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Improved attention linked to sustained phenylalanine reduction in adults with early-treated phenylketonuria

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Abstract

Pegvaliase is approved to reduce phenylalanine (Phe) levels for people with phenylketonuria (PKU). PRISM-1 (NCT01819727) and PRISM-2 (NCT01889862) data were analyzed to evaluate the relationship between Phe and inattention in adult participants with PKU. *In the modified-intent-to-treat population* ($N = 156$), *baseline mean* (*SE*) plasma Phe was 1263 (29) μmol/L and the Attention Deficit Hyperactivity Disorder Rating Scale-IV Inattentive (IA) symptoms score was 9.8 (0.5). Mean (SE) IA scores fell 9.0 (1.1) in Quartile 1 (Phe reduction between 1166 and 2229 μmol/L) versus 4.3 (0.7) in Quartile 4 (Phe reduction of 139 μmol/L to increase of 934 μmol/L), $p = 0.004$. Least squares mean (SE) change from baseline IA score was −7.9 (0.7) for participants with final Phe ≤ 360 μmol/L and −4.5 (0.7) for final Phe > 360 μmol/L, $p < 0.001$. In the inattention subgroup, IA scores fell 13.3 (1.5) in Quartile 1 (Phe reduction between 1288 and 2229 μmol/L) versus 6.2 (1.3) in Quartile 4 (Phe reduction of 247 to increase of 934 μmol/L), $p = 0.009$. Inattention symptoms improved among those whose Phe levels decreased, particularly those with high baseline IA scores. IA improvements were larger among participants with the greatest plasma Phe reductions, supporting this value as a therapeutic goal.

KEYWORDS
inattention, PEGylated ammonia lyase, pegvaliase, phenylalanine, phenylketonuria

1 | BACKGROUND

Phenylketonuria (PKU) is the most common inborn error of amino acid metabolism, affecting approximately 1 in 13,000 births in the United States (Berry et al., 2013). The majority of individuals with PKU have a deficiency of the phenylalanine hydroxylase enzyme (PAH), which leads to elevated phenylalanine (Phe) levels in blood and tissues (van Spronsen et al., 2021). If left untreated during the first years of life, PKU leads to severe neurologic and cognitive impairments, such as intellectual disability, seizures, and autism (Ashe et al., 2019; Bilder et al., 2017; Mainka et al., 2021). The initiation of newborn screening and early treatment for PKU has substantially improved childhood and adult outcomes (Berry et al., 2013). Currently, established treatments focus on Phe reduction primarily through restricting dietary protein intake, including a Phe-free amino acid fortified supplement and low-protein foods (to provide enough energy), and/or use of medication (e.g., sapropterin) to reduce blood Phe in individuals with residual PAH activity (Berry et al., 2013; Rohr et al., 2015; van Wegberg et al., 2017; Vockley et al., 2014). However, these interventions rarely normalize blood Phe levels in individuals with classic PKU, even among those who are able to maintain a Phe-restricted diet (Brown & Lichter-Konecki, 2016) into adulthood.

As a group, adults with early-treated PKU display measurable executive-functioning impairment and elevated rates of mood and anxiety symptoms (Bilder et al., 2016). Adult cognitive and emotional outcomes often correlate better with early childhood metabolic control than more recent blood Phe levels (Pietz et al., 1997; Ris et al., 1997; Weglage et al., 2013). Such findings have been attributed to the assumption that long-standing elevated Phe during childhood and adolescence confers irreversible damage to the brain, resulting in reduced cognitive and psychiatric functioning (Ris et al., 1997). Understanding the contribution to adult functioning of recent fluctuations in Phe levels compared to lifetime Phe levels is confounded by the high correlation between these two Phe values. Additionally, the high burden associated with resuming a Phe-restricted diet may minimize the benefits imparted by sustained Phe reduction on adult executive functioning (Burgess et al., 2021).

Impaired attention is one of the most notable aspects of neurocognitive sequelae reported in adults with early-treated PKU. A meta-analysis and systematic review of neurocognitive functioning and psychiatric symptoms associated with early-treated PKU in adulthood found an effect size of 0.74 for PKU on attention domains of neurocognitive tests (Bilder et al., 2016). Pilotto et al. (2021) evaluated 19 early-treated adults with PKU greater than 30 years of age and found strong evidence of a correlation between concurrent Phe levels and neuropsychological alterations. Changes in attention have also been associated with blood Phe manipulation in small studies of adults with early-treated PKU. Schmidt et al. (1994) demonstrated improved attention in 14 adults with early-treated PKU when returned to a Phe-restricted diet for 4 weeks; of note, three additional participants were unable to sustain a 4-week Phe restriction and a further two were unable to complete the study. Additionally, ten Hoedt et al. (2011) used a 4-week Phe load to demonstrate worsening attention in high versus low blood Phe states among nine adults with early and continuously treated PKU.

Traditionally, the neurocognitive impairment in attention experienced by individuals with PKU has been measured as a component of extensive test batteries that can be prohibitively complex for routine use in genetic clinics and during clinical trials. Through qualitative content validation study methodology, Wyrwich et al. (2015) validated inattentive (IA) symptoms as part of the experience of having PKU in pediatric and adult populations using the Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale-IV (ADHD RS-IV, parent-report) and Adult ADHD Self-Report Scale (ASRS). ADHD is a common neurodevelopmental disorder most recently described in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (American Psychiatric Association, 2013) and symptoms of ADHD fall within the two domains inattention and hyperactivity/impulsivity. In contrast to individuals diagnosed with ADHD, in adults with PKU, problems with inattention may not have been present or identified in childhood. While neurocognitive impairments experienced by individuals with PKU extend far beyond ADHD IA symptoms in breadth and complexity, designing clinical pharmaceutical trials to achieve U.S. Food and Drug Administration (FDA) approval necessitates the use of measurement instruments that have established FDA precedents for measuring symptom domains that define clinically significant impairment and treatment response. IA symptoms have been found to improve among participants with PKU whose blood Phe level decreased by at least 20% in response to sapropterin ($N = 38$) when compared with placebo (Burton et al., 2015).

Pegvaliase, a pegylated derivative of phenylalanine ammonia lyase, has been evaluated in clinical trials as a treatment for PKU (Thomas et al., 2018) and is approved to reduce blood Phe levels in adults with PKU in the United States and in participants ≥16 years of age with PKU in Europe. The current secondary analysis uses pegvaliase phase 3 clinical trial data (baseline and open-label extension study) to examine the relationship between sustained plasma Phe reduction and symptoms of inattention, as assessed with the ADHD RS-IV IA subscale items.

