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CLINICAL TRIAL

Effect of long-term sepiapterin treatment on dietary phenylalanine tolerance in patients with phenylketonuria: Interim results from the phase 3 APHENITY Extension Study

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ABSTRACT

Purpose: To report interim results from the ongoing, open-label, phase 3 APHENITY Extension Study (NCT05166161), evaluating long-term treatment with sepiapterin in patients with phenylketonuria.

Methods: Participants received an age-based dose of oral sepiapterin daily; those with mean blood phenylalanine (Phe) levels <360 μmol/L (<5.95 mg/dL) after 2 weeks underwent a 26-week dietary Phe tolerance assessment, wherein dietary Phe intake was adjusted and blood Phe levels monitored. Other participants continued treatment with optional diet liberalization. Primary endpoints included change from baseline to week 26 in dietary Phe intake and treatment-emergent adverse events (TEAEs).

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Phenylketonuria
Quality of life
Sepiapterin

Results: As of September 2, 2024, 169 participants received sepiapterin (median [minimum, maximum] age: 14.0 [0.2, 55.0] years, median exposure: 72.9 weeks); 102 participants underwent dietary Phe tolerance assessments. Mean (SD) dietary Phe intake increased from 27.6 (18.0) mg/kg/day at baseline to 62.5 (41.5) mg/kg/day at week 26 (least-squares mean change [SE]: 36.4 [2.8] mg/kg/day from baseline) ($P < .0001$ from post hoc analysis). The incidence of treatment-related TEAEs was 29.0%; 3 participants (1.8%) discontinued treatment owing to treatment-related TEAEs. There were no treatment-related serious TEAEs or deaths.
Conclusion: Interim results support the long-term safety of sepiapterin and demonstrate the potential for diet liberalization in adults and children with phenylketonuria.
ClinicalTrials.gov identifier: NCT05166161 (https://www.clinicaltrials.gov/study/NCT05166161; date of registration, December 8, 2021)

Introduction

Phenylketonuria (PKU; OMIM 261600) is an autosomal recessive inborn error of metabolism caused by a deficiency in the enzyme phenylalanine hydroxylase (PAH), which converts phenylalanine (Phe) to tyrosine (Tyr), leading to an increase in Phe levels in the blood and brain.[1,2] High Phe levels are toxic to the brain and, if untreated, can lead to severe, irreversible intellectual disability, neuropsychiatric impairment, and diminished health-related quality of life (HRQoL).[2,3]

The current standard of care for PKU is a Phe-restricted diet, with the goal of maintaining recommended blood Phe levels (United States, ≤360 μmol/L [≤5.95 mg/dL][4,5]; Europe and Australasia, 120-360 μmol/L for ages <12 years [1.98-5.95 mg/dL][2,6]; Europe, 120-600 μmol/L [1.98-9.91 mg/dL] for ages ≥12 years[2]; Australasia, ≤360 μmol/L [≤5.95 mg/dL] for ages ≥12 years, but >360 μmol/L [>5.95 mg/dL] may be appropriate in some cases[6]). However, long-term adherence to dietary management, which involves severe restriction of natural protein intake, can be challenging and may adversely affect growth, health, and nutrition.[7-10] Furthermore, many patients from adolescence onward do not achieve effective blood Phe control with dietary restrictions alone,[11] which can lead to impairments in attention, mood, memory, and executive function.[1,2]

According to European and US guidelines, an increase in natural protein intake is indicative of pharmacological treatment efficacy in patients with PKU[2,4]; in a survey of >600 patients, almost 80% stated a desire to increase their natural protein intake, provided there was no deterioration in PKU symptoms.[12] European guidelines recognize an increase in natural protein intake of >100% in response to sapropterin dihydrochloride as being meaningful, but it is acknowledged that in some patients (eg, those with a higher pretreatment protein tolerance), a smaller increase with reductions in Phe-free/low-Phe protein substitute can still be meaningful.[2]

