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 ☆

B. Burton [a,*,1], M. Grant [b,1], A. Feigenbaum [c], R. Singh [d], R. Hendren [e], K. Siriwardena [b], J. Phillips III [f], A. Sanchez-Valle [g], S. Waisbren [h], J. Gillis [i], S. Prasad [j], M. Merilainen [j], W. Lang [j], C. Zhang [j], S. Yu [j], S. Stahl [k]

[a] The Ann and Robert H. Lurie Children's Hospital and the Northwestern University Feinberg School of Medicine, Chicago, IL, USA
[b] Drexel University College of Medicine, Philadelphia, PA, USA
[c] The Hospital for Sick Children and University of Toronto, ON, Canada
[d] Emory University School of Medicine, Decatur, GA, USA
[e] University of California, San Francisco, San Francisco, CA, USA
[f] Vanderbilt University School of Medicine, Nashville, TN, USA
[g] University of South Florida and Tampa General Hospital, Tampa, FL, USA
[h] Boston Children's Hospital, Boston, MA, USA
[i] IWK Health Centre Maritime Medical Genetics Services, Halifax, NS, Canada
[j] BioMarin Pharmaceutical Inc., Novato, CA, USA
[k] University of California, San Diego School of Medicine, San Diego, CA, USA

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ABSTRACT

Symptoms of attention deficit–hyperactivity disorder (ADHD), particularly inattention, and impairments in executive functioning have been reported in early and continuously treated children, adolescents, and adults with phenylketonuria (PKU). In addition, higher blood phenylalanine (Phe) levels have been correlated with the presence of ADHD symptoms and executive functioning impairment. The placebo-controlled PKU ASCEND study evaluated the effects of sapropterin therapy on PKU-associated symptoms of ADHD and executive and global functioning in individuals who had a therapeutic blood Phe response to sapropterin therapy. The presence of ADHD inattentive symptoms and executive functioning deficits was confirmed in this large cohort of 206 children and adults with PKU, of whom 118 responded to sapropterin therapy. In the 38 individuals with sapropterin-responsive PKU and ADHD symptoms at baseline, sapropterin therapy resulted in a significant improvement in ADHD inattentive symptoms in the first 4 weeks of treatment, and improvements were maintained throughout the 26 weeks of treatment. Sapropterin was well-tolerated with a favorable safety profile. The improvements in ADHD inattentive symptoms and aspects of executive functioning in response to sapropterin therapy noted in a large cohort of individuals with PKU indicate that these symptoms are potentially reversible when blood Phe levels are reduced.

1 . Introduction

In phenylketonuria (PKU), impaired phenylalanine (Phe) breakdown due to deficient phenylalanine hydroxylase (PAH) activity in the liver leads to toxic Phe accumulation in many tissues but is especially detrimental to the brain [1]. Prolonged exposure to elevated Phe levels in the blood results in severe intellectual disability in the majority of untreated individuals [2,3]. With the advent of newborn screening for early detection of PKU and strict dietary restrictions to limit Phe intake (i.e. dietary treatment), severe intellectual disability can be prevented in individuals with PKU [4–6]. The recently published American College of Medical Genetics and Genomics guidelines recommend maintaining blood Phe in the range of 120–360 μmol/L for life [7].

Early and continuous adherence to a Phe-restricted diet is associated with average intellectual abilities. However, a growing body of evidence indicates that neurocognitive and psychosocial outcomes in individuals with PKU are suboptimal [8–10]. Symptoms of attention deficit–hyperactivity disorder (ADHD), particularly inattention, and impairments in executive functioning have been widely reported in early and continuously treated children and adolescents with PKU [8,11–17]. In empirical

studies, higher blood Phe levels have been correlated with ADHD symptoms [12] and executive functioning impairment [13]. While less data are available for continuously treated adults with PKU, those who discontinue treatment have lower intellectual ability and achievement test scores than those who continue to maintain metabolic control [18]. These findings, in aggregate, suggest the possibility that ADHD symptoms and impaired executive functioning may be caused by potentially reversible brain dysfunction that results from disruption in monoamine synthesis by high blood Phe levels rather than irreversible 'toxic' brain damage from high blood Phe levels during early life. In addition, neuroimaging studies have identified white matter abnormalities in both untreated and early treated individuals with PKU, and research has shown this white matter pathology is both associated with dietary Phe control and reversible with adherence to a strict low-Phe diet [19]. Thus, lowering blood Phe levels may ameliorate problems with inattention and executive function in individuals with PKU.

Sapropterin dihydrochloride (KUVAN®, BioMarin Pharmaceutical Inc., Novato, CA) reduces blood Phe levels in individuals with tetrahydrobiopterin (BH$_4$)-responsive PKU. Improvements in neuropsychiatric symptoms, including mood and ability to concentrate, have been reported anecdotally in individuals treated with sapropterin. Sapropterin is an orally active, synthetic version of the 6R-isomer of BH$_4$, a naturally occurring cofactor of PAH that increases the activity of the residual PAH enzyme to metabolize Phe into tyrosine. Clinical studies have demonstrated the efficacy of sapropterin in reducing blood Phe levels in individuals with PKU [20–24]. The proportion of individuals with PKU who responded to sapropterin therapy in clinical studies (defined in those studies as ≥30% reduction in blood Phe level) ranged from 20% to 56% [20,24].

There is a need for clinical outcomes data on ADHD symptoms and executive functioning in PKU. In their two-part neuropsychiatric perspective on PKU, Bone et al. [10] and Angelino et al. [25] call for consistent and integrated mental health screening and treatment to manage these and other neuropsychiatric sequelae in individuals with PKU. The PKU ASCEND study, the largest controlled clinical outcomes study to date in PKU, was conducted to evaluate the therapeutic effects of sapropterin versus placebo on PKU-associated symptoms of ADHD and executive and global functioning in individuals who had a therapeutic blood Phe response to sapropterin therapy.