2 | METHODS

2.1 | Study design

Details of the PRISM-1 (NCT01819727) and PRISM-2 (NCT01889862) (registered March, 28, 2013, https://clinicaltrials.gov/ct2/show/NCT01819727 and https://clinicaltrials.gov/ct2/show/NCT01889862) studies have been described previously (Burton et al., 2015). See Figure S1 for a flowchart describing the study design. Briefly, both PRISM-1 and PRISM-2 were multicenter phase 3 studies to evaluate the safety and efficacy of pegvaliase among adults aged ≥18 years with PKU in the United States. In PRISM-1, the initial study with up to 36 weeks of treatment, participants were randomized in a 1:1 ratio to receive a maintenance dose of pegvaliase at either 20 mg/day or 40 mg/day. Eligible participants then continued into the four-part extension study,

PRISM-2, which, combined with PRISM-1, resulted in up to 66 months of treatment. In Part 1 of the PRISM-2 study, participants maintained their prior dose of pegvaliase while plasma Phe levels were assessed during a maximum of 13 weeks. In Part 2, participants achieving ≥20% decrease in plasma Phe during Part 1 were randomized 2:1 either to continue their maintenance dose of pegvaliase (20 mg/day or 40 mg/day) or to initiate placebo for 8 weeks. (Participants who did not meet criteria to enter Part 2 moved directly to Part 4.) In Part 3, participants continued or, for placebo participants, reinstated their maintenance dose for 5 weeks while completing pharmacokinetic and pharmacodynamic assessments. Finally, Part 4 was an open-label extension study lasting up to 212 weeks, during which doses could be titrated from 5 to 60 mg/day, per investigator discretion. Only participants completing at least 6 months of PRISM-2 Part 4 and had assessments of both plasma Phe and inattention during PRISM-2 Part 4 were included in the current analysis; thus, participants in the current study who fulfilled these criteria are referred to as the modified intention-to-treat (mITT) cohort. These inclusion criteria were implemented to capture the association between inattention symptoms and sustained Phe levels while minimizing the confounding effects of pegvaliase dose adjustments. Follow-up plasma Phe and IA scores were obtained during Part 4 of PRISM-2.

Adults ≥18 years old with PKU and without prior exposure to pegvaliase were eligible for inclusion in PRISM-1 if plasma Phe concentration was >600 μmol/L at screening and average plasma Phe concentration was >600 μmol/L for the prior 6 months. Although co-occurring intellectual disability was not an exclusion criterion, participants were required to have the independent ability to provide informed consent to participate in this study. All participants were counseled to maintain a diet consistent in total protein and Phe intake, as monitored by a dietitian, throughout the study. Participants must have discontinued sapropterin treatment ≥14 days prior to the first dose of pegvaliase. Individuals on psychotropic medications, including those that target ADHD, must have been on a stable dose for ≥8 weeks prior to enrollment.

All protocols were approved by the study institutional review board or independent ethics committee. All participants provided informed consent, and both PRISM-1 and PRISM-2 were conducted in accordance with the Declaration of Helsinki.

2.2 | Treatments

Pegvaliase, recombinant *Anabaena variabilis* phenylalanine ammonia lyase conjugated to polyethylene glycol (PEG), is administered as a subcutaneous injection. Participants were provided with vials and syringes or prefilled syringes for administration. The initial injection was given at the study site, and participants were required to demonstrate competency in self-administration, including an understanding of the signs and symptoms of a hypersensitivity reaction, before continuing their injections at home. In PRISM-1, doses were initiated at 2.5 mg/week. After 4 weeks of initiation, doses were titrated up to 20 mg/day or 40 mg/day during a maximum of 30 weeks. In PRISM-2, during the open-label part of the study, pegvaliase was administered daily.

2.3 | Assessments

Baseline measures (time point 0) for plasma Phe and inattention symptoms occurred at the PRISM-1 baseline visit. Measures of plasma Phe levels were taken weekly throughout PRISM-1 and at least monthly until Week 25 during PRISM-2. Thereafter, plasma Phe levels were measured every other month.

To assess the effects of pegvaliase on inattention symptoms in adults with PKU, the ADHD RS-IV with adult prompts was administered at baseline for PRISM-1 and at least every 12 weeks during PRISM-2.

The ADHD RS-IV is an 18-item questionnaire that queries changes in hyperactivity/impulsivity and inattention symptoms (Gibbins et al., 2010; Rösler et al., 2010). It has an established precedent with the FDA for measuring treatment response in ADHD (Adler et al., 2008; Wyrwich et al., 2015). The nine ADHD IA symptoms, measured by 9-item inattention subscales, have been validated as part of the experience of PKU in pediatric and adult populations using the parent-report ADHD RS-IV and ASRS, respectively (Thomas et al., 2018; Wyrwich et al., 2015). For this study, the clinician-administered ADHD RS-IV with adult prompts was selected over the ASRS to ensure thorough consideration of each item by participants through an interview process that included specific examples for each item.

Participants were asked about the frequency of specific symptoms during the prior month, and their responses were rated according to a Likert scale (0 = none, 1 = mild, 2 = moderate, or 3 = severe). Nine of the items in the ADHD RS-IV assess inattention, and the collective score from these items forms the IA score. IA scores range from 0 to 27, with lower scores corresponding to fewer inattention symptoms. Participants with an IA score of ≥10 were subsequently considered a member of the IA subgroup. The threshold of an IA score ≥ 10 was chosen in this study to indicate the presence of inattention likely to impede daily functioning in adults with PKU (American Psychiatric Association, 2013; Wyrwich et al., 2015). Multiple combinations of individual item scores could lead to a subscale score of 10. For example, a score of 10 corresponds to endorsing five inattention symptoms at moderate severity. Five inattention symptoms also correspond to the minimum number required to meet symptom criteria for ADHD, IA type, in adults (American Psychiatric Association, 2013). Additional ADHD diagnostic criteria components based on the DSM-5 (American Psychiatric Association, 2013) were not evaluated; establishing ADHD diagnosis was not a component of this study.

Safety was assessed by monitoring for adverse events.

2.4 | Statistical analyses

Analyses were completed for participants in the mITT population who had plasma Phe and ADHD RS-IV IA assessments at baseline and ADHD RS-IV IA subscale scores available during Part 4 of PRISM-2. Analyses were also completed on the IA subgroup of participants to

evaluate how this group may be distinguished from the mITT population as a whole in plasma Phe levels and IA score responses. Descriptive statistics were calculated at baseline, Month 54 (the prespecified post-treatment period), and last observation for mITT and IA subgroup populations. A p-value <0.05 was considered statistically significant. Pearson correlation coefficients were calculated for the relationship between change in IA score and change in plasma Phe from baseline to last assessment as well as for change in IA score from baseline with the last measured plasma Phe level (1) for the mITT and (2) IA subgroup.

For the quartile analysis, each population (mITT population and IA subgroup) was divided into four groups based on plasma Phe level change from baseline to last observation. For these analyses, plasma Phe and ADHD RS-IA measures needed to have occurred within a 31 day proximity to each other to be considered as paired so as to coincide with the ADHD RS-IV's 1 month recall period. For each quartile group, mean change from baseline in IA score was calculated. Post hoc tests were used to investigate differences in mean IA score change corresponding to quartile of plasma Phe level change. An analysis of variance (ANOVA) was conducted to test for differences in mean IA score change. The independent variable was the quartile of plasma Phe change. After confirming the significance of the overall ANOVA model based on the F test, post hoc tests using the Scheffé method to correct for multiple comparisons were implemented to compare between quartiles.

An additional analysis was performed to assess mean change from baseline in IA score associated with prespecified ranges of final plasma Phe levels at last observation (<120, 120–360, >360–600, >600–1200, and >1200 μmol/L). Mean change in IA score associated with final plasma Phe ≤ 360 μmol/L was contrasted with mean change in IA score associated with final plasma Phe > 360 μmol/L. A similar analysis was done for mean change in IA score with final plasma Phe ≤600 μmol/L as contrasted with mean change in IA score associated with final plasma Phe > 600 μmol/L. An ANOVA model was used to compare the mean change in IA score between groups. Statistical analyses were conducted in SPSS version 24, and statistical significance was assessed at alpha = 0.05.

