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Long-term comparative effectiveness of pegvaliase versus standard of care comparators in adults with phenylketonuria

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Abstract

Phenylketonuria (PKU) is caused by phenylalanine hydroxylase (PAH) deficiency, resulting in high blood and brain Phenylalanine (Phe) concentrations that can lead to impaired brain development and function. Standard treatment involves a Phe-restricted diet alone or in conjunction with sapropterin dihydrochloride in responsive patients. The Food and Drug Administration approved pegvaliase enzyme substitution therapy for adults with blood Phe > 600 μmol/L in the US. Recently, the European Commission also approved pegvaliase for treatment of PKU patients aged 16 years or older with blood Phe > 600 μmol/L. The analyses presented below were conducted to provide comparative evidence on long-term treatment effectiveness of pegvaliase versus standard of care in adults with PKU.

Adult patients (≥18 years) with baseline blood Phe > 600 μmol/L who had enrolled in the pegvaliase phase 2 and phase 3 clinical trials were propensity score-matched to historical cohorts of patients treated with "sapropterin + diet" or with "diet alone". These cohorts were derived from the PKU Demographics, Outcome and Safety (PKUDOS) registry and compared for clinical outcomes including blood Phe concentration and natural intact protein intake after 1 and 2 years. Propensity scores were estimated using logistic regression with probability of treatment as outcome (i.e. pegvaliase, "sapropterin + diet", or "diet alone") and patient demographic and

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Appendix A. Supplementary data

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disease severity covariates as predictors. An additional analysis in adult PKU patients with baseline blood Phe ≤600 μmol/L comparing non-matched patient groups “sapropterin + diet” to “diet alone” using PKUDOS registry data only was also conducted.

The analyses in patients with baseline blood Phe > 600 μmol comparing pegvaliase with “sapropterin + diet” (*N* = 64 matched pairs) showed lower mean blood Phe concentrations after 1 and 2 years with pegvaliase (505 and 427 μmol/L) versus “sapropterin + diet” (807 and 891 μmol/L); mean natural intact protein intake after 1 and 2 years was 49 and 57 g/day respectively with pegvaliase versus 23 and 28 g/day with “sapropterin + diet”. The analysis comparing pegvaliase with “diet alone” (*N* = 120 matched pairs) showed lower mean blood Phe at 1 and 2 years with pegvaliase (473 and 302 μmol/L) versus “diet alone” (1022 and 965 μmol/L); mean natural intact protein intake after 1 and 2 years was 47 and 57 g/day with pegvaliase and 27 and 22 g/day with “diet alone”. Considerably more patients achieved blood Phe ≤600, ≤360, and ≤120 μmol/L and reductions from baseline of ≥20%, ≥30%, and ≥50% in blood Phe after 1 and 2 years of pegvaliase versus standard treatments. The analysis in patients with baseline blood Phe ≤600 μmol/L showed lower blood Phe after 1 and 2 years with “sapropterin + diet” (240 and 324 μmol/L) versus “diet alone” (580 and 549 μmol/L) and greater percentages of patients achieving blood Phe targets ≤600, ≤360, and ≤120 μmol/L and reductions from baseline of ≥20%, ≥30%, and ≥50% in blood Phe.

These results support pegvaliase as the more effective treatment option to lower Phe levels in adults with PKU who have difficulty keeping blood Phe ≤600 μmol/L with “diet alone”. For patients with blood Phe ≤600 μmol/L, adding sapropterin to dietary management is an appropriate treatment option, for those responsive to the treatment.

Keywords

Diet; Pegvaliase; Phenylalanine; Phenylketonuria; Propensity score matching; Sapropterin dihydrochloride

1. Introduction

Phenylketonuria (PKU) is an autosomal recessively inherited metabolic disease caused by phenylalanine hydroxylase (PAH; EC 1.14.16.1) deficiency. The resulting complete or partial inability to convert phenylalanine (Phe) to tyrosine (Tyr) in the liver leads to high concentrations of Phe in the blood and the brain [1]. Untreated individuals with PKU can develop intellectual disability, behavioral, inattention, and mood problems, psychiatric symptoms, motor deficits, seizures, and eczematous rash [1–3]. PKU phenotypes can vary from mild hyperphenylalaninemia (mostly defined as blood Phe < 360 μmol/L) to severe (classical) PKU with untreated blood Phe concentrations exceeding 1200 μmol/L [1]. Early control of blood Phe with dietary management has reduced the frequency of severe neurological complications related to the growing brain in childhood; however, there remain substantive medical issues [1,4].

Dietary management of PKU consists of a low-protein, Phe-restricted diet in combination with Phe-free or Phe-restricted L-amino acid-rich medical foods and/or specially modified

low-protein foods [3,5]. The complexity and burden of a Phe-restricted diet can significantly affect adherence and quality of life (QoL) [6]. As parents primarily control diet during childhood, children with PKU generally adhere to a Phe-restricted diet. However, as access to different foods increases as children with PKU are in school, adherence to the severe Phe-restricted intake (as the vast majority of foods include Phe) becomes particularly difficult during adolescence and into adulthood, resulting in chronically elevated blood Phe concentrations [1]. Poor control leads to an increased burden of illness in adolescents and adults with PKU. Studies in these patients have revealed deficits in mood, executive function domains of attention, cognitive flexibility, and inhibitory control that exceed general population estimates, as well as a higher than expected prevalence of an array of neuropsychiatric symptoms [7,8]. Recently, an insurance claim-based observational study from the US also suggested an increased prevalence of several non-neuropsychiatric comorbidities in adults with PKU, including pulmonary, renal, metabolic, gastrointestinal, cardiac, and skeletal problems [9]. These comorbidities were associated with healthcare costs four times that of a control population matched for age, sex, insurance type, and geographical area [9].

