163/PT

# Effect of sapropterin dihydrochloride on IQ preservation in children (aged 0–6 years) with phenylketonuria

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## Background

- Phenylketonuria (PKU) is a rare, inherited, inborn error of metabolism characterized by elevated blood phenylalanine (Phe) levels caused by deficient activity of the enzyme phenylalanine hydroxylase (PAH); and is typically diagnosed via newborn screening programs[1]
- Elevated blood-Phe levels are neurotoxic and if untreated or poorly controlled, especially during early development, can lead to mild-to-severe intellectual disability and other neurological sequelae[2–3]
- To prevent neurological damage, ACMG guidelines in the US recommend life-long treatment to maintain blood Phe in the range 120–360 µmol/L
- A Phe-restricted diet, supplemented with Phe-free medical foods, has been associated with nutritional deficiency and impaired growth
- Even those children who initiate diet early have significantly lower IQ scores compared with matched controls[4–9]
- Sapropterin dihydrochloride (sapropterin; Kuvan®, BioMarin Pharmaceutical Inc., Novato, CA), a synthetic formulation of 6R-BH4 (the natural co-factor of PAH), is indicated to reduce blood Phe levels, in conjunction with a Phe-restricted diet, in patients of all ages with BH4-responsive PKU[10]

## Methods

- The primary objective of PKU-015 (NCT00838435) was to evaluate the long-term efficacy of sapropterin (20 mg/kg/day) over the 7-year study period in young children who initiated treatment at 0-6 years
- The primary endpoint was maintenance of Full-Scale Intelligence Quotient (FSIQ), as assessed by the WPPSI-III and WISC-IV; maintenance was defined as a decline of <5 points of the lower confidence limit (LCL) over a 2-year window and over the 7-year study period

### Figure 1. Schedule of age-appropriate neurocognitive assessments

7 years

4 weeks

| PART 1 Sapropterin responsiveness | PART 2 Long-term safety, efficacy, and neurocognitive function | |
|---|---|---|
| | **Assessments** | **Frequency** |
| | Anthropometrics<br>Height<br>Weight<br>Head circumference (<4 years) | Monthly |
| | PKU Specific Measures<br>Dietary Phe Intake<br>Blood Phe | Monthly |
| | Age-Appropriate Neurocognitive Assessments<br>Bayley-III (0 to <30 months)<br>WPPSI-III form 1 (≥30 months to <4 years)<br>WPPSI-III form 2 (≥4 to <7 years)<br>WISC-IV (≥7 years) | <br>Every 6 months ± 2 weeks<br>Once a year ± 2 weeks<br>Once a year ± 2 weeks<br>Every 2 years ± 2 weeks |
| | Safety | Continuously |

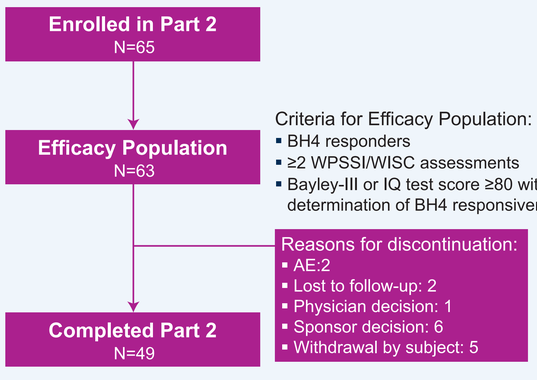
Bayley: Bayley Scales of Infant and Toddler Development
WPPSI: Wechsler Preschool and Primary Scale of Intelligence
WISC: Wechsler Intelligence Scale for Children

## Results

### Participant Disposition

- Of the 95 participants enrolled in Part 1, 71 (74.7%) were BH4-responsive, of which 65 (91.5%) enrolled in Part 2. Part 2 participant disposition is shown in **Figure 2**