3 | RESULTS

3.1 | Participants

The mITT population included 156 participants with data available on plasma Phe and ADHD RS-IV assessments at baseline and during the open-label extension (Part 4) of PRISM-2. Baseline characteristics of participants in the mITT population (taken during screening for the PRISM-1 study) were similar to the overall PRISM population. They had a mean (SE) age of 29.6 (0.7) years and 48.7% were women (Table 1). Mean (SE) plasma Phe concentration at baseline for the mITT population was 1263 (29) μmol/L and mean (SE) IA score was 9.8 (0.5). The IA subgroup included 71 participants whose IA score equaled or exceeded 10 at baseline. In the IA subgroup (Table 1), mean (SE) age was 32.1 (1.2) years, 52.1% were women, mean (SE) plasma Phe concentration was 1320 (45) μmol/L, and mean (SE) IA score was 15.3 (0.5).

3.2 | Treatment protocol

In the mITT population, 156 participants received pegvaliase for a mean (SE) of 1148.1 (32.9) days. In the IA subgroup, 71 participants received pegvaliase for a mean (SE) of 1157.7 (44.8) days and in the 85 participants with an ADHD RS-IV IA score < 10, the mean (SE) duration of pegvaliase treatment was 1140.1 (47.6) days.

3.3 | Plasma Phe levels and ADHD RS-IV IA scores

Figure 1 depicts the change in plasma Phe and IA scores over time, with last IA score carried forward. In the overall mITT population (Figure 1a), mean (SE) plasma Phe levels fell from 1263 (29) μmol/L at baseline to 584 (47) μmol/L at last observation, and mean (SE) ADHD RS-IV IA score declined from 9.8 (0.5) to 3.5 (0.4). In the IA subgroup (Figure 1b), mean (SE) plasma Phe fell from 1320 (45) to

TABLE 1 Baseline characteristics of modified intention-to-treat (mITT) population and inattention (IA) subgroup

Basis: mITT population	All participants ($N = 156$)	IA subgroup only ($N = 71$)
Age (years), mean (SE)	29.6 (0.7)	32.1 (1.2)
Female, *n* (%)	76 (48.7%)	37 (52.1%)
Race, *n* (%)		
White	153 (98.1%)	70 (98.6%)
Black or African American	2 (1.3%)	0
American Indian or Alaska Native	1 (0.6%)	1 (1.4%)
Hispanic or Latino ethnicity, *n* (%)	7 (4.5%)	2 (2.8%)
Height (cm), mean (SE)	168 (0.8)	167 (1.1)
Weight (kg), mean (SE)	79.9 (1.7)	79.8 (2.6)
Baseline Phe (μmol/L), mean (SE)	1263 (29)	1320 (45)
Baseline ADHD RS-IV IA score, mean (SE)	9.8 (0.5)	15.3 (0.5)
Baseline dietary Phe (mg), mean (SE)	1789 (104)	1924 (174)
Baseline dietary protein (g), mean (SE)	67.2 (2.5)	65.8 (3.9)

Note: The IA subgroup includes participants with baseline ADHD RS-IV IA score ≥ 10.
Abbreviations: *ADHD RS-IV*, Attention Deficit Hyperactivity Disorder Rating Scale-IV; *IA*, inattention subscale; *mITT*, modified intention-to-treat; *Phe*, plasma phenylalanine level; *SE*, standard error.

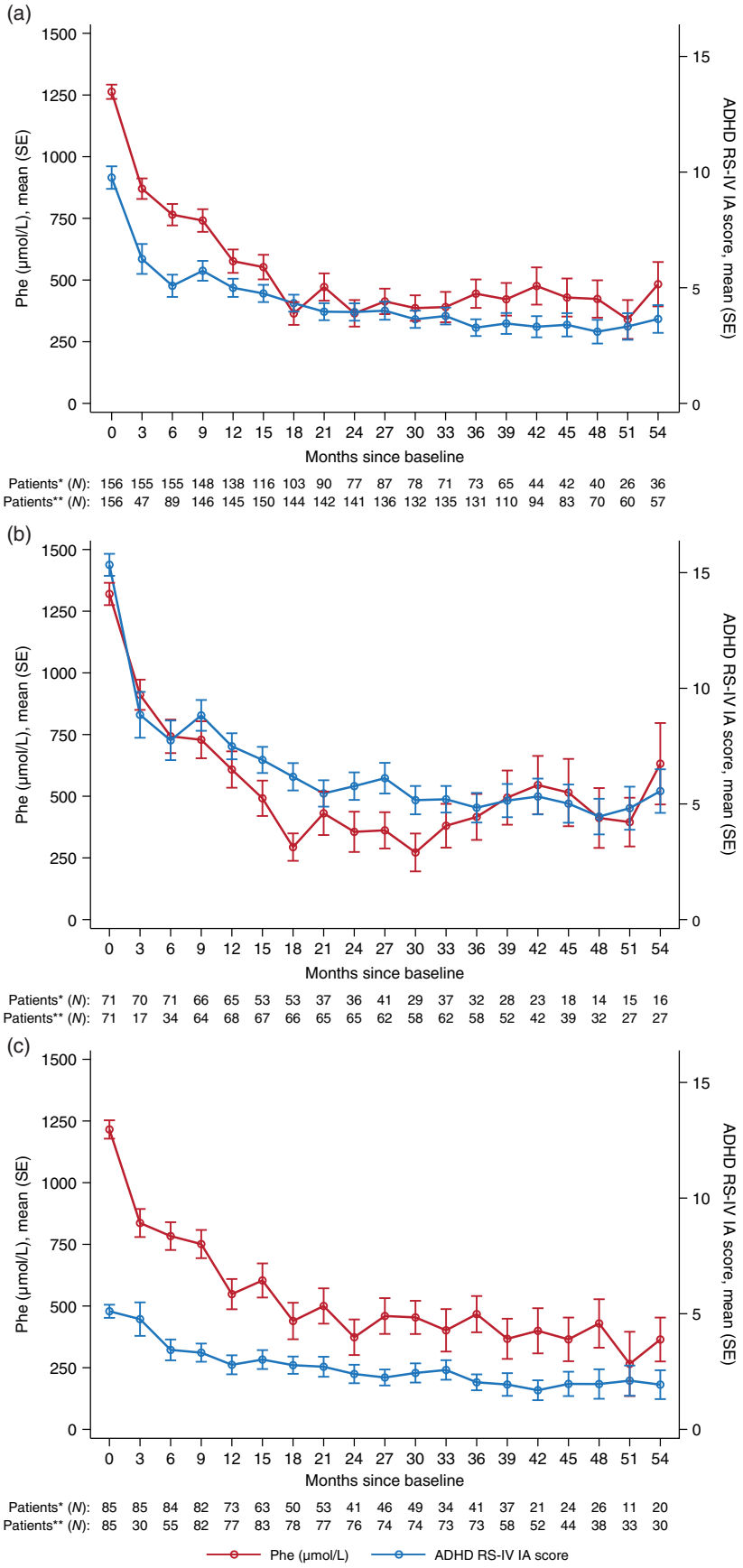

FIGURE 1 Mean (SE) plasma phenylalanine (Phe) concentrations and Attention Deficit Hyperactivity Disorder Rating Scale-IV (ADHD RS-IV) inattention subscale (IA) scores over time. (a) Modified intention-to-treat total population ($N = 156$). (b) Participants with baseline ADHD RS-IV IA score ≥ 10 (IA subgroup; $N = 71$). (c) Participants with baseline ADHD RS-IV IA score ≤ 9 ($N = 85$). Note that number of patients accounted for differs between efficacy parameters per time-point. *Number of patients contributing to Phe evaluation. **Number of patients contributing to ADHD RS-IV IA score evaluation