Historically, the only pharmacotherapy available for individuals with PKU was sapropterin dihydrochloride (sapropterin; KUVAN®, BioMarin Pharmaceutical Inc., Novato, CA, USA). Sapropterin is a synthetic preparation of 6R-tetrahydrobiopterin (BH_4), the naturally occurring cofactor of PAH. It was approved by the Food and Drug Administration (FDA) in 2007 and the European Medicines Agency in 2008 for treatment of BH_4-responsive PKU (in conjunction with a Phe-restricted diet) or BH_4 deficiencies [10,11]. As responsiveness to sapropterin, a cofactor, requires residual PAH activity, the treatment is only applicable for PKU patients with milder phenotypes, associated with lower blood Phe concentrations. Patients with two null-mutations in the *PAH* gene will not respond [12]. Responders to sapropterin can be identified by genotyping and/or a sapropterin response test or trial [13,14]. In responsive patients, sapropterin can significantly reduce blood Phe concentration and increase Phe tolerance [15–20]. Nevertheless, most sapropterin-responsive patients still require dietary treatment in conjunction with sapropterin to achieve recommended blood Phe targets. The PKU Demographics, Outcome and Safety (PKUDOS) registry is a US-based, voluntary, multicenter, observational registry to track individuals with PKU on sapropterin. Patients enrolled in this registry were receiving sapropterin at the time of enrollment, had previously received sapropterin but stopped treatment before enrollment into the registry, or intended to initiate sapropterin therapy within 90 days of enrollment [21]. The PKUDOS registry was initiated in 2008 and currently includes 1997 patients. At the last data-cut in February 2018, patients had been followed for up to 10 years.

In May 2018, the FDA approved a novel enzyme substitution therapy, Pegvaliase (PALYNZIQ®, BioMarin Pharmaceutical Inc., Novato, CA, USA), for adults with PKU who have a blood Phe concentration > 600 μmol/L. The European Commission approved pegvaliase for treatment of PKU patients aged ≥16 years with inadequate blood Phe control (blood Phe > 600 μmol/L) on May 6th 2019 [22]. Pegvaliase is a PEGylated recombinant phenylalanine ammonia lyase (PAL) enzyme isolated from the cyanobacteria *Anabaena variabilis*. PAL converts Phe to ammonia and trans-cinnamic acid, which are metabolized in the liver and excreted in urine, respectively [23]. The pegvaliase clinical program included a

phase 1 study (NCT00634660) [24], three phase 2 studies (NCT01560286, NCT00925054, NCT01212744) with their open-label extension PAL-003 (NCT00924703) [25], and two phase 3 studies, PRISM-1 (NCT01819727) and PRISM-2 (NCT01889862). The open-label, multicenter, parallel-group study PRISM-1, and the subsequent pivotal PRISM-2 study included 261 adults with PKU with blood Phe > 600 μmol/L. PRISM-2 comprised an 8-week, randomized, double-blind, placebo-controlled trial (in a subgroup) and an open-label extension to assess long-term outcomes [23,26]. The design of PRISM-1 and PRISM-2 have been discussed in detail in previous publications [23,26]. The PRISM studies showed meaningful and sustained reductions in blood Phe concentration in patients receiving pegvaliase [23]. After 24 months of treatment, 68%, 61%, and 51% of patients reached blood Phe concentrations ≤600 μmol/L, ≤360 μmol/L, and ≤120 μmol/L, respectively. Long-term results also showed clinically meaningful improvements across inattention and mood outcomes [23]. Overall, the safety results of the PRISM studies showed that pegvaliase has an acceptable safety profile, with most adverse events, mainly hypersensitivity reactions, occurring in the first 6 months of treatment [23].

To minimize disease burden, both American (2014) and European (2017) guidelines for the management of PKU recommend life-long control of blood Phe [2,3]. The European guidelines recommend a blood Phe concentration below 360 μmol/L in children until 12 years of age and pregnant women, and below 600 μmol/L in non-pregnant patients ≥12 years [2]. The American guidelines recommend a target blood Phe concentration in the range of 120–360 μmol/L, regardless of age or pregnancy status [3]. However, some data suggest that better neurocognitive outcomes are achieved with even lower blood Phe concentrations [27]. Due to the challenges in adherence with current treatments (dietary management and sapropterin treatment), these blood Phe targets are very difficult to achieve and maintain for adults with PKU. As a result, most adults with PKU have blood Phe concentrations exceeding the recommended targets [28–31]. Pegvaliase could improve upon the limitations of standard treatments for PKU, since, unlike sapropterin, the efficacy of pegvaliase does not depend on residual PAH activity, and permits an increase in natural protein intake while keeping blood Phe within recommended target concentrations. However, a head-to-head direct comparative study of pegvaliase versus sapropterin has not been performed as of this date.

The objective of the present analyses was to provide insight into the relative effectiveness of treatment choices available for PKU based on long-term comparative evidence, applying best available methodologies to existing data. The analyses used data from pegvaliase clinical trials [23,32] and the PKUDOS registry [21] to compare the effectiveness of pegvaliase with diet alone, and also with diet in conjunction with sapropterin in adults with PKU (≥18 years). As pegvaliase has been approved for adults with blood Phe > 600 μmol/L in the US, the effectiveness of pegvaliase was compared with standard treatments only for this uncontrolled patient population. For patients with better metabolic control (blood Phe ≤600 μmol), dietary treatment was compared with sapropterin in conjunction with diet. The rationale of the study was to generate long-term comparative evidence using the PICOS (Patients/Population, Interventions, Comparators, Outcomes, Study design) criteria (Table 1).

2. Methods

2.1. Patient selection

The analyses comparing pegvaliase with standard of care comparators in patients with baseline blood Phe > 600 μmol/L (uncontrolled patients analysis) used patient level data from the pegvaliase clinical trials, and matched cohorts based on baseline measures in a historical cohort derived from the PKUDOS registry. Both studies were performed in the US.

The pegvaliase-treated patient group was selected from patients in the pegvaliase phase 2 165–205 trial and the phase 3 (PRISM) trials treated with an induction, titration, maintenance (ITM) schedule [23,32]. Both studies included adults with PKU with baseline blood Phe ≥600 μmol/L. The ITM schedule was followed by an active, open-label extension phase [23,32]. A total of 285 patients were enrolled in the ITM population. At last data cut (February 2018), patients had accumulated up to 278 weeks of exposure to pegvaliase. Although patients may have been exposed to different doses of pegvaliase (5–60 mg/kg/day) based on efficacy, driven by the magnitude of a patient's immune response versus dose of the medication, they were all considered "pegvaliase exposed" for the purpose of the analysis. It should be noted that although dietary control of blood Phe was not a requirement for enrollment in the pegvaliase trials, several patients were on diet at baseline. Supplementary Table 1 summarizes baseline characteristics of the pegvaliase ITM full study population. More details about this population can be found in the publications of these studies [23,26,32,33].