### Figure 2. Participant disposition




### Table 1. Baseline characteristics

| Characteristic | Age group (years) 0 to <1 (n=11) | 1 to <2 (n=11) | 2 to <4 (n=23) | 4 to 7 (n=20) | Overall (N=65) |
|---|---|---|---|---|---|
| **Age at enrollment** Mean (SD), years | 0.4 (0.3) | 1.4 (0.3) | 3.0 (0.7) | 5.6 (1.0) | 3.1 (2.0) |
| **Sex** Female, n (%) | 6 (54.5%) | 5 (45.5%) | 15 (65.2%) | 14 (70.0%) | 40 (61.5%) |
| **Race** White, n (%) | 9 (81.8%) | 9 (81.8%) | 18 (78.3%) | 18 (90.0%) | 54 (83.1%) |
| **Blood Phe** Mean (SD), µmol/L | 298.4 (119.7) | 366.5 (107.2) | 337.0 (135.5) | 332.0 (158.8) | 333.9 (135.0) |
| **Weight** | | | | | |
| kg, Mean (SD) | 7.3 (2.0) | 11.1 (1.6) | 15.2 (2.3) | 22.0 (3.6) | 15.2 (5.9) |
| Z-score, Mean (SD) | 0.25 (0.94) | 0.00 (0.86) | 0.48 (0.75) | 0.69 (0.77) | 0.42 (0.83) |
| Percentile, Mean (SD) | 58.9 (28.9) | 51.0 (28.3) | 65.0 (23.1) | 70.6 (22.0) | 63.3 (25.1) |
| **Height** | | | | | |
| cm, Mean (SD) | 64.9 (5.7) | 81.0 (3.8) | 96.0 (7.2) | 114.8 (6.5) | 94.0 (18.7) |
| Z-score, Mean (SD) | 0.21 (1.15) | 0.47 (0.72) | 0.41 (1.05) | 0.47 (0.91) | 0.41 (0.96) |
| Percentile, Mean (SD) | 60.7 (25.6) | 64.7 (20.8) | 61.2 (29.9) | 62.4 (24.6) | 62.1 (25.7) |
| **Head circumference** | | | | | |
| cm, Mean (SD) | 42.1 (2.9) | 47.3 (1.5) | 49.4 (2.4) | 51.3 (1.2) | 48.4 (3.8) |
| Z-score, Mean (SD) | -0.01 (0.66) | 0.38 (1.01) | 0.48 (1.25) | NA | 0.28 (0.99) |
| Percentile, Mean (SD) | 49.4 (22.3) | 64.0 (27.2) | 65.6 (31.2) | NA | 59.6 (27.3) |
| **Baseline FSIQ** | | | | | |
| Efficacy population, n=63, Mean (SD) | – | – | – | – | 101.1 (14.0) |
| Sequence 1, n=4, Mean (SD) | – | – | – | – | 98.8 (15.4) |
| Sequence 2, n=55, Mean (SD) | – | – | – | – | 100.4 (14.0) |
| Sequence 3, n=4, Mean (SD) | – | – | – | – | 113.0 (9.8) |

Baseline is defined as the first available measurement date after determination of BH4 responsiveness. Sequence 1: WPPSI-III (first or second form) at all time points. Sequence 2: WPPSI-III (first or second form) at Baseline and WPPSI-III or WISC-IV at all post-baseline time points. Sequence 3: WISC-IV at all time points.

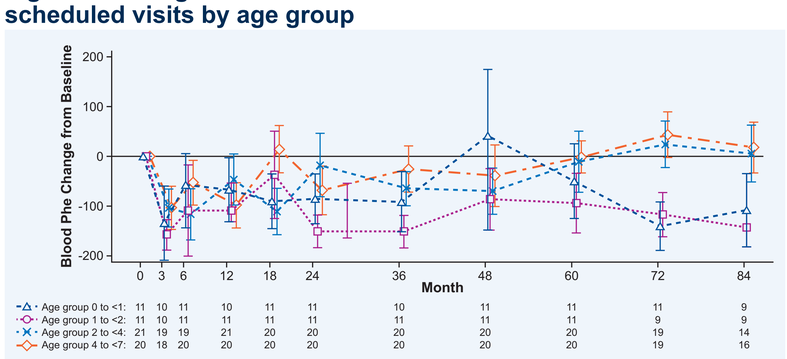
### Sapropterin adherence and exposure

- Adherence to sapropterin prescription during the study was high at 99.1%; the minimum level of adherence was >94% in all age groups. The mean total sapropterin exposure was 2379.5 days (6.5 years) with a maximum duration of 2596.0 days (7.1 years)