549 (74) μmol/L at last observation, and mean (SE) IA score fell from 15.3 (0.5) to 5.1 (0.6). In the subgroup with IA scores <10 at baseline (Figure 1c), mean (SE) plasma Phe fell from 1216 (37) to 614 (62) μmol/L at last observation, and mean (SE) IA score declined from 5.1 (0.3) to 2.2 (0.4). Change from baseline in plasma Phe and IA scores at last assessment were significantly correlated for the mITT population and IA subgroup ($r = 0.26$, $p \leq 0.001$; $r = 0.34$, $p = 0.003$, respectively). Change from baseline in IA score and last plasma Phe value were also significantly correlated for the mITT population and IA subgroup ($r = 0.24$, $p = 0.002$; $r = 0.33$, $p = 0.005$, respectively; Figures S2a and S2b). Participants transitioned between PRISM-1 and PRISM-2 at different time intervals, leading to a discrepancy in number of ADHD RS-IV assessments performed during the early stages of the study.

In the quartile analysis (Figure 2), improvements in IA scores were greatest among participants experiencing the largest plasma Phe reductions in both the mITT population and IA subgroup. In the mITT population, participants in Quartile 1 ($N = 39$, plasma Phe reductions between 1166 and 2229 μmol/L) demonstrated the greatest reduction in mean (SE) IA score (9.0 [1.1]), whereas participants in Quartile 4 ($N = 39$, plasma Phe reduction of 139 μmol/L to an increase of 934 μmol/L) had the least reduction in mean (SE) IA score (4.3 [0.7]). Interestingly, the relationship between plasma Phe reduction and inattention symptom improvement followed a stepwise pattern across all quartiles of the mITT population (Figure 2a). The IA subgroup demonstrated a similar stepwise response (Figure 2b), ranging from a mean (SE) IA score improvement of 13.3 (1.5) in Quartile 1 ($N = 18$, plasma Phe reductions between 1288 and 2229 μmol/L) to an IA score improvement of 6.2 (1.3) in Quartile 4 ($N = 17$, Phe reduction of 247 μmol/L to a Phe increase of 934 μmol/L).

ANOVA test yielded significant overall main effects for quartile of plasma Phe change on IA score change in the mITT population and IA

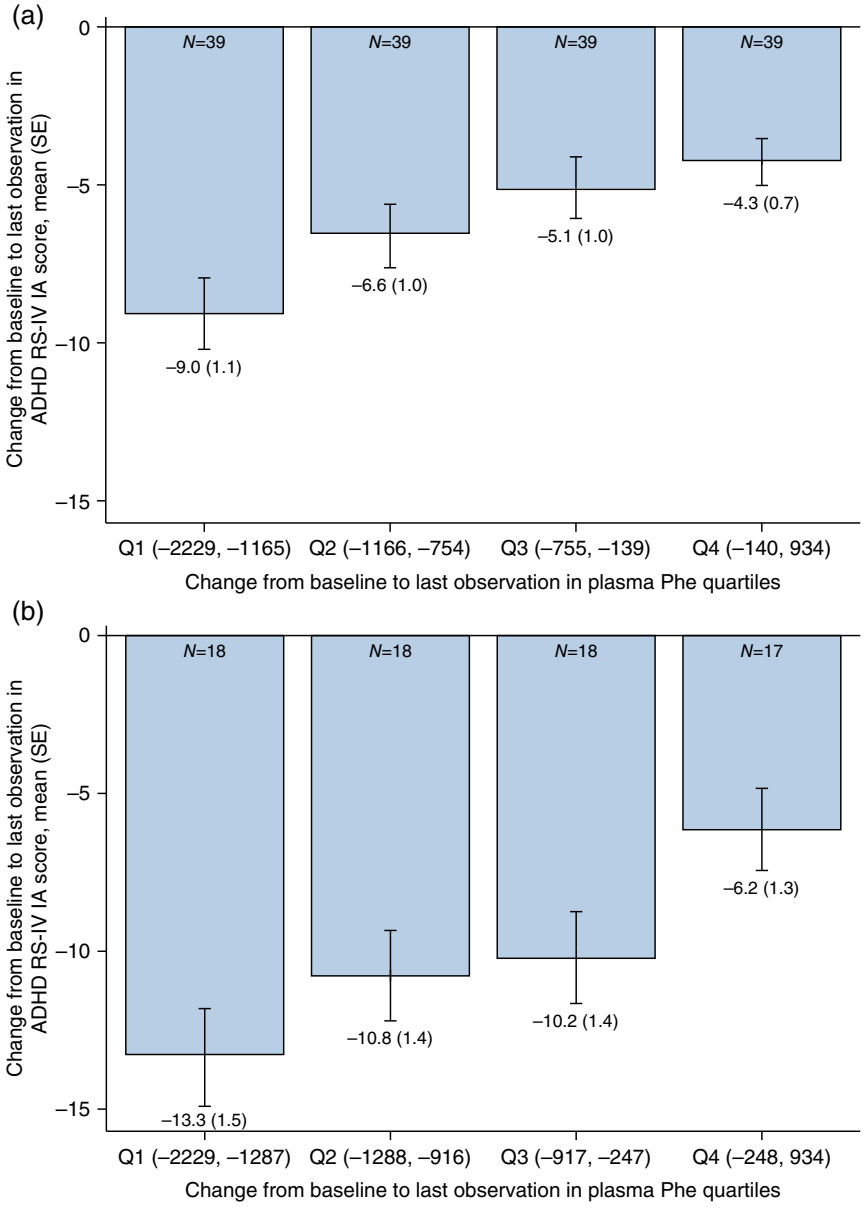

FIGURE 2 Change from baseline in Attention Deficit Hyperactivity Disorder Rating Scale-IV (ADHD RS-IV) inattention subscale (IA) score by change from baseline in plasma phenylalanine (Phe) quartiles. (a) Modified intention-to-treat population ($N = 156$). (b) IA subgroup ($N = 71$)

subgroup. Mean quartile-group change in Phe level was compared with mean ADHD subscale change. In the mITT population, statistically significant differences remained in the least square means of IA score change between Quartiles 1 and 3 (mean difference = −3.9, 95% confidence interval [95% CI] = −7.8, 0.0, $p < 0.05$) and between Quartiles 1 and 4 (mean difference = −4.8, 95% CI = −8.7, −0.9, $p = 0.004$) following correction for multiple comparisons. In the IA subgroup, statistically significant differences remained in the least square means of IA score change between Quartiles 1 and 4 (mean difference = −7.2, 95% CI = −13.0, −1.3, $p = 0.009$) following correction for multiple comparisons.