A comparator population of sapropterin-treated patients, referred to as the "sapropterin + diet" group, was selected from the PKUDOS registry [21]. Baseline characteristics of the PKUDOS full study population are presented in Supplementary Table 2. To best represent patients potentially eligible for entry into the pegvaliase clinical trials, the "sapropterin + diet" group was selected based on the following criteria: 1) intended to initiate sapropterin within 90 days of enrollment (i.e. new users of sapropterin); 2) ≥1 recorded sapropterin-naïve (i.e. pre-treatment) blood Phe value; 3) baseline blood Phe (last available measurement prior to initiating sapropterin) > 600 μmol/L; 4) age ≥ 18 years at initiation of sapropterin; and 5) available information on sapropterin dosing while enrolled. The patients in this subgroup, regardless of sapropterin dose (range 5–20 mg/kg/day), were considered to be actively managed with diet in conjunction with sapropterin, as indicated in the sapropterin label [34].

A second comparator population of patients on a Phe-restricted diet alone, referred to as the "diet alone" group, was also derived from the PKUDOS registry. Selection criteria for the "diet alone" group were 1) had previously received sapropterin before enrolling in PKUDOS or discontinued sapropterin while in the registry, 2) baseline blood Phe > 600 μmol/L, and 3) ≥18 years of age at the time of baseline Phe measurement. See Section 2.2.3 for the definition of baseline blood Phe. The patients in this subgroup were considered to only be potentially managed with diet alone.

An additional analysis comparing the effectiveness of standard of care comparators "sapropterin + diet" versus "diet alone" in adults (baseline age ≥ 18 years) with baseline blood Phe ≤600 μmol/L (controlled patients analysis) was conducted using the PKUDOS registry only and employing the same case definitions described above.

2.2. Statistical methods and endpoints

2.2.1. Rationale for using propensity score matching—The uncontrolled patients analyses aimed to compare effectiveness data derived from a clinical trial population (165–205 and PRISM studies) with historical cohort groups derived from patients enrolled in a registry (PKUDOS). Making comparisons on effectiveness in the absence of randomization requires statistical techniques to match the two groups for comparison with regard to key prognostic factors, such as disease severity, and patient demographics such as age and gender, which may confound whether patients are selected for treatment [35]. One approach to compare populations from different studies and reduce confounding bias is propensity score analysis. The propensity score is a balancing score, which attempts to estimate the effect of a treatment, policy, or other intervention by accounting for the covariates that help to predict appropriateness of treatment intervention. The goal of propensity score methods is to approximate a random experiment, eliminating many of the limitations associated with observational data analysis [36,37]. Frequently used propensity score methods include matching, stratification, inverse probability weighting, and use of the propensity score as a covariate in conventional regression analysis [36]. Here, propensity score matching was used to provide post-hoc comparable groups to explore the effectiveness of alternative treatment regimens in PKU.

2.2.2. Statistical methods—For the uncontrolled patients analyses, propensity scores were estimated using logistic regression with probability of treatment as the outcome (i.e. pegvaliase, "sapropterin + diet", or "diet alone") and demographic and disease severity covariates as the predictors. The following variables, available in both the pegvaliase clinical trial and PKUDOS datasets, were considered the most relevant predictors of treatment group assignment and were explored for inclusion into the propensity score model: baseline blood Phe concentration (μmol/L), baseline dietary Phe (mg/day), baseline age (years), and gender. To maximize patients counts, the primary analyses used a three-variable propensity score (baseline age, gender, and baseline blood Phe concentration) while the fourth factor, baseline dietary Phe, was added to the propensity score in a sensitivity analysis. Patients in the sensitivity analysis were selected using the same criteria as the primary analysis, but were also required to have baseline dietary Phe data available.

Patients from the "sapropterin + diet" group and patients from the "diet alone" group were randomly ordered based on propensity scores and then sequentially matched by propensity score to patients who received pegvaliase. Propensity scores were matched one-to-one based on the nearest neighbor method. This implies that not all pegvaliase patients received a "sapropterin + diet" or "diet alone" match, depending on the distribution of propensity score values. Once matched pairs were established, baseline characteristics, as well as the overlap of propensity score distributions for the matched populations, were calculated to explore the success of the matching. Comparative analyses were conducted for the "sapropterin +

diet" versus pegvaliase-matched pairs and the "diet alone" versus pegvaliase-matched pairs separately.

To assess the statistical significance of differences in blood Phe reductions between treatment groups in the uncontrolled patients analysis, ANCOVA was applied, whereby mean change in blood Phe reduction from baseline was modelled with treatment as the primary factor and propensity score as the secondary factor.

For the controlled patients analysis, comparing "sapropterin + diet" with "diet alone" in adults with baseline blood Phe ≤600 μmol/L conducted in PKUDOS-enrolled patients alone, groups were not matched because sample size in the "diet alone" arm was too limited to allow propensity score matching.

2.2.3. Study endpoints—Clinical endpoints of response were explored over two time periods of interest: baseline to end of year 1 and baseline to end of year 2. Sample size in the pegvaliase ITM population decreases greatly for subjects with > 2 years of treatment due to the timing of the data cut employed in this analysis, not allowing meaningful comparisons beyond 2 years.

Outcome measures included mean blood Phe concentration at 1 and 2 years follow-up and standard deviation (SD) among the patients at both time points; change in blood Phe from baseline (mean/SD); percent of patients achieving blood Phe ≤600 μmol/L, ≤360 μmol/L or≤= 120 μmol/L (normative Phe concentration); percent of patients achieving a ≥ 20%, ≥30% or ≥ 50% reduction from baseline Phe ([baseline blood Phe – Year 1 (or Year 2) blood Phe value]/baseline blood Phe); and natural intact protein intake in g/day (mean/SD). Natural intact protein intake was calculated as the total protein intake minus medical food protein intake for the "sapropterin + diet" and "diet alone" groups, and as average dietary protein intake from intact food for the pegvaliase group.

Baseline blood Phe concentration was defined as the last available measurement prior to the first administration of pegvaliase in the 165–205 or PRISM-1 trials for the pegvaliase group. In the "sapropterin + diet" group, baseline blood Phe was the last available measurement prior to initiating sapropterin. For the 'diet alone' group, baseline blood Phe was defined as the measurement closest to the enrollment date within 90 days in case sapropterin was discontinued before enrollment. If sapropterin was discontinued after enrollment, it was the value closest to the discontinuation date within 90 days of discontinuation. This implies that if patients in the "diet alone" group took sapropterin before enrollment in PKUDOS, assessments after enrollment were used for analysis; if patients took sapropterin after enrollment, assessments after the last sapropterin dose were used for analysis.