Until recently, only 2 pharmacological treatments were approved to treat PKU in some countries.[3] Sapropterin dihydrochloride is an orally active synthetic form of tetrahydrobiopterin (BH_4) approved for the treatment of children and adults with hyperphenylalaninemia due to BH_4-responsive PKU when used in conjunction with a Phe-restricted diet.[13-16] However, only 25% to 50% of the overall PKU population are responsive to treatment,[5] and even in those who do respond, only a minority are able to stop natural protein restriction completely.[17] Pegvaliase is an enzyme substitution therapy indicated in patients with PKU aged ≥15 years (Japan), aged ≥16 years (European Union, Australia, Canada, and Brazil), and adults (United States) with inadequate control of blood Phe levels on existing management.[18-21] Although pegvaliase may increase dietary Phe tolerance,[22] its use is limited by a lengthy dose titration and time to efficacy, frequent hypersensitivity reactions, the need for up to 3-times daily to once weekly injections, and a lack of indication for PKU in infants, children and some adolescents (aged <16 years in the European Union and <18 years in the United States).[1,18,19,23] Therefore, there is an unmet need for more effective oral therapies for a broader PKU population, with minimal side effects and no additional burden.[2,5,12,24] Such therapies should allow for substantial relaxation of dietary restrictions, greater dietary freedom, and safe incorporation of protein with high nutritional biological value while maintaining Phe levels in the target range.

Sepiapterin, a novel treatment for PKU, was approved in the European Union, the United States, Australia, Switzerland, and Canada in 2025. It is a synthetic form of a natural precursor of the PAH cofactor BH_4, which increases intracellular BH_4 bioavailability and acts as a distinct pharmacological chaperone, leading to increased PAH enzymatic activity in both BH_4-responsive and nonresponsive patients.[3,25] In a 6-week phase 3 study in children and adults with PKU (APHENITY; NCT05099640), oral sepiapterin produced significant and clinically meaningful reductions in blood Phe levels (least-squares [LS] mean change versus placebo: −395.9 μmol/L [−6.54 mg/dL]) and was well tolerated, with no serious adverse events or deaths reported.[3]

An ongoing, open-label extension study (NCT05166161), which includes participants from

APHENITY, was initiated in 2022 to assess the long-term safety of sepiapterin and its effect on dietary Phe tolerance in children and adults with PKU. Here, long-term efficacy and safety from a prespecified interim analysis (data cutoff: September 2, 2024) are reported.

Materials and Methods

Study design

This is an ongoing phase 3, international, multicenter, open-label, long-term extension study of sepiapterin in patients with PKU (Supplemental Figure 1), conducted at 45 sites (clinics, hospitals, and university centers) across 19 countries. All participants receive oral sepiapterin once daily for ≥12 months. Participants with mean blood Phe <360 µmol/L (<5.95 mg/dL) during the first 2 weeks of the extension study underwent a 26-week dietary Phe tolerance assessment, during which dietary Phe intake was adjusted according to a prespecified algorithm (Supplemental Table 1) based on blood Phe levels (see Supplemental Methods for further details). Adjustments in prescribed supplemental low-Phe protein substitutes were not stipulated in the algorithm. Participants with mean blood Phe ≥360 µmol/L (≥5.95 mg/dL) (including those with acute illness) during the first 2 weeks of the extension continued sepiapterin but did not participate in the dietary Phe tolerance assessment.

Participants

The extension study includes participants with PKU who completed a phase 3 PTC-sponsored study, including APHENITY (rollover participants), and those not previously involved in a PTC-sponsored phase 3 study (newly enrolled participants). In APHENITY, participants were only eligible to take part in the randomized double-blind period if they responded to open-label sepiapterin.[3] Newly enrolled participants receiving pegvaliase or sapropterin dihydrochloride at study entry completed a washout period of 30 or 7 days, respectively. Those with blood Phe ≥360 µmol/L (≥5.95 mg/dL) after washout who had ≥15% reduction in blood Phe levels during the initial 14 days of sepiapterin treatment entered the extension study; those with <15% reduction discontinued. Participants with blood Phe <360 µmol/L (<5.95 mg/dL) after washout undertook a protein/Phe loading test and entered the extension study if blood Phe levels decreased by ≥15% at 1, 8, or 24 hours after administration of a sepiapterin dose (see Supplemental Methods for details and for full eligibility criteria).