In the analysis based on prespecified levels of plasma Phe at last observation in the mITT population (Figure 3), least squares mean (SE) change from baseline in IA score was −7.9 (0.7) for participants with final plasma Phe ≤ 360 μmol/L ($N = 79$) and −4.5 (0.7) for participants with final plasma Phe > 360 μmol/L ($N = 77$), $p < 0.001$. The least squares mean (SE) change from baseline in IA score was −7.4 (0.7) for participants with final plasma Phe ≤ 600 μmol/L ($N = 89$) and −4.6 (0.8) for participants with final plasma Phe > 600 μmol/L ($N = 67$), $p = 0.005$.

A sensitivity analysis was performed that excluded participants who discontinued pegvaliase ($N = 26$). Results of the sensitivity analysis yielded similar results as the main study. The quartile analysis showed statistically significant differences ($p = 0.019$) between Quartiles 1 and 4 (mean difference −4.7, 95% CI = −9.0, −0.3), and the analysis based on prespecified levels of plasma Phe last observation (i.e., Phe ≤ 360 μmol/L vs. Phe > 360 μmol/L) in the mITT population ($N = 130$), were statistically significant ($p = 0.005$) (Table S1, Figures S3–S5).

3.4 | Safety

Incidence of adverse events was similar in the overall mITT population and the IA subgroup (Table S2).

4 | DISCUSSION

Attention ranks highest among executive functioning domains affected by PKU in early-treated adults. Impaired attention has also been linked to poorer metabolic control (Bilder et al., 2016). Adults with PKU in the current study experienced sustained improvement in inattention symptoms as measured by the ADHD RS-IV coinciding with an extended period of plasma Phe reduction in the context of pegvaliase treatment. The nine symptoms that characterize the IA domain of ADHD were validated in adults with PKU using an ADHD self-report measure. Importantly, an ADHD diagnosis is not conferred solely through the completion of this tool, nor were study participants diagnosed with ADHD as a component of this study. Rather, ADHD IA symptoms were monitored systematically before and during study participation because adults with PKU have endorsed these symptoms as relevant to their experience of PKU.

Both the mITT population and the IA subgroup demonstrated improved inattention symptoms associated with greater plasma Phe reduction, although this relationship was particularly robust for the IA subgroup. The IA subgroup consisted of the 71 participants (46% of the mITT population) who reported inattention symptoms at baseline that corresponded to an IA score ≥ 10. Across this group, declines in plasma Phe levels coincided with declines of IA scores from a temporal perspective, both with regard to initial treatment response (first 3–6 months) and the onset of a plateau (at approximately 18 months; Figure 1b). The change in mean IA score from 15.3 to 5.1 is quite notable, far exceeding a 50% reduction in symptom burden in the IA subgroup. While individuals with PKU have only symptoms and not a diagnosis of ADHD, this greater than 50% reduction in inattention symptoms in PKU participants is comparable to the established threshold for treatment response used in drug trials targeting individuals diagnosed with ADHD (Goodman et al., 2010). Figure 2b depicts differences in IA score response across quartiles of plasma Phe reduction in the IA subgroup. The stepwise reduction in IA score response corresponds to incremental decreases in the plasma Phe response,

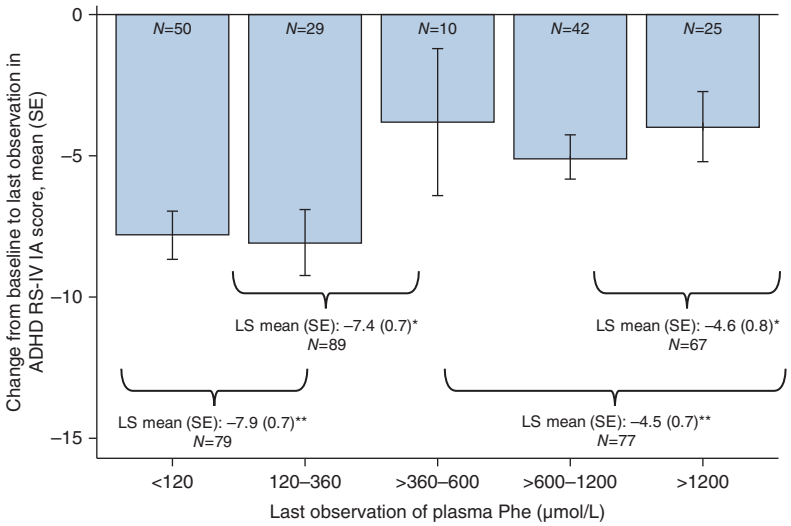

FIGURE 3 Change from baseline to last observation in Attention Deficit Hyperactivity Disorder Rating Scale-IV (ADHD RS-IV) inattention subscale (IA) score by final plasma phenylalanine (Phe) cut off value of 360 μmol/L and 600 μmol/L in modified intention-to-treat population ($N = 156$). These analyses are not reported for the IA subgroup because of the small number of participants available for analysis at last observation. *p-value: 0.005 for LS mean (SE) change from baseline in IA score with final plasma Phe ≤ 600 μmol/L versus >600 μmol/L. **p-value: 0.001 for LS mean (SE) change from baseline in IA score with final plasma Phe ≤ 360 μmol/L versus >360 μmol/L

which suggests a direct relationship between improvements in attention and metabolic control. Although participants who did not meet the IA subgroup threshold for elevated baseline IA score also demonstrated improved inattention symptoms, a benefit related to this endpoint could not be speculated upon in the absence of clinically meaningful impairment at baseline. The burden of reintroducing a Phe-restricted diet in adults with PKU has previously preempted the ability to measure improvements in attention associated with tightened metabolic control during extended periods. Therefore, previous studies linking Phe reduction to better functioning in adults with PKU were limited in participant number and duration (Bik-Multanowski et al., 2011; Brown & Lichter-Konecki, 2016; Finkelson et al., 2001; Gassió et al., 2003; Schuett et al., 1985). While participants were counseled to maintain consistent dietary protein intake throughout the study's duration, dietary protein changes trended upward as previously reported (Thomas et al., 2018). While this study was designed to attribute improved inattention symptoms to sustained plasma Phe reduction, there remains a possibility that increased dietary protein intake may also contribute to reduced IA scores.

Participants in this study had baseline plasma Phe levels > 600 μmol/L, whereas PKU treatment guidelines for adults target Phe levels ≤ 360 μmol/L in the United States and ≤600 μmol/L in Europe (van Wegberg et al., 2017; Vockley et al., 2014). Figure 2a demonstrates the stepwise decline in Phe levels in adults with PKU that corresponds with the degree to which inattention symptoms improve. The results suggest a dose–reponse relationship between change in Phe levels and improved inattention symptoms. Specifically, a progressive decline in mean IA score is associated with each increasing quartile of plasma Phe reduction in the mITT population. Improvements in attention, as demonstrated by reduced IA scores, imply that this component of cognitive deficits is responsive to Phe-lowering intervention in adulthood.

Although smaller than the changes in Quartiles 1–3, IA score improvement was found in Quartile 4 for both the mITT population and IA subgroup despite being associated with minimal plasma Phe improvement or increased plasma Phe levels. These results may be attributed to the Hawthorne effect, in which study participants report symptom improvement as a result of their awareness of being observed (McCambridge et al., 2014). While the Hawthorne effect also applies to participants in the remaining quartiles, the consistency in dose–response patterns demonstrated across quartiles and both mITT population and IA subgroup support the attribution of IA score improvement to sustained plasma Phe response. As this study's primary focus was on the relationship between prolonged Phe reduction and inattention, rather than pegvaliase, participants who discontinued pegvaliase after reaching Part 4 of the clinical trial remained in this analysis. The sensitivity analysis (Table S1) demonstrated similar results as the primary analysis following exclusion of participants who discontinued pegvaliase prematurely. Interestingly, Quartile 4 continued to include participants with a net increase in plasma Phe up to 879 μmol/L.