For the evaluation of blood Phe concentrations at 1-year and 2-year time points, only patients who had a Phe assessment recorded at 365 ± 45 days follow-up (for the 1-year analysis), or at 730 ± 90 days follow-up (for the 2-year analysis) were included. If a patient had more than one assessment during these time periods, the median of those assessments was used.

Safety data (adverse events [AEs], and study-drug related AEs and serious adverse events [SAEs]), based on the first 2 years after the first dose or enrollment, were compared for the comparator groups used in the uncontrolled patients primary analyses, i.e. pegvaliase versus "sapropterin + diet" and sapropterin versus "diet alone".

3. Results

3.1. Selection of patients for propensity score matching

Of the patients enrolled in PKUDOS, 64 met the criteria for inclusion in the "sapropterin + diet" group, and 125 met the criteria for inclusion in the "diet alone" group. Of the patients in the "diet alone" group, 111 stopped sapropterin before enrollment into PKUDOS (mean [SD] duration since last sapropterin intake to baseline Phe assessment 815 [641] days) and 14 stopped sapropterin after enrollment (mean [SD] duration since last sapropterin intake to baseline Phe assessment 23 [20] days). All patients could be propensity score-matched to a pegvaliase patient for the primary pegvaliase comparative analyses using a three-variable propensity score (baseline age, gender, and baseline blood Phe concentration) (Fig. 1). Supplementary Fig. 1 shows overlap of propensity score distributions for the matched groups.

When baseline dietary Phe was added as a fourth factor in the propensity score, the sample of "sapropterin + diet" patients available for matching decreased from $N = 64$ to $N = 28$ patients and the available "diet alone" patients decreased from $N = 125$ to $N = 56$ due to missing dietary data collected in PKUDOS. Because of the relatively small patient numbers, the results of these analyses are presented as sensitivity analyses.

3.2. Uncontrolled patients primary analysis: pegvaliase versus standard treatments in adult PKU patients with baseline blood Phe > 600 μmol/L

3.2.1. "Sapropterin + diet" versus pegvaliase—Baseline characteristics of the patients selected for the "sapropterin + diet" versus pegvaliase primary analysis showed a good balance with regard to the propensity-matched variables (baseline age, gender, and baseline blood Phe concentration) (Table 2).

Follow-up data at 1 and 2 years were available for 25 patients (both time points) from the "sapropterin + diet" group, and for 43 and 40 patients, respectively, from the pegvaliase group. Patients in the pegvaliase group showed considerably lower mean blood Phe concentrations and higher natural intact protein intake versus those in the "sapropterin + diet" group after 1 and 2 years (Table 3). It should be noted that only a limited number of patients had natural intact protein intake data available at 1 and 2 years in the "sapropterin + diet" group (4 and 7 patients at 1 and 2 years, respectively). The percentages of subjects achieving blood Phe target concentrations ≤600 μmol/L, ≤360 μmol/L, and ≤120 μmol/L and reductions ≥20%, ≥30%, and ≥50% in blood Phe at both time points were considerably higher in the pegvaliase versus the "sapropterin + diet" group (Table 3). The least square (LS) mean difference in blood Phe reduction between the pegvaliase and "sapropterin + diet" groups was −399.4 (95% CI −660.2 to −138.7) μmol/L at 1 year ($P = .0032$) and −647.6 (95% CI −910.0 to −385.3) μmol/L at 2 years follow-up ($P < .0001$).

3.2.2. "Diet alone" versus pegvaliase—Baseline characteristics of the patients selected for the "diet alone" versus pegvaliase primary analysis showed a good balance with regard to the propensity-matched variables (baseline age, gender, and baseline blood Phe concentration) (Table 4). Baseline natural intact protein intake was higher in the pegvaliase group.

Follow-up data at 1 and 2 years were available for 51 and 42 patients, respectively, from the "diet alone" group, and for 87 and 80 patients, respectively, from the pegvaliase group.

Patients in the pegvaliase group showed considerably lower mean blood Phe concentrations and higher natural intact protein intake versus those in the "diet alone" group after 1 and 2 years (Table 5). The percentages of subjects achieving blood Phe target concentrations ≤600 μmol/L, ≤360 μmol/L, and ≤120 μmol/L and reductions ≥20%, ≥30%, and ≥50% in blood Phe at both time points were considerably higher with pegvaliase than with "diet alone" (Table 5). The LS mean difference in blood Phe reduction between the pegvaliase and "diet alone" groups was −567.8 (95% CI −708.3 to −427.4) μmol/L at 1 year ($P < .0001$) and −670.9 (95% CI −824.1 to −517.7) μmol/L at 2 years follow-up ($P < .0001$).

3.2.3. Uncontrolled patients sensitivity analyses—Propensity score matching using four variables (baseline age, gender, baseline blood Phe concentration, and baseline dietary Phe) yielded 29 matched patient pairs for the pegvaliase versus "sapropterin + diet" analysis, and 56 matched patient pairs for the pegvaliase versus "diet alone" analysis. The results of these analyses were comparable to those of the primary analyses, showing considerably lower mean blood Phe concentrations and higher natural intact protein intake in the pegvaliase group versus the "sapropterin + diet" (limited data for natural intact protein intake) and "diet alone" groups at 1 and 2 years follow-up. In addition, higher percentages of subjects achieved blood Phe target concentrations ≤600, ≤360, and ≤120 μmol/L and reductions ≥20%, ≥30%, and ≥50% in blood Phe after 1 and 2 years with pegvaliase versus standard treatments (Supplementary Tables 3–6). The LS mean difference in blood Phe reduction between the pegvaliase and "sapropterin + diet" groups was −335.2 (95% CI −743.5 to 73.2) μmol/L at 1 year ($P = .1037$) and − 674.1 (95% CI −1096.0 to −252.4) μmol/L at 2 years follow-up ($P = .0028$). The LS mean difference in blood Phe reduction between the pegvaliase and "diet alone" groups was −482.9 (95% CI −710.2 to −255.7) μmol/L at 1 year ($P < .0001$) and − 546.4 (95% CI −803.5 to −289.2) μmol/L at 2 years follow-up ($P < .0001$).

