successive SPR categories SPR600, SPR360, and SPR120 vs "Not in SPR" (BPPr>0 = 0.99)



Phe, phenylalanine; PKU, phenylketonuria; PKU-POMS TMD, PKU Profile of Mood States Total Mood Disturbance; SPR, sustained Phe response

Conclusions

- Analyses reliant on individual concurrent Phe measures involve strong assumptions, and as a proxy for longitudinal exposure or efficacy outcome they have poor reliability and predictive value as indicators of treatment response
- SPR may be a more reliable representation of the persistent improvement in Phe levels necessary for improvement in clinical outcomes
- Secondary analyses of the PRISM program demonstrated substantial improvements in measures of inattention and mood associated with the achievement of lower blood Phe levels, expressed as an index of SPR
- Recently updated guidelines indicated that lower blood Phe levels were consistently associated with better intellectual outcomes, revising recommendations to target blood Phe ≤360 µmol/L[11]
- Notably, ADHD RS-IV IA and PKU-POMS TMD scores for sustained Phe levels ≤120 µmol/L were significantly better than those at sustained levels of ≤600 µmol/L or ≤360 µmol/L, suggesting that achievement of blood Phe in the normal range may provide additional benefit in patient outcomes

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