The ADHD RS-IV inattention subscale was selected to measure inattention symptom response in PKU because this tool has established a precedent with the FDA through its use in demonstrating treatment response in ADHD. Questionnaires are frequently used in both FDA clinical trials and clinical practice to monitor treatment response. While providing a systematic means of capturing an individual's experience of IA as applied to activities of everyday life, self- and clinician-reported measurements are inherently influenced by other intrinsic factors like mood and anxiety. As such, changes—or even the absence of changes—in IA scores are not equivocal to changes in direct performance measures of attention. Neuropsychological testing measures individual components of attentional control that involve the ability to voluntarily direct, shift, and sustain attention. The interpretation of this study's results is subsequently limited to symptoms of inattention rather than performance on an attention-specific standardized task. The clinician-administered ADHD RS-IV IA subscale itself has not been validated for use in adults with PKU, which is a significant limitation of this study. The clinician-administered ADHD RS-IV IA subscale measure was selected over the corresponding IA subscale of the ASRS (the self-report ADHD IA symptom subscale that was validated in adults with PKU; Wyrwich et al., 2015) to ensure thorough consideration of each item by participants through an interview process that included specific examples for each item. No clear cutoff exists on the IA subscale score to indicate the presence of impairment in the PKU population. In this study, a score of 10 was selected to define the minimum value needed to classify participants as having problematic inattention because this score would be consistent with the presence of five symptoms at moderate severity, meeting the symptom number and severity components of the DSM-5 criteria for ADHD, IA type, in adulthood. It is important to note that participants were not diagnosed with ADHD as number and severity of ADHD symptoms is just one of multiple criteria required to establish this diagnosis.

During the placebo-controlled phase of this clinical trial, participants were randomized to active drug or placebo arms for 8 weeks (during PRISM-2). Results of this study phase have been published previously (Harding et al., 2018). The ADHD-RS IV performed at the beginning, during (at 4 weeks), and at the end (at 8 weeks) of the randomization period found no increase in inattention symptoms among participants who switched to placebo compared with those who remained on pegvaliase. However, executive functioning was also measured with a computerized, performance-based neuropsychological battery, the Cambridge Neuropsychological Test Automated Battery (CANTAB), in nine participants (six receiving pegvaliase and three receiving placebo) during this randomization phase (Harding et al., 2018). Among this small group, CANTAB findings favored pegvaliase treatment for measures of inhibitory control, sustained attention, and visuospatial working memory. The discrepancy between results of executive functioning, as measured with CANTAB and symptoms of inattention, as measured with ADHD RS-IV, may reflect the subjective nature of IA symptoms, as well as the potential for stress related to participation in a randomized discontinuation trial that may have confounded these symptoms. Cognitive processing speed has also long been recognized as an important area for potential impairment in individuals with PKU (Albrecht et al., 2009; Anderson

et al., 2007; Moyle, Fox, Arthur, et al., 2007; Moyle, Fox, Bynevelt, et al., 2007; Palermo et al., 2017). Two of the three CANTAB measures used to assess neurocognitive skills were timed tasks, and results revealed better response times on measures of inhibitory control in the treatment group who remained on pegvaliase compared with those randomized to placebo.

During the past decade, lifelong treatment to regulate plasma Phe has become the standard of care in published PKU management guidelines in both the United States and Europe (van Wegberg et al., 2017; Vockley et al., 2014). Therapeutic targets for plasma Phe in adults with PKU have evolved over time, as research has provided additional support for tighter metabolic control in this population. However, discrepancies still exist, as the upper limits of the target blood Phe for adults with PKU differ between United States and European guidelines (i.e., <360 μmol/L in the United States vs. <600 μmol/L in Europe) (van Wegberg et al., 2017; Vockley et al., 2014). Although this study was not designed to support specific Phe target levels, analyses were performed comparing target blood Phe ranges. Results of these analyses showed that improvements in IA scores were notably larger among participants who achieved final plasma Phe levels ≤360 μmol/L and ≤ 600 μmol/L. These findings may support the therapeutic goals of reducing blood Phe levels to ≤360 μmol/L in adults, as stated in the U.S. guidelines, and to ≤600 μmol/L as stated in the European guidelines (van Wegberg et al., 2017; Vockley et al., 2014). Current study findings support further investigations to define optimal targets for sustained plasma Phe levels, inclusive of measures of inattention symptoms and neurocognitive performance through performance-based testing. Results from this study show that greater symptom improvement for inattention is associated with larger decreases in plasma Phe levels.

5 | CONCLUSIONS

The findings of this study are consistent with previous studies among adults with PKU (Burton et al., 2015; Schmidt et al., 1994; ten Hoedt et al., 2011). However, this is the first study to demonstrate sustained plasma Phe reduction and corresponding improvement in inattention symptoms. This study is also the first to demonstrate a significant improvement in symptoms of inattention in adults with PKU when plasma Phe levels are decreased to ≤360 μmol/L and ≤ 600 μmol/L, providing support for published PKU guidelines in both the United States (Vockley et al., 2014) and Europe (van Wegberg et al., 2017), respectively. Although treatment of adults with PKU cannot reverse intellectual disability incurred from early childhood exposure to elevated Phe, symptoms of inattention can improve in adults with early-treated PKU through sustained reductions in plasma Phe levels.

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CONFLICT OF INTEREST

Deborah A. Bilder has received consulting fees as a Phase 3 Clinical Trials Steering Committee member for pegvaliase from BioMarin Pharmaceutical and consulting fees from Audentes Therapeutics, Encoded Therapeutics, Synlogic Therapeutics, and Taysha GTx. Georgianne L. Arnold has received funding for clinical trial activities involving pegvaliase from BioMarin Pharmaceutical. David Dimmock has received consulting fees from Audentes Therapeutics, Ichorion Therapeutics, BioMarin Pharmaceutical, Complete Genomics, Taysha GTx, and Flagship Pioneering. Mitzie L. Grant has received consulting fees, speaker fees and travel support and has participated as a clinical trial investigator for BioMarin Pharmaceutical. Darren Janzen and Mina Nguyen-Driver have received speaker fees and travel support from BioMarin Pharmaceutical. Nicola Longo has received consulting fees as a Phase 3 Clinical Trials Steering Committee member and funds for clinical trial activities involving pegvaliase from BioMarin Pharmaceutical. Elaina Jurecki and Markus Merilainen are employees and shareholders of BioMarin Pharmaceutical. Gianni Amato was an employee of BioMarin Pharmaceutical at the time of manuscript initiation. Susan Waisbren has received consulting fees from BioMarin Pharmaceutical.