2. Materials and methods

2.1. Patient selection

The PKU ASCEND study enrolled adults and children ≥ 8 years old with PKU who were willing to continue their current diet during the study period and comply with all study procedures. Individuals were excluded if they had known hypersensitivity to sapropterin or its excipients; had taken sapropterin within 16 weeks of randomization; or had initiated or adjusted medication for treatment of ADHD, depression, or anxiety ≤8 weeks prior to randomization. Individuals who were breastfeeding, pregnant or planning to become pregnant (subject or partner) during the study were also excluded.

PKU ASCEND was conducted in compliance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the ethical principles for research on human subjects in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board (IRB), Ethics Committee (EC), or Research Ethics Board (REB) of each participating institution or a central IRB. Written informed consent was obtained from each subject or the subject's parent or legal guardian prior to study enrollment.

2.2. Study design

PKU ASCEND was a double-blind, placebo-controlled, parallel-arm study, in which subjects were randomized 1:1 by interactive response technology to receive treatment with either sapropterin or placebo for 13 weeks. At Week 13, placebo subjects were crossed over to sapropterin therapy for an open-label treatment period that continued until Week 26. To ensure a balance of ages, baseline ADHD symptoms, and ADHD medication use between treatment groups, subjects were stratified by age < 18 or ≥18 years old, the presence or absence of ADHD symptoms, and ADHD medication use. The presence of ADHD symptoms at baseline was defined as a response of "Often" or "Very Often" on ≥5 of the 9 questions on either the inattentive or hyperactivity/impulsivity domains of the ADHD RS or the ADHD ASRS (described in detail below).

The study was designed to evaluate the therapeutic effects of sapropterin on ADHD symptoms and global function in subjects who had a therapeutic Phe response to sapropterin (i.e. the responder population) compared with placebo-treated subjects. Therapeutic Phe response was defined in this study as a mean reduction of ≥20% in blood Phe levels following sapropterin treatment. This was calculated as the difference between the mean of the baseline and screening values and the mean of the three lowest blood Phe levels during the first four weeks after starting sapropterin treatment.

We report here the baseline ADHD symptoms and measurements of executive function, the Clinical Global Impression of Improvement at Week 13 in sapropterin Phe responders, and the changes in ADHD symptoms and executive function between baseline and Week 13 in sapropterin Phe responders with ADHD symptoms at baseline. We also report the status of ADHD symptoms following the open-label treatment phase (Weeks 13 to 26) for all sapropterin Phe responsive individuals.

2.3. Efficacy endpoints

The primary efficacy endpoint for symptoms was the change seen in the Total Score on the ADHD Rating Scale (RS), [26] completed by parents of child/adolescent participants, or adult ADHD Self-Report Scale (ASRS) [27] in sapropterin Phe responders with ADHD symptoms after 13 weeks of treatment. The primary efficacy endpoint for global function was the proportion of subjects with Clinical Global Impression of Improvement (CGI-I) scale [28] rating of 1 (very much improved) or 2 (much improved) at Week 13 in the sapropterin responder cohort. ADHD RS/ASRS and Clinical Global Impression of Severity (CGI-S) were done at screening and Weeks 4, 8, 13, and 26; CGI-I assessments were done at Weeks 4, 8, 13, and 26. Secondary endpoints included the Global Executive Composite and Index scores from the Behavior Rating Inventory of Executive Function (BRIEF) [29] completed by parents of child participants and the adult self-reported BRIEF completed by adult participants at baseline and Weeks 13 and 26 (Week 26 data are not reported here).

The ADHD RS reflects parent ratings of ADHD symptoms for subjects 8–17 years of age [26]. The ADHD ASRS, an adapted version of the ADHD RS designed for adults to self-rate their ADHD symptoms, [27] was completed by subjects ≥ 18 years of age. Both the ADHD RS and ADHD ASRS are composed of two 9-question subscales rating frequency of Inattention and Hyperactivity/Impulsivity separately; the two subscale scores are combined to generate a Total Score based on all 18 questions. The ADHD RS uses a 4-point Likert scale with a maximum possible Total Score of 54 and maximum possible subscale score of 27; the ADHD ASRS uses a 5-point Likert scale with a maximum possible Total Score of 72. A correction factor/multiplier of 0.75 was applied to the ASRS score to enable the ADHD RS and ASRS scores to be numerically combined for analysis. Although a numeric threshold for the presence of ADHD has not yet been defined, in pediatric ADHD medication trials, an ADHD RS Total Score > 18 is considered symptomatic and a score ≤ 18 considered to reflect symptom remission [30]. For adults, the World Health Organization (WHO)/Workgroup on Adult ADHD has identified an ADHD ASRS Total Score ≥ 24 as suggesting a high likelihood of ADHD and a score of 17–23 as suggesting likely ADHD [31]. While the ADHD RS and ASRS assessments are derived directly from

the diagnostic criteria for ADHD as delineated in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*), these assessments alone are not diagnostic for ADHD. A diagnosis of ADHD is made using the full DSM-IV criteria, which include, among other things, consideration of the patient's age and clinical situation.

The parent-rated BRIEF is a rating scale designed for parents to evaluate 8 domains of executive functioning in children and adolescents [29]. The adult self-reported BRIEF includes one additional domain for task monitoring [32]. The Global Executive Composite (GEC) score represents the total score from all 8 (or 9 for adults) domains. The domains are grouped into two indices: the Behavior Regulation Index (BRI), which includes the inhibition, shift, and emotional control domains, and the Metacognition Index (MI), which includes the initiation, working memory, planning/organizing, organizing materials, and monitoring domains. To score a BRIEF assessment, the raw scores from each domain are totaled and used to generate the BRI, MI, and overall GEC scores. Scores for each domain, index, and the overall GEC are compared to normative tables that provide T-scores, percentiles, and 90% confidence intervals (CI) by age and gender. Standard T-scores have a mean of 50 points and a standard deviation (SD) of 10 points. T-scores are used to interpret the level of executive functioning and provide information about individual scores relative to scores of respondents in the normative sample. Although higher T-scores indicate greater degrees of executive dysfunction, there are no absolute cut-off scores at which a behavior or characteristic is considered problematic [33]. T-scores > 65 are typically considered clinically significant, but T-scores > 60 on BRIEF self-reports may also warrant clinical interpretation [34].

