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Kuvan® Adult Maternal Paediatric European Registry (KAMPER): Final results in phenylketonuria (PKU) patients

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Introduction

- Phenylketonuria (PKU) is a rare inherited metabolic disorder leading to the accumulation of phenylalanine (Phe) in the blood and brain[1,2]
- If left untreated, high Phe levels can result in neurodevelopmental delay in infants and young children, and decreased neurocognitive function in older children and adults[3]
- Sapropterin dihydrochloride (Kuvan®, BioMarin Pharmaceutical Inc., Novato, CA) is approved for use in Europe for the treatment of hyperphenylalaninaemia (HPA) in tetrahydrobiopterin (BH_4)-responsive patients with PKU or BH_4 deficiency, to reduce blood Phe levels and improve Phe tolerance[4]

Objective

- To provide results from the final analysis of the KAMPER registry to assess the long-term safety and efficacy of sapropterin treatment in patients with HPA associated with PKU, in a real-world setting

Methods

- The Kuvan Adult Maternal Paediatric European Registry (KAMPER; NCT01016392) is an observational, multi-centre, multinational drug registry to assess long-term safety and efficacy of patients with HPA associated with PKU[5]
- Adult or paediatric patients recruited into KAMPER had HPA due to phenylalanine hydroxylase deficiency, had been responsive to sapropterin or BH_4 (≥30 % reduction in blood Phe level), and were receiving sapropterin treatment
- Exclusion criteria included patients with known hypersensitivity to sapropterin and patients who were breast-feeding (temporary exclusion for breastfeeding was allowed for patients already in the study)
- Five years of follow-up data are reported for blood Phe levels, sapropterin dose, dietary Phe intake, neurological/behavioral outcomes and work/academic assessments. Full follow-up data are reported for growth and adverse events (AEs)

Results

Patient Disposition

- Across nine countries (Austria, France, Germany, Italy, the Netherlands, Portugal, Slovakia, Spain and Sweden), 627 patients were enrolled at 69 sites and data from 576 patients with PKU were included (**Table 1**)
- Most PKU patients (89.8%, n=517) were diagnosed via newborn screening

Table 1. Patient demographics

	PKU population (n=576)
Age* (years), median (min; max)	10.1 (1.4; 46.5)
<4 years, n (%)	11 (1.9)
4–<12 years, n (%)	329 (57.1)
12–<18 years, n (%)	141 (24.5)
18–<65 years, n (%)	95 (16.5)
Gender, n (%)	
Male	284 (49.3)
Female	292 (50.7)
Ethnicity, n (%)	
White	554 (96.2)
Black	1 (0.2)
Asian	0
Other	22 (3.8)

*Age at informed consent

Safety

- Overall, 401 (69.6%) of PKU patients experienced a total of 1960 AEs
- The most frequently reported sapropterin-related AEs were nervous system disorders (32 events in 25 patients: 25 events of headache, 3 of migraine, 2 of disturbance in attention, 1 of hyposmia, 1 of tremor) and gastrointestinal disorders (17 events in 16 patients: 11 events of abdominal pain, 2 of nausea, 1 of upper abdominal pain, 1 of diarrhea, 1 of gastritis, 1 of vomiting) (**Table 2**)
- A total of 61 events in 42 PKU patients were considered SAEs, of which only two were considered sapropterin-related by the investigator: severe headache and mild sapropterin overdose (considered unrelated by the sponsor)

Table 2. Adverse events considered sapropterin-related, occurring in ≥1 patients with PKU

System organ class	Patients n (%)	Events n
Any AE	56 (9.7)	76
Nervous system disorders	25 (4.3)	32
Gastrointestinal disorders	16 (2.8)	17
Respiratory, thoracic and mediastinal disorders	6 (1.0)	7
Infections and infestations	6 (1.0)	6
Investigations	3 (0.5)	3
Skin and subcutaneous tissue disorders	3 (0.5)	3
Musculoskeletal and connective tissue disorders	2 (0.3)	3
Injury, poisoning and procedural complications	2 (0.3)	2
General disorders and administration site conditions	1 (0.2)	1
Metabolism and nutrition disorders	1 (0.2)	1
Psychiatric disorders	1 (0.2)	1