### Blood Phe control

- Overall blood Phe levels **(Figure 3)** decreased from baseline of mean (SD) 333.9 (135.5) µmol/L to the 3- and 6-month time points, then remained stable within the guideline-recommended range. This was consistent for all age groups

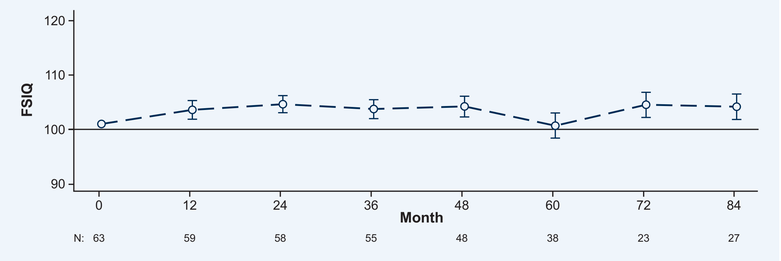
### Figure 3. Change in blood Phe concentrations from baseline to scheduled visits by age group




### Preservation of FSIQ was demonstrated in study participants

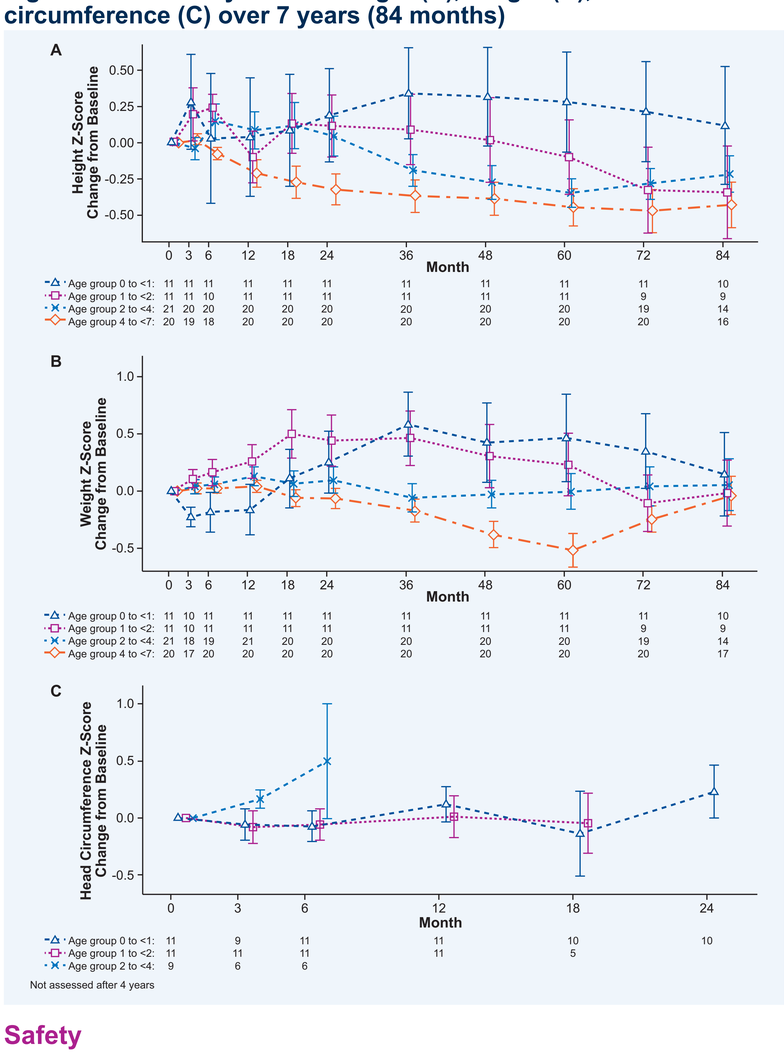
- The estimated mean change per year of FSIQ over the entire study period was -0.2884 with a 95% confidence interval (CI) of -0.8002 (lower limit), 0.2234 (upper limit). This yields a two-year window estimate of -0.5768 with a lower limit of the 95% CI of -1.6004, meeting the primary endpoint
- Consistent with the primary endpoint, an exploratory analysis in participants with at least 84 months of follow-up (n=27) found a change of FSIQ from baseline to 84 months (n=27) of 1.14, and a lower limit of the 95% CI of -3.53