2.4. Safety evaluation

Data collected for safety evaluation included adverse events (AEs), clinical laboratory assessments (blood chemistry, hematology, urinalysis and other laboratory analytes), vital signs assessments, and physical examinations. Adverse events (AEs) were recorded at each visit and classified by severity (mild, moderate or severe) and likelihood of relationship to the study drug (not related, possibly related, or probably related).

2.5. Statistical analyses

Enrollment of 200 subjects (100 in each treatment group) was planned to obtain an approximate sample size of 50 sapropterin Phe responders (≥20% blood Phe level reduction) randomized to each treatment group at baseline. It was estimated that a total of 20 sapropterin Phe responders in each treatment group with symptoms of ADHD at baseline was needed to provide 80% power to detect projected differences between the sapropterin and placebo arms, assuming mean improvements in ADHD RS/ASRS score of 13 in sapropterin-treated subjects and 5 in placebo-treated subjects, a common standard deviation of 9, and a 2-sided Type I error rate of 0.05. A sample size of 50 sapropterin Phe responsive subjects in each treatment group was calculated to yield 80% power to detect a projected 30% difference between treatment groups at Week 13 in the proportion of subjects with a CGI-I scale rating of 1 or 2 (very much improved or much improved), assuming that 60% of subjects with a CGI-I scale rating of 1 or 2 were included in the sapropterin arm and 30% in the placebo arm.

The primary efficacy endpoint analysis of change in ADHD RS/ASRS Total Score from baseline to Week 13 compared the treatment effect between sapropterin-treated and placebo-treated subjects, with randomization stratification factors entered as covariates, in the sapropterin Phe responder population and in the subset of sapropterin Phe responders with ADHD symptoms at baseline. Treatment effect estimates in primary and secondary efficacy endpoints from baseline to Week 13 were generated by analysis of covariance (ANCOVA) using least squares (LS) mean with standard error (SE), 95% confidence intervals (CI), and

P value determined by *t*-test. Change from baseline was also analyzed with mixed-effect model repeated measure (MMRM) analysis using LS mean to impute for missing data and stratified Wilcoxon rank-sum test.

3. Results

3.1. Patient disposition and baseline characteristics

Of the 206 subjects enrolled at 36 clinical sites in the United States and Canada, 118 (57%) were sapropterin Phe responders based on achieving a mean reduction of ≥20% in blood Phe levels after sapropterin treatment (Fig. 1). Among the sapropterin Phe responders, 38/118 (32%) subjects had ADHD symptoms at baseline. Table 1 shows the baseline characteristics for the 118 sapropterin Phe responders and the 38 sapropterin Phe responders with ADHD symptoms. Mean age at enrollment was 20 years. Most subjects were white of non-Hispanic heritage, and slightly more subjects were male. On average, placebo subjects had slightly higher mean blood Phe at baseline than subjects randomized to sapropterin (790 vs 680 μmol/L), but this difference was not statistically significant. Among subjects with ADHD symptoms at baseline, 84% were not taking ADHD medication. A greater number of subjects were taking ADHD medication in the sapropterin responder population than in the subpopulation with ADHD symptoms at baseline, suggesting that the ADHD medication was effectively managing their symptoms at baseline.

3.2. Baseline ADHD and executive functioning status

Baseline scores on the ADHD RS/ASRS assessments are shown in Table 2. In the primary analysis population of sapropterin Phe responders who had ADHD symptoms at baseline, the baseline mean ADHD RS/ASRS Total Score was 31.2 in the placebo group and 28.9 in the sapropterin group, with a mean Inattention Subscale Score of 19.2 for placebo and 18.0 for sapropterin, and a mean Hyperactivity/Impulsivity Subscale Score of 12.0 for placebo and 10.9 for sapropterin.

Baseline BRIEF assessment scores for the overall Global Executive Composite (GEC), the Metacognition Index (MI), and the Behavior Regulation Index (BRI) are shown in Table 3. On the parent-reported BRIEF, mean T-scores for GEC and MI were elevated and greater than one SD above the normative mean. Mean T-scores for parent-reported BRI were slightly elevated (within 1 SD of the normative mean). With the exception of the placebo group MI at baseline, mean T-scores for GEC, BRI, and MI on the adult self-reported BRIEF were only slightly elevated and within one SD of the normative mean.

3.3. Efficacy evaluation

The mean blood Phe level in the sapropterin group dropped within the first 4 weeks of treatment and remained lower through Week 26 (Fig. 2). In the placebo group, the mean Phe level remained higher than the sapropterin-treated group through Week 13 (i.e. the randomized treatment period) and also declined during the 4 weeks after initiating sapropterin treatment in the open-label treatment phase (Fig. 2).

The primary endpoint of change in ADHD RS/ASRS Total Score in sapropterin Phe responders with ADHD symptoms did not differ statistically between the sapropterin and placebo groups from baseline to Week 13, though there was an additional decline of −4.2 points (P = 0.085) in the sapropterin group (Table 2). The Inattention Subscale Score was statistically different between the groups at Week 13, reflecting a significant reduction of −3.4 points (P = 0.036) for sapropterin treatment compared with placebo (Table 2). The decline in Hyperactivity/Impulsivity Subscale Scores from baseline to Week 13 did not differ statistically between the sapropterin and placebo groups (Table 2).
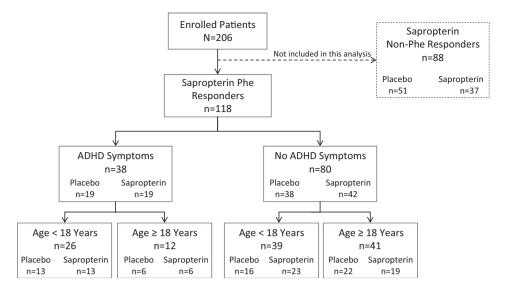
Fig. 1. Study flow diagram with subject disposition.