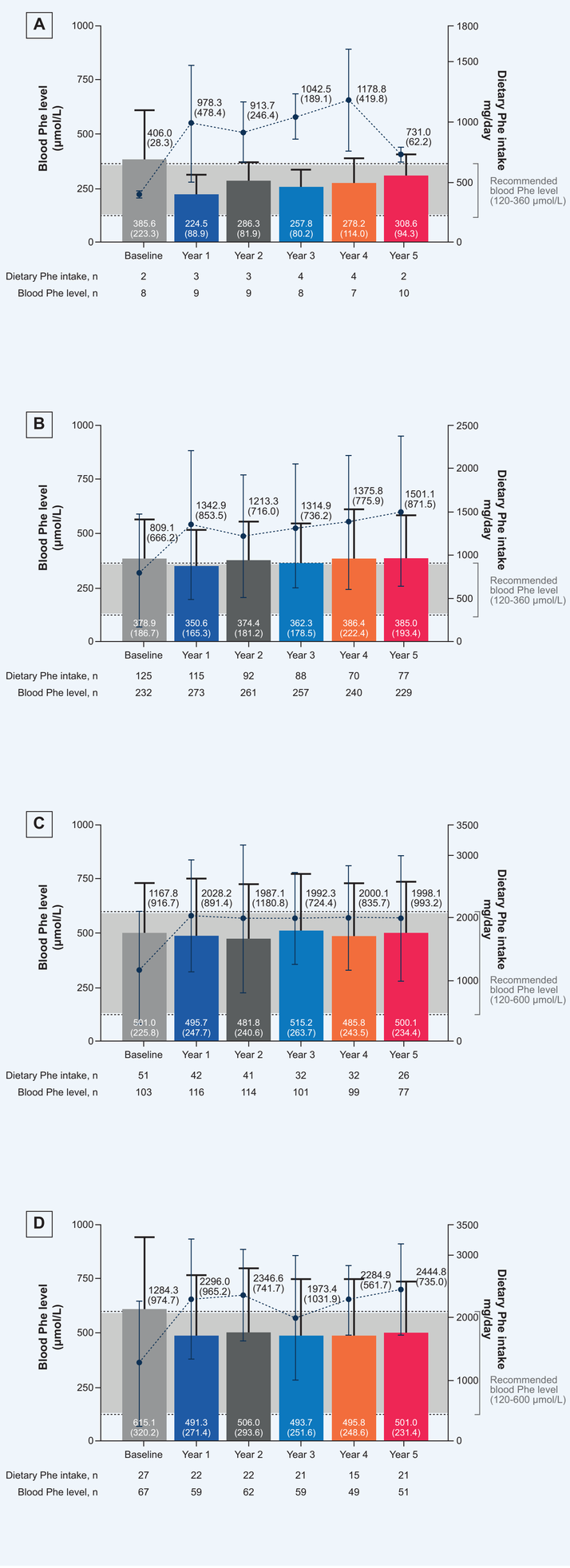
Blood Phe levels

- Mean blood Phe levels remained within recommended EU guideline levels of 120–≤360 µmol/L for younger patients aged 0–<12 years of age and 120–≤600 µmol/L for older patients aged 12–<65 years over 5-years of follow-up (**Figure 1**)

Dietary Phe Intake

- Overall, PKU patients increased their natural protein and dietary Phe intake from baseline to Year 1, which remained relatively stable for all age groups over 5-years of follow up **(Figure 1)**
- In patients with PKU, dietary Phe tolerance increased from baseline to Year 5 of follow-up. Dietary Phe increased from 957.0 (799.1) mg/day to 1748.7 (945.7) mg/day while blood Phe levels were maintained within the recommended range (120–≤360 µmol/L for children and 120–≤600 µmol/L for adults) (**Figure 1**)

Figure 1. Mean (SD) blood Phe level and mean dietary Phe intake by age group at baseline and five years of follow-up in patients with PKU. (A) <4 years; (B) 4–<12 years; (C) 12–<18 years; (D) 18–<65 years