AUTHOR CONTRIBUTIONS

Deborah A. Bilder planned the study, analyzed and interpreted the data, assisted with developing the outline, and drafted and revised the manuscript. Georgianne L. Arnold examined the participants, collected data, and revised the manuscript. David Dimmock helped plan the study, interpreted the data, assisted with developing the outline and revising the manuscript. Mitzie L. Grant helped plan the study, interpreted the data, assisted with developing the outline and revising the manuscript. Darren Janzen helped plan the study, interpreted the data, assisted with developing the outline and revising the manuscript. Nicola Longo helped plan the study, collected data, and revised the manuscript. Mina Nguyen-Driver helped plan the study, interpreted the data, assisted with developing the outline and revising the manuscript. Elaina Jurecki planned the study, analyzed and interpreted the data, developed the outline and drafted and revised the manuscript. Markus Merilainen planned the study, analyzed and interpreted the data, developed the outline and drafted and revised the manuscript. Gianni Amato collected the data, analyzed and interpreted the data and assisted with drafting the manuscript. Susan Waisbren helped plan the study and collect and interpret data as well as revising the manuscript.

DATA AVAILABILITY STATEMENT

The de-identified individual participant data that underlie the results reported in this article (including text, tables, figures, and appendices)

will be made available together with the research protocol and data dictionaries, for non-commercial, academic purposes. Additional supporting documents may be available on request. Investigators will be able to request access to these data and supporting documents via a data sharing portal (www.BioMarin.com/patients/publication-data-request/) beginning 6 months and ending 2 years after publication. Data associated with any ongoing development program will be made available within six (6) months after approval of the relevant product. Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology. Research proposals will be evaluated relative to publicly available criteria available at www.BioMarin.com/data-request-form to determine if access will be given, contingent on execution of a data access agreement with BioMarin Pharmaceutical Inc.

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REFERENCES

Adler, L. A., Goodman, D. W., Kollins, S. H., Weisler, R. H., Krishnan, S., Zhang, Y., & Biederman, J. (2008). Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry*, *69*(9), 1364–1373. https://doi.org/10.4088/jcp.v69n0903

Albrecht, J., Garbade, S. F., & Burgard, P. (2009). Neuropsychological speed tests and blood phenylalanine levels in patients with phenylketonuria: A meta-analysis. *Neuroscience and Biobehavioral Reviews*, *33*(3), 414–421. https://doi.org/10.1016/j.neubiorev.2008.11.00

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Association Publishing. https://doi.org/10.1176/appi.books.9780890425596

Anderson, P. J., Wood, S. J., Francis, D. E., Coleman, L., Anderson, V., & Boneh, A. (2007). Are neuropsychological impairments in children with early-treated phenylketonuria (PKU) related to white matter abnormalities or elevated phenylalanine levels? *Developmental Neuropsychology*, *32*(2), 645–668. https://doi.org/10.1080/87565640701375963

Ashe, K., Kelso, W., Farrand, S., Panetta, J., Fazio, T., De Jong, G., & Walterfang, M. (2019). Psychiatric and cognitive aspects of phenylketonuria: The limitations of diet and promise of new treatments. *Frontiers in Psychiatry*, *10*, 1–20. https://doi.org/10.3389/fpsyt.2019.00561

Berry, S. A., Brown, C., Grant, M., Greene, C. L., Jurecki, E., Koch, J., Moseley, K., Suter, R., van Calcar, S. C., Wiles, J., & Cederbaum, S. (2013). Newborn screening 50 years later: Access issues faced by adults with PKU. *Genetics in Medicine*, *15*(8), 591–599. https://doi.org/10.1038/gim.2013.10

Bik-Multanowski, M., Pietrzyk, J. J., & Mozrzymas, R. (2011). Routine use of CANTAB system for detection of neuropsychological deficits in patients with PKU. *Molecular Genetics and Metabolism*, *102*(2), 210–213. https://doi.org/10.1016/j.ymgme.2010.10.003

Bilder, D. A., Kobori, J. A., Cohen-Pfeffer, J. L., Johnson, E. M., Jurecki, E. R., & Grant, M. L. (2017). Neuropsychiatric comorbidities in adults with phenylketonuria: A retrospective cohort study. *Molecular Genetics and Metabolism*, *121*(1), 1–8. https://doi.org/10.1016/j.ymgme.2017.03.002

Bilder, D. A., Noel, J. K., Baker, E. R., Irish, W., Chen, Y., Merilainen, M. J., Prasad, S., & Winslow, B. J. (2016). Systematic review and meta-analysis of neuropsychiatric symptoms and executive functioning in adults with phenylketonuria. *Developmental Neuropsychology*, *41*(4), 245–260. https://doi.org/10.1080/87565641.2016.1243109

Brown, C. S., & Lichter-Konecki, U. (2016). Phenylketonuria (PKU): A problem solved? *Molecular Genetics and Metabolism Reports*, *6*, 8–12. https://doi.org/10.1016/j.ymgmr.2015.12.004

Burgess, N. M., Kelso, W., Malpas, C. B., Winton-Brown, T., Fazio, T., Panetta, J., De Jong, G., Neath, J., Atherton, S., Velakoulis, D., & Walterfang, M. (2021). The effect of improved dietary control on cognitive and psychiatric functioning in adults with PKU: The ReDAPT study. *Orphanet Journal of Rare Diseases*, *16*, 35. https://doi.org/10.1186/s13023-020-01668-2

Burton, B., Grant, M., Feigenbaum, A., Singh, R., Hendren, R., Siriwardena, K., Phillips, J., Sanchez-Valle, A., Waisbren, S., Gillis, J., Prasad, S., Merilainen, M., Lang, W., Zhang, C., Yu, S., & Stahl, S. (2015). A randomized, placebo-controlled, double-blind study of sapropterin to treat ADHD symptoms and executive function impairment in children and adults with sapropterin-responsive phenylketonuria. *Molecular Genetics and Metabolism*, *114*(3), 415–424. https://doi.org/10.1016/j.ymgme.2014.11.011

Finkelson, L., Bailey, I., & Waisbren, S. E. (2001). PKU adults and their return to diet: Predicting diet continuation and maintenance. *Journal of Inherited Metabolic Diseases*, *24*(4), 515–516. https://doi.org/10.1023/a:1010546000617

Gassió, R., Campistol, J., Vilaseca, M. A., Lambruschini, N., Cambra, F. J., & Fusté, E. (2003). Do adult patients with phenylketonuria improve their quality of life after introduction/resumption of a phenylalanine-restricted diet? *Acta Paediatrica*, *92*(12), 1474–1478.

Gibbins, C., Weiss, M. D., Goodman, D. W., Hodgkins, P. S., Landgraf, J. M., & Faraone, S. V. (2010). ADHD-hyperactive/impulsive subtype in adults. *Mental Illness*, *2*(1), e9. https://doi.org/10.4081/mi.2010.e9

Goodman, D., Faraone, S. V., Adler, L. A., Dirks, B., Hamdani, M., & Weisler, R. (2010). Interpreting ADHD rating scale scores: Linking ADHD rating scale scores and CGI levels in two randomized controlled trials of lisdexamfetamine dimesylate in ADHD. *Primary Psychiatry*, *17*(3), 44–52.