For the primary endpoint of CGI-I in sapropterin Phe responders (n = 117), the proportion of subjects rated by clinicians as 1 (very much improved) or 2 (much improved) at Week 13 was similar in the placebo (26.3%) and sapropterin (21.7%) arms (relative risk ratio 0.87 [95% CI: 0.46 to 1.64], P = 0.670).

The protocol-specified analyses by age subgroup (Fig. 3) showed improvement in the estimated treatment effects for the ADHD RS Total score (-6.2, P = 0.034) and the Inattention Subscale Score (-4.7, P = 0.030) in the <18 year old sapropterin-treated subjects with ADHD symptoms (n = 13) compared with the placebo group (n = 13). Among the very small subsample of adult sapropterin Phe responders with ADHD symptoms, there was a drop in scores for both treatment groups on ADHD ASRS Total, Inattention Subscale, and Hyperactivity/Impulsivity Subscale scores but no significant difference in level of improvement between the sapropterin (n = 6) and placebo (n = 6) groups from baseline to Week 13 (Fig. 3).

Fig. 4 shows the MMRM analysis of change over time in ADHD RS/ASRS Total and Inattention Subscale Scores in the sapropterin Phe responders with ADHD symptoms for both the randomized trial period (baseline to Week 13) and the open-label treatment period (Week 13 to Week 26). The Total Scores in the sapropterin-treated subjects (n = 19) declined significantly relative to the placebo group (n = 19) from baseline to Week 4 (-5.0, P = 0.032) and this reduction remained stable over time and was maintained through the end of the study (Week 26). The Inattention Subscale Scores in the sapropterin group (n = 19) also declined significantly relative to placebo (n = 19) from baseline to Week 4 (-3.6, P = 0.016) and Week 13 (-3.6 P = 0.027) and symptom reduction was maintained through Week 26. After transitioning to the open-label treatment phase of the study at Week 13 and initiating treatment with sapropterin, the mean Total Score and Inattention Subscale Score in the initial placebo-treated group (n = 19) also declined significantly and, at Week 26, their scores were comparable to the original sapropterin-treated group (Fig. 4).

Mean changes in BRIEF T-scores from Baseline to Week 13 are shown Table 3. On the parent-rated BRIEF assessment (all sapropterin Phe responders < 18 years old), the mean GEC T-score decreased by -4.1 (P = 0.034) among sapropterin-treated subjects compared with placebo subjects. Compared to the placebo group, the sapropterin treatment group also had a mean decrease of -4.4 in the MI T-score (P = 0.038) and a mean drop of -3.4 in the BRI T-score (P = 0.053). On the adult self-reported BRIEF (all sapropterin Phe responders ≥ 18 years old), changes in GEC, MI, or BRI T-scores from baseline to Week 13 did not differ significantly between the sapropterin and placebo groups.

Table 1
Baseline patient characteristics.

Characteristic	Sapropterin Phe responders n = 118		Sapropterin Phe responders with ADHD symptoms n = 38	
	Placebo n = 57	Sapropterin n = 61	Placebo n = 19	Sapropterin n = 19
Age (years) at enrollment, mean (SD)	20.2 (10.1)	19.6 (10.1)	19.0 (11.2)	19.5 (12.7)
<18 years	29 (50.9)	36 (59.0)	13 (68.4)	13 (68.4)
≥18 years	28 (49.1)	25 (41.0)	6 (31.6)	6 (31.6)
Sex, n (%)				
Female	26 (46)	23 (38)	9 (47)	6 (32)
Male	31 (54)	38 (62)	10 (53)	13 (68)
Race, n (%)				
White	56 (98)	60 (98)	19 (100)	19 (100)
Asian	1 (2)	1 (2)	0 (0)	0 (0)
Ethnicity, n (%)				
Hispanic or Latino	2 (4)	4 (7)	0 (0)	2 (11)
Not Hispanic or Latino	55 (96)	57 (93)	19 (100)	17 (89)
Blood Phe concentration (μmol/L), mean (SD)	789.5 (465.0)	680.2 (435.4)	709.1 (477.3)	687.9 (521.9)
ADHD symptoms, n (%)	19 (33)	19 (31)	19 (100)	19 (100)
ADHD medication, n (%)	7 (12)	5 (8)	4 (21)	2 (11)

No statistically significant differences between treatment groups in any of the populations presented.

Table 2

ADHD RS/ASRS Scores at baseline and Week 13.