3.2.4. Uncontrolled patients safety analyses—Supplementary Tables 8 and 9 provide safety data over 2 years for the comparator groups used in the uncontrolled patients primary analyses comparing pegvaliase versus "sapropterin + diet" and pegvaliase versus "diet alone".

3.3. Controlled patients analysis: "Diet alone" versus "sapropterin + diet" in adult PKU patients with baseline blood Phe ≤600 μmol/L (PKUDOS registry only)

The mean (SD) baseline blood Phe concentration of patients from PKUDOS with baseline blood Phe ≤600 μmol/L and age ≥ 18 years receiving "diet alone" ($N = 46$) was comparable to that of the patients receiving "sapropterin + diet" ($N = 22$; unmatched population), i.e.

400 (133) μmol/L and 414 (135) μmol/L, respectively (Supplementary Table 7). The "diet alone" group included relatively more males and had a lower mean natural intact protein intake versus the "sapropterin + diet" group.

Follow-up data suggested lower mean blood Phe concentrations in the "sapropterin + diet" group versus the "diet alone" group after 1 and 2 years (Table 6). The percentages of subjects achieving blood Phe target concentrations ≤600 μmol/L, ≤360 μmol/L, and ≤120 μmol/L and reductions ≥20%, ≥30%, and ≥50% in blood Phe after 1 and 2 years were higher in the "sapropterin + diet" versus the "diet alone" group. No conclusions can be made regarding natural intact protein intake, given the limited data available for this outcome in the analysis.

4. Discussion

The recent regulatory approval of pegvaliase for adults with PKU with blood Phe > 600 μmol/L has opened the discussion on selection of the optimal treatment strategy for these patients. Clinical studies in PKU have generally focused on the efficacy of a single treatment against placebo or looked at changes over time versus baseline measurements. The present analyses aimed at addressing the lack of direct comparative studies of treatments for adults with PKU with blood Phe > 600 μmol/L and ≤600 μmol/L by applying novel statistical techniques on existing study datasets.

The results of the analyses comparing pegvaliase with standard treatments in adults with baseline blood Phe > 600 μmol/L (uncontrolled patients analyses) suggested that pegvaliase allows for a considerably greater reduction in blood Phe and a higher natural intact protein intake than diet alone or diet in conjunction with sapropterin. Pegvaliase reduced blood Phe to the European target level for adults of ≤600 μmol/L and the US target level of ≤360 μmol/L in most patients (≤600 μmol/L in 70–79% and ≤360 μmol/L in 65–72% after 2 years), while only a minority achieved these target levels after 2 years with dietary management alone ("diet alone": ≤600 μmol/L in 12% and ≤360 μmol/ in 2% of patients after 2 years) or in conjunction with pharmacological treatment as specified in the standard of care treatment guidelines ("sapropterin + diet": ≤600 μmol/L in 20% and ≤360 μmol/ in 8% after 2 years). Reducing blood Phe concentrations in adults with PKU is key given the considerable neurological, somatic, and economic burden of persistently elevated blood Phe in this population [7,9]. While Phe concentrations dropped to historic low levels, natural intact protein intake increased considerably over time, although the protocol of the pegvaliase studies mandated consistent protein intake from natural food and medical food (unless blood Phe levels decreased to ≤30 μmol/L). Natural intact protein intake could increase as protein intake from medical food decreased [23]. This increase in natural intact protein intake, while continuing to maintain metabolic control, is particularly relevant, as evidence supports that relaxation of a Phe-restricted diet (i.e., increasing protein tolerance) has a positive impact on patient QoL [6,38,39].

Longitudinal data up to 2 years suggested that the differences in effectiveness of the different treatments increase over time. Whereas outcomes in the pegvaliase group continued to improve between 1 and 2 years follow-up, the reduction over time in blood Phe in the

"sapropterin + diet" group appeared to be limited. This difference cannot be explained by a greater number of patients discontinuing sapropterin versus pegvaliase, as patients in the "sapropterin + diet" group had a longer mean follow-up time on treatment than those on pegvaliase (see Table 2). More likely, the difference is due to differences in the mechanism of action of both treatments. Whereas sapropterin is a synthetic preparation of the naturally occurring cofactor of PAH, causing a more immediate effect on blood Phe, pegvaliase demonstrates increasing efficacy over time as the dose is increased and the immunological response settles. The high SDs in the pegvaliase group reflect the considerable variation between patients in response to pegvaliase after 1 and 2 years of treatment. This variation is likely due to differences in immune response to pegvaliase. The immune response influences the dosing and the time period necessary to achieve efficacy.

The smaller proportion of patients reaching a blood Phe level of ≤600 and ≤360 μmol/L in the "sapropterin + diet" group in the uncontrolled patients analyses may be partly explained by the fact that some patients may have become less adherent to the dietary restriction that is still required when receiving sapropterin treatment. In addition, patients with more residual enzyme activity tend to have the best response to sapropterin [14]. These are generally the patients with lower blood Phe concentrations, who were excluded from the uncontrolled patients analyses. The analyses also showed a lack of change in blood Phe in the "diet alone" group, confirming the significant body of evidence regarding challenges with long-term adherence to a Phe-restricted diet [6].

The comparative safety results show that all patients treated with pegvaliase experienced drug-related AEs, mostly hypersensitivity events. About 10% of patients experienced drug-related SAEs, including anaphylaxis. This observation is in line with published findings [23], which also showed that most AEs associated with pegvaliase are mild or moderate in severity and mainly occur during induction and titration (first 6 months of treatment). Sapropterin previously showed good tolerability in clinical trials, with most AEs being mild or moderate in severity [15,16]. However, the incidence of AEs in the present analysis was considerably lower than that reported in the clinical trials, despite a longer follow-up time [15–20]. This is likely due to the voluntary nature of the PKUDOS registry, resulting in a less thorough documentation of AEs. Due to the differences in study designs between the pegvaliase clinical trials and the PKUDOS registry, the comparative safety data presented here should be interpreted with caution.

The results of the controlled patients analysis comparing the effectiveness of "diet alone" and "sapropterin + diet" in adult patients with blood Phe ≤600 μmol/L suggested a long-term favorable impact of sapropterin on blood Phe concentration versus diet alone, confirming published clinical study data [15,18–20]. It should be noted that the favorable effects of sapropterin are limited to those patients responsive to the therapy (generally defined as a decrease in blood Phe ≥30% [14]). The decision whether to try sapropterin treatment in adults with blood Phe ≤600 μmol/L depends on genotype (suggestive of residual enzymatic activity), untreated blood Phe concentration, the patient's level of compliance, and other factors such as pregnancy, executive function deficits, attention problems, and patient preference. Published studies overall report response rates to sapropterin between 20% and 60%, depending on the study population selected and response criteria used [14].