Harding, C. O., Amato, R. S., Stuy, M., Longo, N., Burton, B. K., Posner, J., Weng, H. H., Merilainen, M., Gu, Z., Jiang, J., & Vockley, J. (2018). Pegvaliase for the treatment of phenylketonuria: A pivotal, double-blind randomized discontinuation phase 3 clinical trial. *Molecular Genetics and Metabolism*, *124*(1), 20–26. https://doi.org/10.1016/j.ymgme.2018.03.003

Mainka, T., Fisher, J.-F., Huebl, J., Jung, A., Lier, D., Mosejova, A., Skorvanek, M., de Koning, T. J., Kuhn, A. A., Fresisinger, P., Zaigaki, A., & Ganos, C. (2021). The neurological and neurophychiatric spectrum of adults with late-treated phenylketonuria. *Parkinsonism & Related Disorders*, *89*, 167–175. https://doi.org/10.1016/j.parkreldis.2021.06.011

McCambridge, J., Witton, J., & Elbourne, D. R. (2014). Systematic review of the Hawthorne effect: New concepts are needed to study research participation effects. *Journal of Clinical Epidemiology*, *67*(3), 267–277. https://doi.org/10.1016/j.jclinepi.2013.08.015

Moyle, J. J., Fox, A. M., Arthur, M., Bynevelt, M., & Burnett, J. R. (2007). Meta-analysis of neuropsychological symptoms of adolescents and adults with PKU. *Neuropsychology Review*, *17*(2), 91–101. https://doi.org/10.1007/s11065-007-9021-2

Moyle, J. J., Fox, A. M., Bynevelt, M., Arthur, M., & Burnett, J. R. (2007). A neuropsychological profile of off-diet adults with phenylketonuria. *Journal of Clinical and Experimental Neuropsychology*, *29*(4), 436–441. https://doi.org/10.1080/13803390600745829

Palermo, L., Geberhiwot, T., MacDonald, A., Limback, E., Hall, S. K., & Romani, C. (2017). Cognitive outcomes in early-treated adults with phenylketonuria (PKU): A comprehensive picture across domains. *Neuropsychology*, *31*(3), 255–267. https://doi.org/10.1037/neu0000337

Pietz, J., Fätkenheuer, B., Burgard, P., Armbruster, M., Esser, G., & Schmidt, H. (1997). Psychiatric disorders in adult patients with early-

treated phenylketonuria. *Pediatrics*, *99*(3), 345–350. https://doi.org/10.1542/peds.99.3.345

Pilotto, A., Zipser, C. M., Leks, E., Haas, D., Gramer, G., Freisinger, P., Schaeffer, E., Liepelt-Scarfone, I., Brockmann, K., Maetzler, W., Schulte, C., Deuschle, C., Hauser, A. K., Hoffmann, G. F., Scheffler, K., van Spronsen, F. J., Padovani, A., Trefz, F., & Berg, D. (2021). Phenylalanine effects on brain function in adult phenylketonuria. *Neurology*, *96*(3), e399–e411. https://doi.org/10.1212/WNL.0000000000011088

Ris, M. D., Weber, A. M., Hunt, M. M., Berry, H. K., Williams, S. E., & Leslie, N. (1997). Adult psychosocial outcome in early-treated phenylketonuria. *Journal of Inherited Metabolic Disease*, *20*(4), 499–508. https://doi.org/10.1023/a:1005389110739

Rohr, F., Wessel, A., Brown, M., Charette, K., & Levy, H. L. (2015). Adherence to tetrahydrobiopterin therapy in patients with phenylketonuria. *Molecular Genetics and Metabolism*, *114*(1), 25–28. https://doi.org/10.1016/j.ymgme.2014.10.013

Rösler, M., Retz, W., & Stieglitz, R. D. (2010). Psychopathological rating scales as efficacy parameters in adult ADHD treatment investigations - benchmarking instruments for international multicentre trials. *Pharmacopsychiatry*, *43*(3), 92–98. https://doi.org/10.1055/s-0029-1242819

Schmidt, E., Rupp, A., Burgard, P., Pietz, J., Weglage, J., & de Sonneville, L. (1994). Sustained attention in adult phenylketonuria: The influence of the concurrent phenylalanine-blood-level. *Journal of Clinical and Experimental Neuropsychology*, *16*(5), 681–688. https://doi.org/10.1080/01688639408402681

Schuett, V. E., Brown, E. S., & Michals, K. (1985). Reinstitution of diet therapy in PKU patients from twenty-two US clinics. *American Journal of Public Health*, *75*(1), 39–42. https://doi.org/10.2105/ajph.75.1.39

ten Hoedt, A. E., de Sonneville, L. M., Francois, B., ter Horst, N. M., Janssen, M. C., Rubio-Gozalbo, M. E., Wijburg, F. A., Hollak, C. E., & Bosch, A. M. (2011). High phenylalanine levels directly affect mood and sustained attention in adults with phenylketonuria: A randomised, double-blind, placebo-controlled, crossover trial. *Journal of Inherited Metabolic Disease*, *34*(1), 165–171. https://doi.org/10.1007/s10545-010-9253-9

Thomas, J., Levy, H., Amato, S., Vockley, J., Zori, R., Dimmock, D., Harding, C. O., Bilder, D. A., Weng, H. H., Olbertz, J., Merilainen, M., Jiang, J., Larimore, K., Gupta, S., Gu, Z., & Northrup, H. (2018). Pegvaliase for the treatment of phenylketonuria: Results of a long-term phase 3 clinical trial program (PRISM). *Molecular Genetics and Metabolism*, *124*(1), 27–38. https://doi.org/10.1016/j.ymgme.2018.03.006

van Spronsen, F. J., Blau, N., Harding, C., Burlina, A., Longo, N., & Bosch, A. M. (2021). Phenylketonuria. *Nature Reviews Disease Primers*, *7*(1), 36. https://doi.org/10.1038/s41572-021-00267-0

van Wegberg, A., MacDonald, A., Ahring, K., Bélanger-Quintana, A., Blau, N., Bosch, A. M., Burlina, A., Campistol, J., Feillet, F., Giżewska, M., Huijbregts, S. C., Kearney, S., Leuzzi, V., Maillot, F., Muntau, A. C., van Rijn, M., Trefz, F., Walter, J. H., & van Spronsen, F. J. (2017). The complete European guidelines on phenylketonuria: Diagnosis and treatment. *Orphanet Journal of Rare Diseases*, *12*(1), 162. https://doi.org/10.1186/s13023-017-0685-2

Vockley, J., Andersson, H. C., Antshel, K. M., Braverman, N. E., Burton, B. K., Frazier, D. M., Mitchell, J., Smith, W. E., Thompson, B. H., & Berry, S. A. (2014). Phenylalanine hydroxylase deficiency: Diagnosis and management guideline. *Genetics in Medicine*, *16*(2), 188–200. https://doi.org/10.1038/gim.2013.157

Weglage, J., Fromm, J., van Teeffelen-Heithoff, A., Moller, H. E., Koletzko, B., Marquardt, T., Rutch, F., & Feldman, R. (2013). Neurocognitive functioning in adults with phenylketonuria: Results of a long term study. *Molecular Genetics and Metabolism*, *110*, S44–S48. https://doi.org/10.1016/j.ymgme.2013.08.013

Wyrwich, K. W., Auguste, P., Yu, R., Zhang, C., Dewees, B., Winslow, B., Yu, S., Merilainen, M., & Prasad, S. (2015). Evaluation of neuropsychiatric function in phenylketonuria: Psychometric properties of the ADHD rating scale-IV and adult ADHD self-report scale inattention subscale in phenylketonuria. *Value in Health*, *18*(4), 404–412. https://doi.org/10.1016/j.jval.2015.01.008

SUPPORTING INFORMATION

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