	All sapropterin Phe responders n = 118		Sapropterin Phe responders with ADHD symptoms n = 38	
	Placebo n = 57	Sapropterin n = 61	Placebo n = 19	Sapropterin n = 19
ADHD RS/ASRS Total Score				
Baseline	23.7 (1.3) (0.0 , 49.5)*	21.5 (1.4) (2.0, 38.0)*	31.2 (2.2) (15.0 , 49.5)*	28.9 (2.4) (14.0 , 38.0)*
Change from baseline to Week 13	−1.9 (1.1) (−4.0, 0.2)	−3.7 (1.1) (−5.9,−1.6)	−4.9 (2.0) (−8.9,−0.9)	−9.1 (2.2) (−13.5,−4.7)
Change difference from placebo	–	−1.8 (1.1) (−4.0, 0.4) P = 0.102	–	−4.2 (2.3) (−8.9, 0.6) P = 0.085
ADHD RS/ASRS Inattention Subscale Score				
Baseline	14.6 (0.7) (0.0 , 26.3)*	13.0 (0.8) (0.0 , 26.0)*	19.2 (1.2) (14.0 , 26.3)*	18.0 (1.3) (9.0 , 26.0)*
Change from baseline to Week 13	−1.2 (0.7) (−2.5, 0.0)	−2.6 (0.7) (−3.9,−1.2)	−2.5 (1.3) (−5.2, 0.1)	−5.9 (1.4) (−8.9,−3.0)
Change difference from placebo	–	−1.3 (0.7) (−2.7, 0.0) P = 0.058	–	−3.4 (1.6) (−6.6,−0.2) P = 0.036
ADHD RS/ASRS Hyperactivity/Impulsivity Subscale Score				
Baseline	9.1 (0.9) (0.0 , 23.3)*	8.5 (0.9) (0.0 , 18.8)*	12.0 (1.8) (1.0 , 23.3)*	10.9 (2.0) (0.0 , 18.8)*
Change from baseline to Week 13	−0.3 (0.6) (−1.5, 0.8)	−1.0 (0.6) (−2.2, 0.2)	−2.3 (1.0) (−4.3,−0.3)	−3.3 (1.1) (−5.6,−1.1)
Change difference from placebo	–	−0.7 (0.6) (−1.9, 0.5) P = 0.269	–	−1.0 (1.2) (−3.4, 1.4) P = 0.396

Data are LS mean (SE) (95% CI) from analysis of covariance (ANCOVA). ADHD RS/ASRS = Attention Deficit-Hyperactivity Disorder Rating Scale/Adult Self-Report Scale. LS Mean = least squares mean. SE = standard error. *Min, max scores at baseline.

3.4. Safety evaluation

Table 4 shows non-serious adverse events occurring in ≥5% of subjects in either treatment group during both the randomized trial (baseline to Week 13) and the open-label treatment period (Weeks 13 to 26). Most adverse events (95%) were mild or moderate. The one adverse event that led to withdrawal from the study was heart rate increase classified as possibly or probably drug-related in a subject taking sapropterin. Three serious adverse events (increased amino acid level, concussion, and necrotizing fascitis) occurred during the randomized trial, all were in the placebo group and none were considered by the investigator to be drug-related. Two additional serious adverse events (animal bite and petit mal epilepsy) occurred during the open-label treatment period in placebo subjects who had switched to sapropterin. The petit mal epilepsy in a subject with a history of seizures was considered by the investigator to be possibly or probably drug-related. None of the serious adverse events led to subjects discontinuing the study drug.

4 . Discussion

Our results confirmed the presence of ADHD inattentive symptoms and executive functioning deficits, as reported in previous studies, in a subset of this large cohort of children and adults with PKU. In individuals with PKU and ADHD symptoms, sapropterin treatment was associated with a significant improvement in ADHD inattentive symptoms. Improvements in ADHD inattentive subtype symptoms occurred in the first 4 weeks of sapropterin treatment, and these improvements

were maintained through 26 weeks of treatment (Fig. 4). As in prior studies of sapropterin in PKU, sapropterin was well-tolerated and had a favorable safety profile [21,23,24,35].

4.1. ADHD inattentive subtype

Our finding of primarily ADHD inattentive symptoms in approximately one third of this cohort of 118 individuals with PKU is consistent with the findings of a smaller empirical study by Antshel et al. of 46 children aged 8 to 14 years with PKU and 18 control children [12]. They found that the mean number of ADHD inattentive symptoms on the ADHD RS was higher in children with PKU than control children (5.7 vs 1.3, P < 0.001) and higher than the mean number of hyperactivity/impulsivity symptoms (1.1). Antshel et al. also documented a significant correlation between higher blood Phe levels and the presence of ADHD symptoms. Similarly, we observed a concomitant decline in mean blood Phe levels (Fig. 2) and mean ADHD scores (Fig. 3) from baseline to Week 13 in sapropterin-treated individuals that was not seen in placebo-treated individuals. Furthermore, after placebo-treated subjects switched to sapropterin at Week 13, mean blood Phe level and ADHD scores in that arm declined by Week 26.
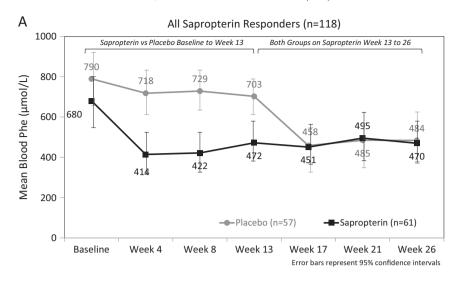
The clinical relevance of change in ADHD RS/ASRS Total and Subscale Scores has been documented in placebo-controlled studies evaluating medications for treatment of ADHD in non-PKU populations. In some of those ADHD studies, inclusion criteria included minimum Total Score of 24 to 26 and the range of baseline mean Total Scores of 36 to 45 were higher than scores among individuals with ADHD symptoms

Table 3

T-scores from BRIEF assessments at baseline and Week 13 for sapropterin Phe responders.