For the analyses comparing pegvaliase with standard treatments (uncontrolled patients analyses), the ITM population from the pegvaliase clinical trials and the PKUDOS registry were selected as the most suitable data sources. The ITM dosing regimen used in the clinical trials best approximates dosing as per on the label. PKUDOS is currently the largest and most complete database following long-term safety and efficacy of subjects on or previously on sapropterin [21]. Nevertheless, comparing clinical trial data with an historical comparator is subject to several challenges [40]. The quality of the outcome information extracted and recording criteria differed between studies. The pegvaliase clinical trial protocol mandates regular blood Phe measurements, while PKUDOS is a voluntary observational registry based on routine care with a higher proportion of missing data and no protocol-required measurements. Patients in the clinical trials with pre-defined study visits may have received preferential monitoring and care compared to the historical comparator participants, who may not have been included in a study at the time of their observation. We attempted to compensate for the more frequent measurements in the pegvaliase clinical trials versus PKUDOS by conducting the outcomes comparison at set cross-sectional time points, which included only patients with data recorded near that time point. Although some of the matched pair patients were excluded in the year 1 and year 2 analysis due to lack of data near the time point, the baseline Phe concentration and natural intact protein intake for the patients contributing outcomes data were similar (Tables 3 and 5).

As the patient populations derived from the pegvaliase clinical trials and PKUDOS were not randomized to treatment regimens, a post-hoc controlled analysis had to be applied. To address potential selection bias and confounding baseline factors, propensity score matching was applied [36,37]. This method was selected because it provides a covariate balance in most circumstances, and yields results that are easy to analyze and interpret [36]. It is particularly useful for assessing the relative effectiveness of promising new treatments for rare diseases such as PKU, for which only a few treatment options are available and comparative data are limited.

One limitation of the propensity score approach used in the pegvaliase comparative analyses is a loss of patient numbers with each additional covariate, due to missing or incomplete data from the historical cohorts (PKUDOS). However, the propensity score variables age, gender, and baseline blood Phe used in the primary uncontrolled patients analyses are considered clinically relevant, as they provide information on disease severity and patient characteristics that may impact treatment adherence and outcomes [35]. While treatment adherence tends to decrease with age [28], female patients may have better adherence than men, as women of reproductive age are generally followed up more closely to prevent maternal issues and adverse fetal outcomes [9]. Higher (untreated) blood Phe concentrations have been linked to a greater disease severity [1]. However, it should be noted that baseline Phe data used in the analyses may be diet-treated values rather than untreated values. The addition of baseline dietary Phe (which may provide an inference of Phe tolerance, used in the determination of disease severity) in the sensitivity analyses did not change the results appreciably, suggesting age, gender, and baseline blood Phe do an adequate job of balancing the two groups. Other factors that could have given more information about PKU severity are genotype, measured Phe tolerance, and untreated blood Phe concentration. However, these data were only very sparsely reported in PKUDOS, or not measured in a standardized fashion (Phe

tolerance), and thus could not be used. It was also not possible to control/match for other comparators that could impact outcome such as intelligence quotient, neuropsychological deficits, socioeconomic status, insurances status, or differences in clinical approach among healthcare providers.

Although the impact of differences in confounding baseline variables was minimized by applying propensity score matching, certain potential selection biases should be kept in mind when interpreting the results of the uncontrolled patients analyses, including patients with baseline blood Phe > 600 μmol/L. As all patients in the "diet alone" group had previous exposure to sapropterin, they may not be fully representative of typical patients on diet alone. These patients may have discontinued sapropterin due to a lack of response, or due to changes in insurance status or personal reasons. Additionally, in the uncontrolled patients primary analysis, mean natural intact protein intake in the "diet alone" group was somewhat lower at baseline than in the pegvaliase group. As baseline blood Phe was matched, this suggests a selection bias towards slightly more severe phenotypes in the "diet alone" group (i.e. comparable blood Phe despite lower natural intact protein intake). The impact of this selection bias on treatment outcome was likely limited, as results were comparable in the sensitivity analysis, which also balanced both populations for baseline dietary Phe. The "sapropterin + diet" group used in the pegvaliase comparative analyses likely only included patients responsive to sapropterin, who typically have milder phenotypes with lower untreated blood Phe concentrations than non-responders. Despite these potential biases, the "diet alone" and "sapropterin + diet" groups were considered acceptable to act as 'controls' in the pegvaliase comparative analyses as baseline patient characteristics are not expected to influence outcomes of pegvaliase treatment, which is mainly driven by immunological factors rather than phenotype.

A limitation of the controlled patient analysis, including patients with blood Phe ≤600 μmol/L, is that the "diet alone" and "sapropterin + diet" groups were not matched. Nevertheless, both groups were derived from the same registry (PKUDOS) and had a comparable mean blood Phe concentration at baseline. The higher mean baseline natural intact protein intake in the "sapropterin + diet" versus the "diet alone" group suggests a selection bias towards less severe PKU in the "sapropterin + diet" group. As the patients in the "diet alone" group recently discontinued sapropterin, some of them may have been more closely managing their diet since they no longer had the additional pharmacological support, possibly explaining their lower dietary Phe intake at baseline. The differences in baseline characteristics between both groups may have slightly influenced the analysis towards better outcomes in the "sapropterin + diet" group.

5. Conclusions

In the absence of head-to-head comparative clinical trials, the present analyses provide valuable new insights into the relative effectiveness of currently available treatments for adults with PKU. Overall, the outcomes of the analyses suggest that pegvaliase more effectively reduces blood Phe concentration and increases natural intact protein intake than "sapropterin + diet" in patients with blood Phe > 600 μmol/L. Pegvaliase is the first treatment for PKU that reduces blood Phe to target levels, while allowing a diet with

intact protein intake approaching amounts meeting the recommended dietary intake for this macronutrient for the general population. Therefore, it can be considered the more effective treatment option for adults with PKU who have difficulty keeping blood Phe ≤600 μmol/L with diet alone or diet + sapropterin. Given the neurological and systemic burden of elevated blood Phe, and the burden of a Phe-restricted diet for adults with PKU, the effects of pegvaliase may considerably improve patients' long-term outcome and overall QoL [23].