Endpoints

The primary efficacy endpoint is the mean change in dietary Phe intake from baseline to weeks 25 and 26 (herein referred to as week 26) of the dietary Phe tolerance assessment period. Primary safety endpoints include treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, and physical examinations. Secondary endpoints include BH_4 and sepiapterin plasma concentrations and change from baseline in HRQoL scores, assessed using age-appropriate versions of the phenylketonuria-quality-of-life (PKU-QOL) questionnaire. Changes from baseline in blood Phe, Tyr, and Phe:Tyr ratio are exploratory efficacy endpoints. See Supplemental Methods for details.

Statistical analysis

The sample size calculation and the study populations analyzed (Dietary Phe Tolerance Analysis Set, Full Analysis Set, Safety Analysis Set, and Pharmacokinetic Analysis Set) are detailed in the Supplemental Methods.

Descriptive statistics were used to summarize baseline characteristics, daily dietary Phe intake, prescribed daily dietary Phe, and blood Phe levels. For the primary efficacy endpoint (change in Phe intake from baseline to week 26), a mixed model for repeated measures was fitted for all participants and for certain subgroups, including age, BH_4-responsiveness, pharmacological therapy at screening, and classic PKU diagnosis (defined as participants having a blood Phe level ≥1200 µmol/L [≥19.82 mg/dL] in their medical history; information on classic PKU was not captured for newly enrolled participants). The model accounted for fixed effects of baseline Phe intake and visit (categorical) and random effects of participants. Statistical analysis of additional endpoints is summarized in the Supplemental Methods. *P* values for the primary endpoint and PKU-QOL scores were calculated post hoc.

Results

Participant disposition and baseline characteristics

The first patient was enrolled on February 14, 2022. The cutoff date for this interim analysis was September 2, 2024; at this time, 169 participants had been treated with sepiapterin and were included in the Safety Analysis Set. By the cutoff date, 129 participants (76.3%) had completed 6 months of sepiapterin treatment, and 95 participants (56.2%) had completed 12 months of sepiapterin treatment. Four participants (2.4%) completed the study and 35 (20.7%) discontinued; in the remaining 130 participants (76.9%), treatment is ongoing (Figure 1).

Overall, 102 of 169 participants (60.4%) (including 29 newly enrolled participants) had blood Phe levels <360 µmol/L (<5.95 mg/dL) after the first 2 weeks of the extension study and entered the 26-week dietary Phe tolerance assessment (Dietary Phe Tolerance Analysis Set). At the

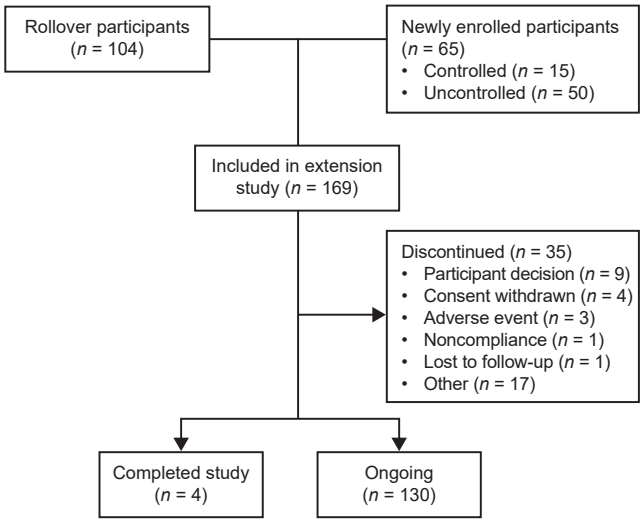

Figure 1 Participant disposition at time of data cutoff (September 2, 2024). Adverse events leading to sepiapterin discontinuation were constipation and nausea (moderate; $n = 1$), increased bleeding time (hemorrhagic diathesis) (severe; $n = 1$), and headache (moderate; $n = 1$).