	BRIEF parent report (Subjects <18 years old)		BRIEF adult self-report (Subjects ≥18 years old)	
	Placebo n = 29	Sapropterin n = 36	Placebo n = 28	Sapropterin n = 25
Global Executive Composite (GEC)				
Baseline	63.7 (2.0)	63.9 (1.9)	59.2 (3.1)	55.4 (3.8)
Change from baseline to Week 13	−0.7 (1.7) (−4.0, 2.7)	−4.8 (1.6) (−8.0,−1.6)	−8.1 (2.2) (−12.6,−3.6)	−9.1 (2.7) (−14.6,−3.5)
Change difference from placebo	–	−4.1 (1.9) (−7.9,−0.3) P = 0.034	–	−1.0 (2.2) (−5.5, 3.6) P = 0.661
Metacognition Index (MI)				
Baseline	66.6 (2.0)	64.9 (1.9)	60.2 (3.3)	54.2 (4.0)
Change from baseline to Week 13	0.3 (1.9) (−3.4, 4.0)	−4.1 (1.7) (−7.5,−0.6)	−7.3 (2.3) (−11.9,−2.8)	−7.9 (2.8) (−13.5,−2.2)
Change difference from placebo	–	−4.4 (2.1) (−8.5,−0.2) P = 0.038	–	−0.5 (2.3) (−5.3, 4.2) P = 0.824
Behavior Regulation Index (BRI)				
Baseline	56.9 (2.6)	59.6 (2.5)	56.3 (2.9)	56.3 (3.6)
Change from baseline to Week 13	−0.9 (1.5) (−3.8, 2.1)	−4.3 (1.4) (−7.1,−1.4)	−7.2 (2.0) (−11.3,−3.1)	−8.9 (2.5) (−14.0,−3.9)
Change difference from placebo	–	−3.4 (1.7) (−6.8, 0.0) P = 0.053	–	−1.7 (2.0) (−5.8, 2.3) P = 0.396

Data are T-score LS mean (SE) (95% CI) from analysis of covariance (ANCOVA). BRIEF = Behavior Rating Inventory of Executive Function. LS Mean = least squares mean. SE = standard error.
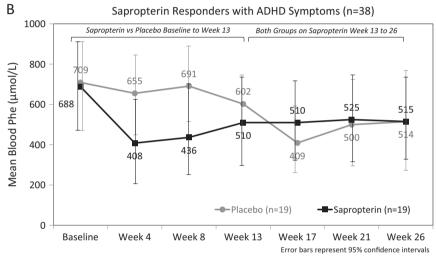
Fig. 2. Blood Phe levels from baseline to Week 26.

LS=least squares; SE=standard error; CI=confidence interval

Fig. 3. Treatment effect of sapropterin vs. placebo at Week 13 in sapropterin Phe responders with ADHD symptoms at baseline by age group.

A

ADHD RS/ASRS Total Score

B

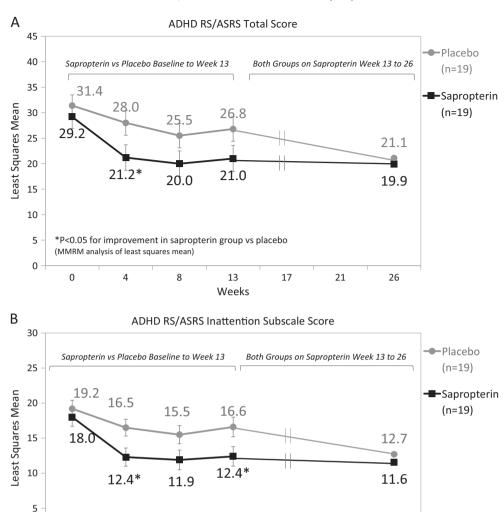**ADHD RS/ASRS Inattention Subscale Score**

Fig. 4. MMRM Analysis of ADHD RS/ASRS Total Score (A) and Inattention Subscale Score (B) from Baseline to Week 26 in Sapropterin Phe Responders with ADHD Symptoms (N=38).

in our PKU population (range of mean baseline Total Scores: 29 to 31) [36–38]. Similarly, the mean Total Score improvements of −8 to −10 for medication-treated ADHD patients compared with placebo-treated patients were higher than the mean Total Score improvement of −4.2 for sapropterin compared with placebo in our study [36–38]. Importantly, the mean improvement of −3.4 in Inattention Subscale Score with sapropterin compared with placebo in our study is close to the range of −4 to −6 associated with the ADHD medications in ADHD patients [36–38]. The content validity of the ADHD RS and ADHD ASRS for evaluating inattentive and hyperactive/impulsive symptoms in adults and children with PKU has been demonstrated in a study of 15 parent/child pairs and 13 adults with PKU [39]. Both scales demonstrated clinical relevance as assessments of inattentive symptoms associated with PKU, but less so for hyperactive/impulsive symptoms [39].

4.2. Neurobiology

Our data also agree with previous reports that suboptimally treated individuals with PKU may have significant neurocognitive and psychosocial symptoms [8,9] as well as anecdotal reports that some of these symptoms appear to be ameliorated when blood Phe levels are reduced. Antshel et al. reported that ADHD and PKU may be linked by low levels

of dopamine and norepinephrine in the prefrontal cortex, although the evidence for a hypodopaminergic/hyponoradrenergic state is stronger for ADHD than for PKU [11]. Theoretically, since PAH deficiency in PKU results in impaired conversion of Phe to tyrosine, higher Phe levels and limited tyrosine concentration in the blood means that available tyrosine must compete with Phe to cross the blood–brain barrier, resulting in lower levels of tyrosine available in the brain to synthesize dopamine and norepinephrine [11]. Large neutral amino acids (LNAA), which are essential for protein and neurotransmitter synthesis in the brain, are also decreased in the brains of individuals with PKU, likely as a result of competition with high Phe levels in the blood for the transporter LAT1 [40].

Treatment with sapropterin may improve neurocognitive and psychosocial symptoms in individuals with PKU through several possible mechanisms related to PKU. Treatment with sapropterin lowers blood Phe levels by activating PAH and restoring oxidative metabolism of Phe. Neurochemical research has suggested that the elevated blood Phe concentration in PKU increases free Phe in the brain contributing to its neurologic sequelae [41] and may also disrupt the transport of LNAA from the blood into brain, with subsequent negative effects on cerebral neurotransmitter and protein synthesis [42]. Furthermore, plasma Phe concentrations above 600–800 μmol/L have been linked to

Table 4
Adverse events occurring in all enrolled subjects (N = 206).