For adults with PKU who have a milder PKU phenotype or a better control of blood Phe, adding sapropterin to dietary treatment may be a valid option to further reduce blood Phe, for those responsive to the treatment. As demonstrated by the analysis of the "diet alone" versus "sapropterin + diet" groups, many patients cannot achieve blood Phe targets via diet alone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing 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 upon request. Investigators will be able to request access to these data and supporting documents via a website (www.BioMarin.com) beginning 6 months and ending 2 years after publication. Data associated with any ongoing development program will be made available within 6 months after approval of 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 publically available criteria available at www.BioMarin.com to determine if access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc.

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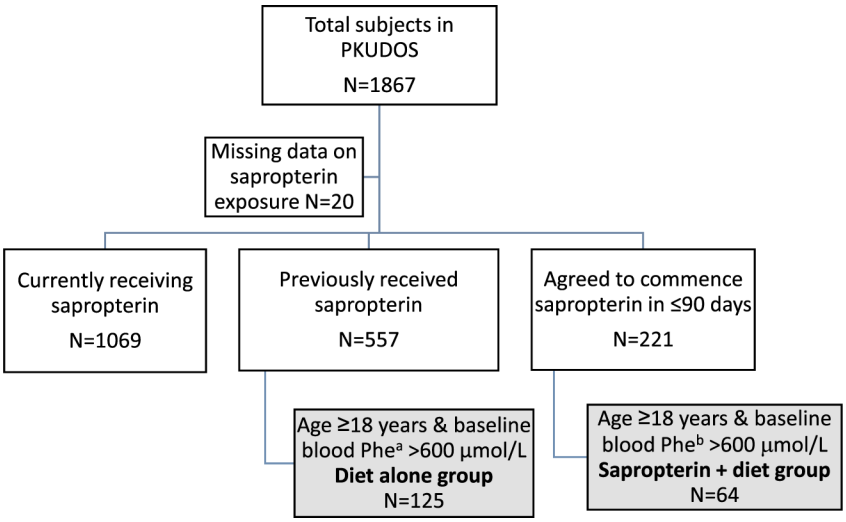

Fig. 1.

Selection of historical cohort patients for the “sapropterin + diet” and “diet alone” groups from PKUDOS. [a]In the "diet alone" group, baseline blood Phe was the measurement closest to the enrollment date within 90 days in case sapropterin was discontinued before enrollment. If sapropterin was discontinued after enrollment, it was the value closest to the discontinuation date within 90 days of discontinuation. [b]In the “sapropterin + diet” group, baseline blood Phe was the last available measurement prior to initiating sapropterin.

Table 1

PICOS criteria used in the selection of studies for generating evidence on the comparative effectiveness of treatments for adults with phenylketonuria (PKU).

Parameter	Inclusion criteria	
	Uncontrolled patients analyses	**Controlled patients analysis**
Patients	Adult US PKU patients with blood Phe > 600 μmol/L	Adult US PKU patients with blood Phe ≤600 μmol/L
Interventions	Diet alone or sapropterin in conjunction with diet or pegvaliase	Diet alone or sapropterin in conjunction with diet
Comparators	Data from PKU patients from the PKUDOS registry versus patients receiving ITM dosing (as per FDA approved label) in the pegvaliase phase 2 (165–205 study) and phase 3 (PRISM) clinical trials	Data from PKU patients from the PKUDOS registry
Outcomes	Change in blood Phe and natural protein intake	Change in blood Phe and natural protein intake
Study design	1 and 2 years, to align with the long-term pegvaliase clinical trial data	1 and 2 years

FDA: Food and Drug Administration; ITM: induction, titration, and maintenance; PKUDOS: PKU Demographics, Outcome and Safety.

Table 2

Baseline characteristics of the “sapropterin + diet” and pegvaliase groups for the uncontrolled patients analyses (baseline Phe > 600 μmol/L) generated using three factor (baseline age, gender, and baseline blood Phe concentration) propensity score matching.

		Sapropterin + diet (N = 64)	**Pegvaliase (N = 64)**
Gender	Female n (%)	37 (58%)	38 (59%)
	Male n (%)	27 (42%)	26 (41%)
Age, years	Mean (SD)	33 (10)	32 (9)
	Min, Max	18, 55	18, 54
Baseline blood Phe, μmol/L	Mean (SD)	1176 (383)	1172 (329)
	Median	1198	1146
	Min, Max	624, 2258	601, 1942
Baseline natural intact protein intake, g/day[a]	N	31	56
	Mean (SD)	36 (31)	33 (19)
	Median	30	29
	Min, Max	0, 120	4, 85
Follow-up duration for Phe assessment during treatment, days	Mean (SD)	1392 (1079)	840 (562)
	Median	1103	904
	Min, Max	1, 3386	22, 1869

[a]For “sapropterin + diet” subjects: natural intact protein intake (g/day) = total protein intake - medical food protein intake; for pegvaliase subjects: natural intact protein intake = average dietary protein intake from intact food (g/day). Treatment groups were not matched for baseline natural intact protein intake.

Table 3

Clinical outcomes of the uncontrolled patients analysis (baseline Phe > 600 μmol/L) comparing "sapropterin + diet" versus pegvaliase at 1 and 2 years follow-up using three-factor (baseline age, gender, and baseline blood Phe concentration) propensity score matching.

		Year 1		Year 2	
		Sapropterin + diet *N* =25	**Pegvaliase *N* =43**	**Sapropterin + diet *N*= 25**	**Pegvaliase *N*= 40**
Blood Phe (μmol/L): mean (SD) year 1&2[a]		807 (389)	505 (509)	891 (381)	427 (527)
Natural intact protein intake (g): mean (SD) year 1&2[b]		23 (18)[c]	49 (28)[d]	28 (18)[e]	57 (29)[f]
N (%) of patients achieving at year 1&2	≤600 μmol/L	7 (28%)	24 (56%)	5 (20%)	27 (68%)
	≤360 μmol/L	2 (8%)	22 (51%)	2 (8%)	26 (65%)
	≤120 μmol/L	0 (0%)	18 (42%)	0 (0%)	18 (45%)
N (%) of patients achieving percent reduction from baseline at year 1&2	≥20% reduction in blood Phe	16 (64%)	28 (65%)	10 (40%)	30 (75%)
	≥30% reduction in blood Phe	10 (40%)	27 (63%)	8 (32%)	30 (75%)
	≥50% reduction in blood Phe	5 (20%)	26 (61%)	3 (12%)	26 (65%)

[a] Mean (SD) baseline blood Phe concentration for patients included in 1-year analysis: "sapropterin + diet" 1075 (SD 419) μmol/L, pegvaliase 1180 (SD 317) μmol/L; 2-year analysis: "sapropterin + diet" 1060 (SD 337) μmol/L, pegvaliase 1195 (323) μmol/L.