time of data cutoff, 81 of 102 participants (79.4%) completed the 26-week dietary Phe tolerance assessment, and 4 of 102 (3.9%) discontinued owing to adverse events, noncompliance, lost to follow-up, and consent withdrawal ($n = 1$ each). Overall, 162 participants had ≥1 postbaseline efficacy measurement and were included in the Full Analysis Set; 160 had ≥1 measurable plasma concentration of sepiapterin or BH_4 and were included in the PK Analysis Set.

Baseline characteristics of participants are shown in Table 1. Median (minimum [min], maximum [max]) age in the overall study population was 14.0 (0.2, 55.0) years; 64.5% ($n = 109/169$) of participants were <18 years of age, and 5 were aged <12 months (range, 2 to 5 months). See Supplemental Results for details of concomitant medications.

Sepiapterin exposure

Mean (standard deviation [SD]) treatment compliance with sepiapterin, based on reconciliation of used and unused study drug, was 98.2% (5.3%). Median (min, max) sepiapterin exposure (Safety Analysis Set) was 510.0 (1, 932) days, ie, 72.9 (0.1, 133.1) weeks. Median (min, max) exposure in the Dietary Phe Tolerance Analysis Set was 527.0 (26, 932) days, ie, 75.3 (3.7, 133.1) weeks (see Supplemental Table 2 for number of participants exposed to each dose).

Change in dietary Phe intake (Dietary Phe Tolerance Analysis Set)

Mean (SD) dietary Phe intake increased from 27.6 (18.0) mg/kg/day at baseline to 62.5 (41.5) mg/kg/day at week 26 (LS mean change [standard error (SE)] of 36.4 [2.8] mg/kg/day from baseline; $P < .0001$ from post hoc analysis; Figure 2A). Mean (SD) dietary natural protein intake increased from 22.7 (18.3) g/day (0.81 [0.65] oz/day) at baseline to 51.4 (43.4) g/day (1.84 [1.55] oz/day) at week 26 (Figure 2B), an LS mean (SE) increase of 30.4 (2.8) g/day (1.09 [0.10] oz/day) from baseline (169% increase). Over the same period, mean (SD) intake of prescribed low-Phe protein substitutes decreased from 36.1 (24.7) g/day (1.29 [0.88] oz/day) to 21.0 (21.4) g/day (0.75 [0.76] oz/day) (Figure 2B), an LS mean (SE) reduction of 17.7 (1.6) g/day (0.63 [0.06] oz/day) (50% reduction). In total, 13.7% ($n = 14/102$) of participants were not taking any supplemental protein at baseline; this increased to 32.1% ($n = 26/81$) at week 26.

Nearly all participants (97.1%; $n = 99/102$) increased their dietary Phe intake at any time during the 26-week assessment period. Overall, 73.0% ($n = 74/102$) of participants doubled and 34.3% ($n = 35/102$) tripled their Phe intake from baseline at some time point. The proportion of participants reaching their age-adjusted recommended daily allowance (RDA) for natural protein[26] throughout the study is shown in Supplemental Figure 2; overall, 70.4% ($n = 57/81$) of participants were able to reach their age-adjusted RDA at any time point.