Characteristic	Randomized trial baseline to Week 13		Open-label treatment period Weeks 13 to 26 (all subjects on sapropterin)	
	Placebo n = 108	Sapropterin n = 98	Placebo/sapropterin n = 104	Sapropterin n = 95
Adverse events occurring in ≥5% of subjects in either treatment group, n (%)				
Abdominal pain, upper	5 (4.6%)	4 (4.1%)	2 (1.9%)	7 (7.4%)
Cough	8 (7.4%)	7 (7.1%)	8 (7.7%)	8 (8.4%)
Diarrhea	4 (3.7%)	10 (10.2%)	8 (7.7%)	4 (4.2%)
Headache	28 (25.9%)	25 (25.5%)	16 (15.4%)	17 (17.9%)
Nasal congestion	11 (10.2%)	7 (7.1%)	4 (3.8%)	12 (12.6%)
Nasopharyngitis	9 (8.3%)	11 (11.2%)	12 (11.5%)	11 (11.6%)
Nausea	10 (9.3%)	4 (4.1%)	10 (9.6%)	7 (7.4%)
Oropharyngeal pain	10 (9.3%)	6 (6.1%)	11 (10.6%)	11 (11.6%)
Pain in extremity	3 (2.8%)	1 (1.0%)	3 (2.9%)	7 (7.4%)
Pyrexia	5 (4.6%)	1 (1.0%)	5 (4.8%)	7 (7.4%)
Upper respiratory tract infection	7 (6.5%)	4 (4.1%)	10 (9.6%)	3 (3.2%)
Vomiting	14 (13.0%)	4 (4.1%)	12 (11.5%)	3 (3.2%)
Serious adverse events, n (%)				
Amino acid level increased	1 (0.9)	0 (0)	0 (0)	0 (0)
Animal bite	0 (0)	0 (0)	1 (1.0)	0 (0)
Concussion	1 (0.9)	0 (0)	0 (0)	0 (0)
Necrotizing fasciitis	1 (0.9)	0 (0)	0 (0)	0 (0)
Petit mal epilepsy	0 (0)	0 (0)	1 (1.0)	0 (0)

Subjects who experienced more than 1 AE within a preferred term were counted once within that preferred term.

decreased rates of cerebral protein synthesis in humans [43]. Thus, lower blood Phe levels may well decrease brain Phe levels, possibly decreasing the direct neurotoxic effects. In addition, decreases in blood Phe levels may result in increased transport of tyrosine, tryptophan and other LNAA into the brain, which could improve both neurotransmitter and protein synthesis [40,44]. Finally, increased BH4 levels might further improve neurotransmitter levels because BH4 is the essential cofactor for tyrosine-3-hydroxylase and tryptophan-5-hydrolase, key enzymes in the production of dopamine, norepinephrine, and serotonin [44]. Improvements in white matter integrity (as measured by mean diffusivity from diffusion tensor imaging) following six months of sapropterin treatment have been reported in a series of 12 patients with PKU [45,46]. Oral sapropterin at doses of 20–30 mg/kg/day was shown to increase BH4 levels in the cerebrospinal fluid of 12 patients with autosomal dominant DOPA-responsive dystonia, suggesting the ability of oral BH4 to impact brain levels of this cofactor [47].

4.3. Executive functioning

Our data on early treated individuals with PKU confirm the presence of executive functioning deficits known to exist among a portion of early and continuously treated individuals with PKU [15,17,48] and suggest that reductions in the Phe level following sapropterin therapy are associated with improvement in the BRIEF GEC and MI scores among children and adolescents (Table 3). Just as the improvement in Inattention Subscale Score was the primary contributor to improvement in ADHD Total Score in children and adolescents, improvement in the MI score appeared to be the driver of improvement in the overall GEC score for children and adolescents. This finding is consistent with a clinical comparison of the BRIEF and ADHD RS rating scales, in which the parent-reported BRIEF MI scale (which includes initiation, working memory, planning/organizing, organizing materials, and monitoring) was shown to be more strongly related to inattention, while the BRI scale items related more to impulsivity and hyperactivity [29].

4.4. Study strengths and limitations

This large, randomized, placebo-controlled, multicenter trial contributes substantially to the understanding of mental health functioning and impairments in both children and adults with PKU and highlights the importance of neuropsychiatric assessment in this population,

using scales that are validated and commonly used in psychiatric medicine. Our findings show that inattention is an important component of ADHD symptoms in PKU that appears to be linked with higher blood Phe levels and may be reversible.

Although this is the largest study of ADHD symptoms and executive functioning in individuals with PKU to date, it has inherent limitations. More frequent clinic visits during the study may have increased patient and provider attention to dietary treatment, thereby improving blood Phe levels in both treatment groups. In any study evaluating mental health, there is increased potential for a placebo effect. ADHD symptoms and executive functioning were assessed using parent-reported and adult self-reported measures, which could differ from assessments made by a health care professional. In particular, self-report instruments may not be ideal for evaluating ADHD symptoms and executive functioning in individuals with PKU, as suggested not only by anecdotal experience regarding limited self-awareness in adults with PKU, [10] but also by self-versus-informant methodological studies of adults and children with ADHD symptoms that have delineated a pattern of higher symptom rating by informants [49–51].