### Figure 4. Change in FSIQ over time overall




- Growth was maintained within expected percentiles over seven years for height **(Figure 5A)**, weight **(Figure 5B)**, and head circumference **(Figure 5C)**

### Figure 5. Z-Score by visit for height (A), weight (B), and head circumference (C) over 7 years (84 months)




Not assessed after 4 years

### Safety

- Sapropterin was well tolerated in all age groups and there were no new safety signals
- All 65 subjects (100%) reported at least 1 AE during the study **(Table 2)**; AEs were largely mild to moderate
- The most common drug-related AEs (in >10% of participants) were upper respiratory tract infection (n=12, 18.5%), abdominal pain (n=10, 15.4%), vomiting (n=10, 15.5%), and diarrhea (n=8, 12.3%)
- Serious AEs (SAEs) assessed as possibly drug-related occurred in 2 subjects; events resolved in both subjects and though 1 subject required a dose interruption, neither discontinued sapropterin

### Table 2. Summary of AEs by age group

| Subjects with | Age group (years) 0 to <1 (n=11) | 1 to <2 (n=11) | 2 to <4 (n=23) | 4 to <7 (n=20) | Overall (N=65) |
|---|---|---|---|---|---|
| **Any AE** | 11 (100%) | 11 (100%) | 23 (100%) | 20 (100%) | 65 (100%) |
| Any drug-related AE | 6 (54.5%) | 4 (36.4%) | 14 (60.9%) | 11 (55.0%) | 35 (53.8%) |
| Any drug-related AE causing study discontinuation | 0 | 0 | 2 (8.7%) | 0 | 2 (3.1%) |
| Any drug-related AE causing permanent study drug discontinuation | 0 | 0 | 2 (8.7%) | 0 | 2 (3.1%) |
| **Any SAE** | 2 (18.2%) | 4 (36.0%) | 3 (13.0%) | 2 (10.0%) | 11 (16.9%) |
| Any drug-related SAE | 0 | 0 | 1 (4.3%) | 1 (5.0%) | 2 (3.1%) |
| Any drug-related SAE causing study discontinuation | 0 | 0 | 0 | 0 | 0 |
| **Death** | 0 | 0 | 0 | 0 | 0 |

Drug-related AE's were classified by the investigator as possibly or probably related to Kuvan. Mapping was based on MedDRA version 15.1.

## Conclusions

- Rigorous control of blood Phe is thought to be particularly critical during the rapid cognitive developmental periods in young children with PKU. However, blood Phe control with diet alone can be difficult, and studies have shown that children with PKU have lower IQ than matched controls[4–6]
- Despite advances in dietary management, achieving adequate nutrition can be challenging. This may be related to suboptimal growth in children with PKU, as demonstrated in a 2019 meta-analysis[9]
- In BH4-responsive participants who initiated therapy between 0–6 years of age, long-term use of sapropterin, in concert with a Phe-restricted diet, was associated with preserved IQ, normal growth, and a favorable safety profile in this study

**References**

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**Acknowledgments**

The authors would like to thank the study investigators, study coordinators, study site support staff, and study participants. Medical writing support was provided by Kaleigh Bulloch Whitehall (BioMarin). Poster design was provided by Terry Manspeaker.