The change in dietary Phe intake from baseline to week 26 by subgroup (age, BH_4-responsiveness, pharmacological therapy at screening, and classic PKU diagnosis) was consistent with the primary analysis (Figure 3, Supplemental Table 3). There were corresponding increases in dietary natural protein intake (Supplemental Figure 3) and decreases in intake of low-Phe protein substitutes (Supplemental Figure 4) across subgroups. Natural protein intake increased by 127% in BH_4-nonresponsive participants ($n = 21$), by 88% in participants receiving sapropterin dihydrochloride at study screening ($n = 21$), and by 96% in participants with classic PKU ($n = 8$). In the 14 participants who were not prescribed low-Phe protein substitutes at baseline, mean (SD) daily dietary natural protein intake increased from 46.2 (30.5) g/day (1.65 [1.09] oz/day) ($n = 14$) to 118.1 (62.9) g/day (4.22 [2.25] oz/day) ($n = 7$) (Supplemental Figure 5), an LS mean (SE) increase of 63.0 (10.1) g/day (2.25 [0.36] oz/day) (155% increase); they were consuming a mean (SD) of 108% (54%) of their RDA at baseline, and at week 26 this increased to 256% (83%). Three children aged <6 months underwent dietary Phe tolerance assessment, and 1 had data available at week 26; mean (SD) dietary Phe intake increased from 38.8 (12.3) mg/kg/day ($n = 3$) to 76.4 mg/kg/day ($n = 1$) during this time.

Safety outcomes

Overall, 49 of 169 participants (29.0%) had treatment-related TEAEs (Table 2); in all but 1 participant, these events were mild or moderate. The most common

Table 1 Participant demographics and baseline characteristics

Demographic/Characteristic	Dietary Phe Tolerance Assessment ($n = 102$)	No Dietary Phe Tolerance Assessment ($n = 49$)	Nonresponsive Newly Enrolled ($n = 18$)	Overall Participants ($N = 169$)
Age at study start, years				
Mean (SD)	15.2 (11.4)	22.7 (13.2)	12.3 (11.8)	17.1 (12.5)
Median (min, max)	13.0 (0.2, 54.0)	17.0 (5.0, 55.0)	11.5 (0.3, 44.0)	14.0 (0.2, 55.0)
Age at study start, *n* (%)				
0 to <6 months	3 (2.9)	0	2 (11.1)	5 (3.0)
≥6 to <12 months	0	0	0	0
≥1 to <2 years	6 (5.9)	0	3 (16.7)	9 (5.3)
≥2 to <6 years	14 (13.7)	3 (6.1)	2 (11.1)	19 (11.2)
≥6 to <12 years	22 (21.6)	8 (16.3)	2 (11.1)	32 (18.9)
≥12 years to <18 years	25 (24.5)	14 (28.6)	5 (27.8)	44 (26.0)
≥18 years	32 (31.4)	24 (49.0)	4 (22.2)	60 (35.5)
Sex, *n* (%)				
Male	53 (52.0)	24 (49.0)	8 (44.4)	85 (50.3)
Female	49 (48.0)	25 (51.0)	10 (55.6)	84 (49.7)
BMI,[a] kg/m^2				
Mean (SD)	21.0 (5.0)	24.9 (7.2)	21.2 (6.5)	22.1 (6.1)
Median (min, max)	19.8 (13.2, 37.6)	23.9 (14.8, 53.2)	18.6 (13.9, 35.5)	21.1 (13.2, 53.2)
Ethnicity (category 1), *n* (%)				
White	89 (87.3)	41 (83.7)	12 (66.7)	142 (84.0)
Native American or Alaska Native	4 (3.9)	1 (2.0)	0	5 (3.0)
Asian	6 (5.9)	5 (10.2)	4 (22.2)	15 (8.9)
Other	3 (2.9)	2 (4.1)	2 (11.1)	7 (4.1)
Ethnicity (category 2), *n* (%)				
Hispanic or Latino	25 (24.5)	5 (10.2)	2 (11.1)	32 (18.9)
Not Hispanic or Latino	76 (74.5)	42 (85.7)	16 (88.9)	134 (79.3)
Not reported	1 (1.0)	0	0	1 (0.6)
Unknown	0	2 (4.1)	0	2 (1.2)
Classic PKU, *n* (%)[b]				
Yes	8 (7.8)	10 (20.4)	0	18 (10.7)
No	65 (63.7)	21 (42.9)	0	86 (50.9)
Missing	29 (28.4)	18 (36.7)	18 (100)	65 (38.5)
Baseline blood Phe, µmol/L[c,d]				
Mean (SD)	433.3 (275.2)	639.4 (298.0)	644.8 (423.0)	515.6 (315.2)
Median (min, max)	389.7 (44.2, 1220.0)	628.0 (104.0, 1630.0)	629.5 (45.0, 1245.6)	486.0 (44.2, 1630.0)
Baseline dietary Phe intake, mg/kg/day				
Mean (SD)	27.6 (18.0)	N/A	N/A	N/A
Median (min, max)	21.9 (5.3, 113.8)	N/A	N/A	N/A
Baseline dietary natural protein intake, g/day[e]				
Mean (SD)	22.7 (18.3)			
Median (min, max)	17.9 (3.1, 128.1)	N/A	N/A	N/A