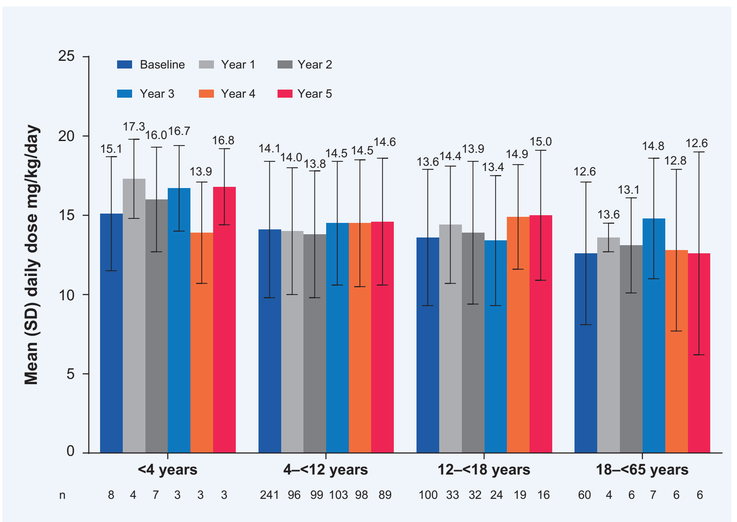


n and means are calculated from the patients with intake>0. Data shown are at yearly visits only, measures were also made at interim 6, 18, 30, 42 and 50 month visits.

Sapropterin dose

- Median (Q1; Q3) sapropterin dose was 14.2 mg/kg/day (10.0; 17.6) at baseline and 15.7 mg/kg/day (11.5; 18.1) at 5-years of follow-up
- Mean daily dose remained relatively stable throughout 5 years of follow-up in all age groups (**Figure 2**)

Figure 2. Mean daily dose of sapropterin by age group at baseline and five years of follow-up



Data shown are at yearly visits only, measures were also made at interim 6, 18, 30, 42 and 50 month visits.

Growth rates

- Overall, across gender and age groups for the majority of PKU patients, z-scores for height, weight and BMI did not deviate greater than one standard deviation (SD) from baseline, or at any follow-up time point
- A small proportion of females were overweight (n=13, 13.7%) or obese at baseline (n=2, 2.1%), with fluctuations of 2.4–10.1% throughout follow-up

Neurological/Behavioural Outcomes

- At baseline, the most common psychiatric/behaviour symptoms reported overall included attention deficit disorder (ADD)/attention deficit hyperactivity disorder (ADHD) and anxiety disorders
- At baseline, refusal to drink formula, bed wetting, anger management and aggression were the most commonly reported behavioural conditions
- At follow-up, 28 new neurological conditions emerged: tremor (n=26), ataxia (n=1) and history or seizures (n=1), but most pre-existing conditions remained unchanged or improved

School/Work Performance

- At baseline, of 390 PKU patients in school, 355 patients (91.0%) were at the appropriate school level. At 5 years of follow-up, <4 years: 100.0% (n=8), 4–<12 years: 95.3% (n=221), 12–<18 years: 90.0% (n=40), 18–<65 years: 100.0% (n=4) were at the appropriate school level
- At baseline, of 50 patients with work performance data 27 patients (54.0%) worked full-time, 9 (18.0%) worked part-time, and 14 (28.0%) were unemployed. At 5 years of follow-up, of 38 patients 18–<65 years with work performance data, 26 patients (68.4%) worked full-time, 5 (13.2%) worked part-time, and 7 (18.4%) were unemployed

Limitations

- Blood Phe level was not routinely collected at all follow-up visits. In addition, blood collection and blood analysis methods differed across sites
- Most PKU patients enrolled were 4–<18 years of age, and patients in specific subgroups of interest, such as patients <4 years of age, had limited enrolment in the registry. Other subgroups of interest such as elderly patients, and patients with renal or hepatic insufficiency, were not enrolled in the registry

Conclusions

- Results from the final analysis of the KAMPER registry for PKU patients continues to show that sapropterin treatment has a favourable safety profile with long-term use, demonstrates appropriate growth rates, and maintains education status
- Most PKU patients increased their dietary Phe intake while maintaining mean blood Phe levels around the recommended levels from baseline to Year 5 of follow-up, suggesting an increase in Phe tolerance
- No new safety concerns have been identified

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Disclosures

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