[b] Mean (SD) baseline natural intact protein intake for patients included in 1-year analysis: "sapropterin + diet" 36 (38) g/day, pegvaliase 34 (20) g/day; 2-year analysis: sapropterin + diet" 35 (25) g/day, pegvaliase 35 (21) g/day.

[c] N = 4.

[d] N = 38.

[e] N = 7.

[f] N = 35.

Table 4

Baseline characteristics of the “diet alone” and pegvaliase groups for the uncontrolled patients analyses (baseline Phe > 600 µmol/L) generated using three-factor (baseline age, gender, and baseline blood Phe concentration) propensity score matching.

Parameters		Diet alone (N = 125)	Pegvaliase (N = 125)
Gender	Female n (%)	56 (45%)	56 (45%)
	Male n (%)	69 (55%)	69 (55%)
Age, years	Mean (SD)	31 (11)	30 (8)
	Min, Max	18, 68	18, 56
Baseline blood Phe, µmol/L	Mean (SD)	1089 (302)	1085 (294)
	Median	1038	1051
	Min, Max	605, 1872	601, 1764
Baseline natural intact protein intake, g/day[a]	N	62	107
	Mean (SD)	25 (19)	34 (24)
	Median	20	28
	Min, Max	0, 75	5, 156
Follow-up duration for Phe assessment during treatment, days	Mean (SD)	1149 (979)	883 (598)
	Median	1086	953
	Min, Max	1, 3254	14, 1986

[a]For “diet alone” subjects: natural intact protein intake (g/day) = total protein intake - medical food protein intake; for pegvaliase subjects: natural intact protein intake = average dietary protein intake from intact food (g/day). Treatment groups were not matched for baseline natural intact protein intake.

Table 5

Clinical outcomes of the uncontrolled patients analysis (baseline Phe > 600 μmol/L) comparing "diet alone" versus pegvaliase at 1 and 2 years follow-up using three-factor (baseline age, gender, and baseline blood Phe concentration) propensity score matching.

		Year 1		Year 2	
		Diet alone *N* = 51	**Pegvaliase *N* = 87**	**Diet alone *N* = 42**	**Pegvaliase *N* = 80**
Blood Phe (μmol/L): mean (SD) year 1&2[a]		1022 (322)	473 (451)	965 (359)	302 (392)
Natural intact protein intake (g): mean (SD) year 1&2[b]		27 (25)[c]	47 (22)[d]	22 (16)[e]	57 (26)[f]
N (%) of patients achieving at year 1&2	≤600 μmol/L	3 (6%)	52 (60%)	5 (12%)	63 (79%)
	≤360 μmol/L	0 (0%)	41 (47%)	1 (2%)	58 (72%)
	≤120 μmol/L	0 (0%)	34 (39%)	0 (0%)	37 (46%)
N (%) of patients achieving percent reduction from baseline at year 1&2	≥20% reduction in blood Phe	13 (26%)	62 (71%)	13 (31%)	68 (85%)
	≥30% reduction in blood Phe	9 (18%)	58 (67%)	9 (21%)	65 (81%)
	≥50% reduction in blood Phe	0 (0%)	50 (58%)	3 (7%)	59 (74%)

[a]Mean (SD) baseline blood Phe concentration for patients included in 1-year analysis: "diet alone" 1037 (271) μmol/L, pegvaliase 1089 (289) μmol/L; 2-year analysis: "diet alone" 1051 (302) μmol/L, pegvaliase 1107 (293) μmol/L.

[b]Mean (SD) baseline natural intact protein intake for patients included in 1-year analysis: "diet alone" 22 (20) g/day, pegvaliase 33 (20) g/day; 2-year analysis: "diet alone" 23 (22) g/day, pegvaliase 33 (20) g/day.

[c]N = 18.

[d]N = 76.

[e]N = 16.

[f]N = 71.

Table 6

Clinical outcomes of the controlled patients analysis (baseline Phe ≤600 μmol/L) comparing “diet alone” versus “sapropterin + diet” at 1 and 2 years follow-up in patients from PKUDOS with baseline blood Phe ≤600 μmol/L and age ≥ 18 years.

		Year 1		Year 2	
		Diet alone N = 22	**Sapropterin + diet N = 11**	**Diet alone *N* = 21**	**Sapropterin + diet *N* = 11**
Blood Phe (μmol/L): mean (SD) year 1&2[a]		580 (324)	240 (92)	549 (282)	324 (157)
Natural intact protein intake (g): mean (SD) year 1&2[b]		9 (6)[c]	12 (12)[d]	14 (10)[e]	42 (12)[f]
N (%) of patients achieving at year 1&2	≤600 μmol/L	13 (59%)	11 (100%)	11 (52%)	10 (91%)
	≤360 μmol/L	6 (27%)	10 (91%)	5 (24%)	9 (82%)
	≤120 μmol/L	1 (5%)	0 (0%)	1 (5%)	0 (0%)
N (%) of patients achieving percent reduction from baseline at year 1&2	≥20% reduction in blood Phe	3 (14%)	10 (91%)	5 (24%)	9 (82%)
	≥30% reduction in blood Phe	2 (9%)	8 (73%)	4 (19%)	7 (64%)
	≥50% reduction in blood Phe	0 (0%)	6 (55%)	3 (14%)	2 (18%)

[a] Mean (SD) baseline blood Phe concentration for patients included in 1-year analysis: “diet alone” 408 (134) μmol/L, “sapropterin + diet” 403 (151) μmol/L; 2-year analysis: “diet alone” 431 (139) μmol/L, “sapropterin + diet 422 (156) μmol/L.

[b] Mean (SD) baseline natural intact protein intake for patients included in 1-year analysis: “diet alone” 21 (17) g/day, “sapropterin + diet” 31 (18) g/day; 2-year analysis: “diet alone” 18 (14) g/day, “sapropterin + diet” 26 (17) g/day.

[c] N = 3.

[d] N = 3.

[e] N = 7.

[f] N = 2.