BMI, body mass index*; max,* maximum; *min*, minimum; *N/A*, not applicable; *Phe*, phenylalanine; *PKU*, phenylketonuria; *SD*, standard deviation.

[a]Height data missing for 7 participants.

[b]In rollover participants, biochemically diagnosed classic PKU was defined as having a blood Phe level ≥1200 µmol/L (≥19.82 mg/dL) in their medical history. Information on a diagnosis of classic PKU was not captured for newly enrolled participants.

[c]For rollover participants, the baseline blood Phe value was the last available Phe value in the APHENITY study, and these participants may therefore already have been receiving sepiapterin treatment depending on which treatment arm they were randomized to in APHENITY; for newly enrolled participants, the baseline value was the Phe value collected at study entry before sepiapterin treatment.

[d]1 umol/L blood Phe = 0.0165 mg/dL blood Phe.

[e]1 g = 0.04 oz.

treatment-related TEAEs (incidence ≥2%) were headache (8.3%), diarrhea (7.7%), discolored feces (4.1%), vomiting (3.0%), and fatigue (2.4%) (Supplemental Table 4).

Three participants (1.8%) discontinued sepiapterin owing to treatment-related TEAEs: constipation and nausea (moderate; $n = 1$), increased bleeding time (severe; $n = 1$),