For the primary endpoint analysis, ADHD RS for subjects < 18 years old and ASRS for subjects ≥ 18 years old were combined to derive an overall ADHD RS/ASRS Total Score for sapropterin Phe responders with ADHD. This is a new approach that has not been used previously in PKU or in other disease areas. Combining the scales has good clinical rationale, as both scales include 18 questions and each question assesses a specific DSM-IV-defined clinical symptom or behavior. Including a large age range (age 8 years and older) was considered appropriate, partly to increase the size of the analysis population and improve the feasibility of proper and timely enrolment in this rare disease population, but also because understanding mental health aspects of both children and adults with PKU is clinically important. Despite the small sample sizes (i.e. limited statistical power) for the separate analyses of children and adolescents with ADHD symptoms (n = 26) and adults with ADHD symptoms (n = 12), a significant improvement in ADHD RS score for sapropterin versus placebo was seen in children and adolescents with ADHD. However, among the adults reporting ADHD symptoms at baseline, mean improvements in ADHD RS/ASRS Total, Inattention, and Hyperactivity/Impulsivity scores were reported in both the placebo and sapropterin groups, resulting in a lack of significant improvement for sapropterin relative to placebo. The very small number of adults with ADHD symptoms precludes our ability to

generate clinical conclusions regarding whether or not these adults benefit from sapropterin therapy. Furthermore, self-report of attention and hyperactivity/impulsivity may be particularly problematic given that the primary efficacy endpoint for this intervention was related to improvements in an individual's capacity to monitor his/herself. If the intervention was effective, the raters themselves changed in their ability to recognize and monitor their own impairment during the course of treatment, making it difficult to interpret pre- vs post-intervention data, as well as post-intervention data for treatment relative to placebo. This does not negate the importance of obtaining self-reported information but rather suggests that collection of collateral information from another informant is advisable for future intervention studies in this population.

4.5 . Conclusions

Health care professionals, teachers, and families of children and adolescents with PKU need to be cognizant of the ADHD inattentive symptoms and executive functioning deficits that are associated with PKU and the potentially negative impact of these problems on academic or vocational performance and daily functioning. Importantly, sapropterin therapy was found to be associated with improvements in ADHD inattentive symptoms and aspects of executive functioning in this large cohort of individuals with PKU, indicating that these symptoms are potentially reversible when blood Phe levels are reduced. Careful clinical evaluation with appropriate questioning may elucidate problems in these areas not previously detected in standard clinical visits. It is our hope that this study will facilitate collaborations between metabolic specialists and psychiatry/psychology professionals that will improve the care of children and adults with PKU and associated ADHD and executive function deficits.

Acknowledgments

Appendix A: Investigators and Sites

University of North Carolina at Chapel Hill, Chapel Hill, NC, Joseph Muenzer, MD, PhD; Vanderbilt University School of Medicine, Nashville, TN, John A. Phillips III, MD; UT Southwestern Medical Center, Dallas, TX, Graham Emslie, MD; UCSD Clinical Center of Research, La Jolla, CA, Bruce Barshop, MD, PhD; University of Minnesota Medical Center, Fairview, Minneapolis, MN, Chester Whitley, PhD, MD; Oregon Health & Science University, Portland, OR, Cary Owen Harding, MD; Ann & Robert H. Lurie Children's Hospital of Chicago, Barbara K. Burton, MD; Children's Hospital of Boston, Boston, MA, Susan Waisbren, PhD; Children's Hospital of UPMC, Pittsburgh, PA, Georgianne Lee Arnold, MD; Hospital for Sick Children, Toronto, Ontario, Canada, Komudi Siriwardena, MD; University of Wisconsin, Madison, WI; Gregory Rice, MD; Stanford University, Palo Alto, CA, Gregory Enns, MD, ChB; University of California San Francisco, San Francisco, CA, Robert Hendren, DO; University of South Florida, Tampa, FL, Amarilis Sanchez-Valle MD; The Children's Hospital, Aurora, CO, Janet Thomas, MD; Investigational Drug Services, Indiana University Simon Cancer Center, Indianapolis, IN, Mary Stuy, MD, FAAP; University of Tennessee Health Science Center, Memphis, TN, Lee Wallace, RD; Emory University, Atlanta, GA, Rani Singh, PhD, RD, LD; St. Christopher's Hospital for Children, Drexel University College of Medicine, Philadelphia, PA, Mitzie Grant, PhD; University of Rochester Medical Center, Rochester, NY, Jennifer Kwon, MD; Penn State University, Pediatric Clinical Research Office, Hershey, PA, Patricia Gordon, MD; University Hospitals Case Medical Center, Center for Human Genetics, Cleveland, OH, Laura Konczal, MD, FACMG, FAAP; Children's Hospital of Wisconsin, Milwaukee, WI, David Dimmock, MD; Alberta Children's Hospital, Calgary, Alberta, Canada, Robin Casey, MD; Montreal Children's Hospital, Montreal, Quebec, Canada, John Mitchell, MD; Children's and Women's Health Centre of British Columbia, Vancouver, BC, Canada, Sylvia Stockler-Ipsiroglu, MD, PhD, MAS, MBA; Children's National Medical Center, Center for Clinical and Community Research (CCCR), Washington, DC, Uta Lichter-Konecki, MD; Women & Children's Hospital of Buffalo, Buffalo, NY, Richard Erbe, MD; Maritime Medical Genetics Service, IWK Health Center, Halifax, Canada, Jane Gillis, MD; University of Alberta, Medical Genetics Clinic, Edmonton, Alberta, Canada, Linda Casey, MD, FRCPC, FAAP, MSc, Alicia Chan, MD; Children's Hospital, Winnipeg, Manitoba, Canada, Aizeddin Mhanni, MB, ChB, FRCPC, FCCMG, FACMG, PhD; McMaster Children's Hospital, Hamilton, Ontario, Canada, Murray Potter, MD; London Health Sciences Center, London, Ontario, Canada, Chitra Prasad, MD, FRCPC, FCCMG, FACMG; University of Florida, Department of Pediatrics, Division of Genetics and Metabolism, Gainesville, FL, Roberto Zori, MD; Cincinnati Children's Hospital Medical Center, Cincinnati, OH, Nancy Leslie, MD; Kingston General Hospital, Division of Medical Genetics, Kingston, Ontario, Canada, Jennifer MacKenzie, MD; Albany Medical Center, Department of Pediatrics, Section of Genetics and Metabolism, Albany, NY, Darius Adams, MD; Akron Children's Hospital, Akron, OH, Thaddeus Kurczynski, MD, PhD; Kaiser Permanente Regional Metabolic Services, Los Angeles, CA, Rebecca Mardach, MD

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