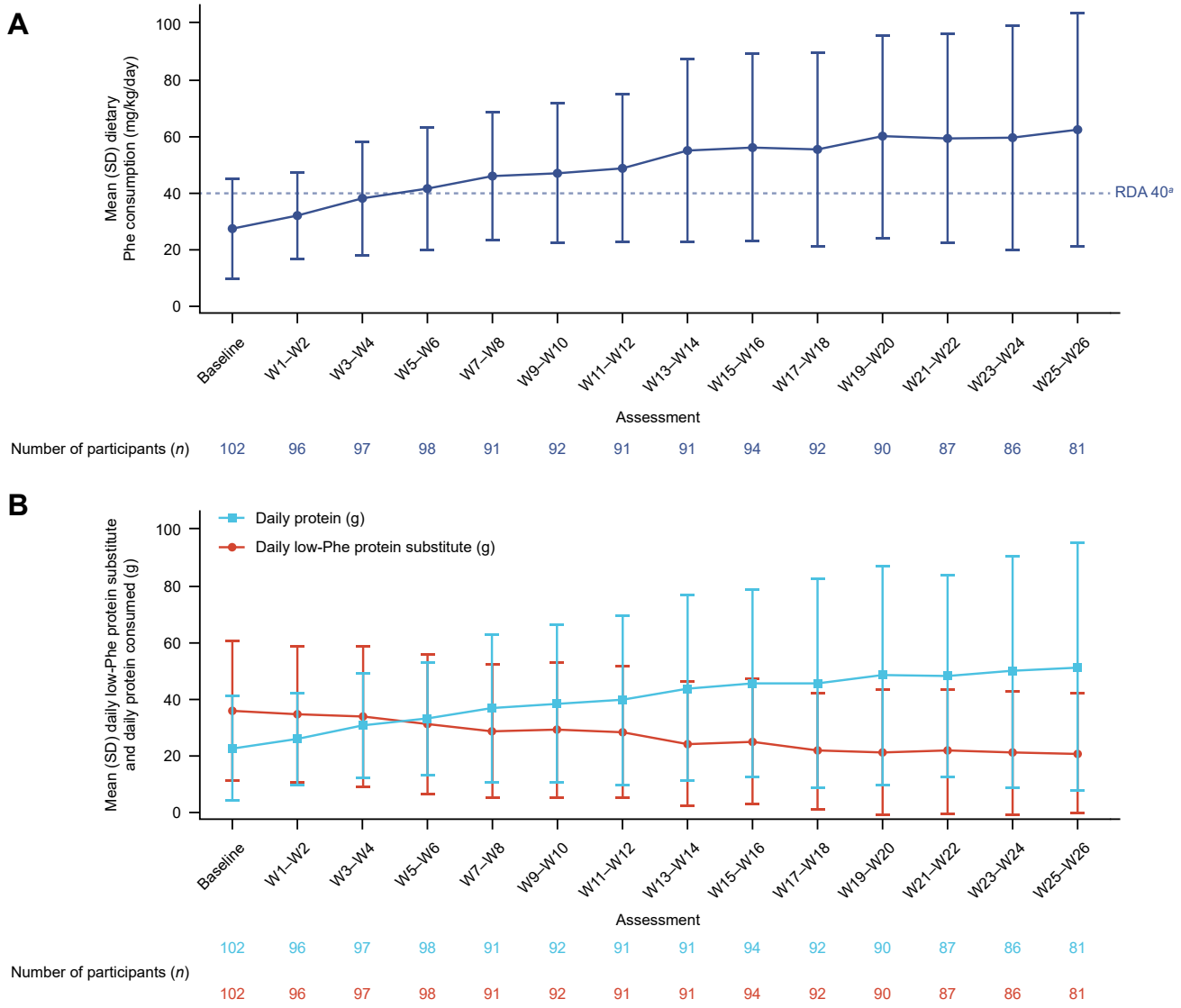

Figure 2 Dietary Phe intake (A) and dietary natural protein and low-Phe protein substitute intake (B) from baseline to week 26 in participants undertaking the dietary Phe tolerance assessment ($n = 102$). Phe, phenylalanine; RDA, recommended daily allowance; SD, standard deviation; W, week. 1 g = 0.04 oz.

and headache (moderate; $n = 1$). Headache was ongoing at the last assessment; the other events resolved upon treatment discontinuation. There were no serious treatment-related TEAEs or deaths.

There were no abnormalities in clinical laboratory tests, vital signs, or physical examinations. Relative to World Health Organization growth standards, height and weight in pediatric participants were largely within the 5th and 95th percentiles throughout the study (Supplemental Figure 6).

BH_4 and sepiapterin concentrations in plasma

Mean BH_4 plasma concentrations increased between approximately 8- and 13-fold 4 hours postdose (Supplemental Figure 7). Mean sepiapterin plasma concentrations were undetectable predose and increased to 2.6 to 4.5 ng/mL (10.96-18.97 nmol/L) 4 hours postdose.

PKU-QOL

Of the 102 participants who underwent the dietary Phe tolerance assessment, 72 were aged ≥9 years (range, 9-54 years) and were able to complete the PKU-QOL questionnaire themselves. Of these, 49 to 57 reported baseline PKU-QOL assessments, depending on the module(s), as the questionnaire is available in certain languages only. After approximately 1 year of sepiapterin treatment, improvements were seen in 21 of 24 domains, with significant improvements ($P < .05$ from post hoc analysis) in 9 domains (Supplemental Table 5). For example, for the PKU

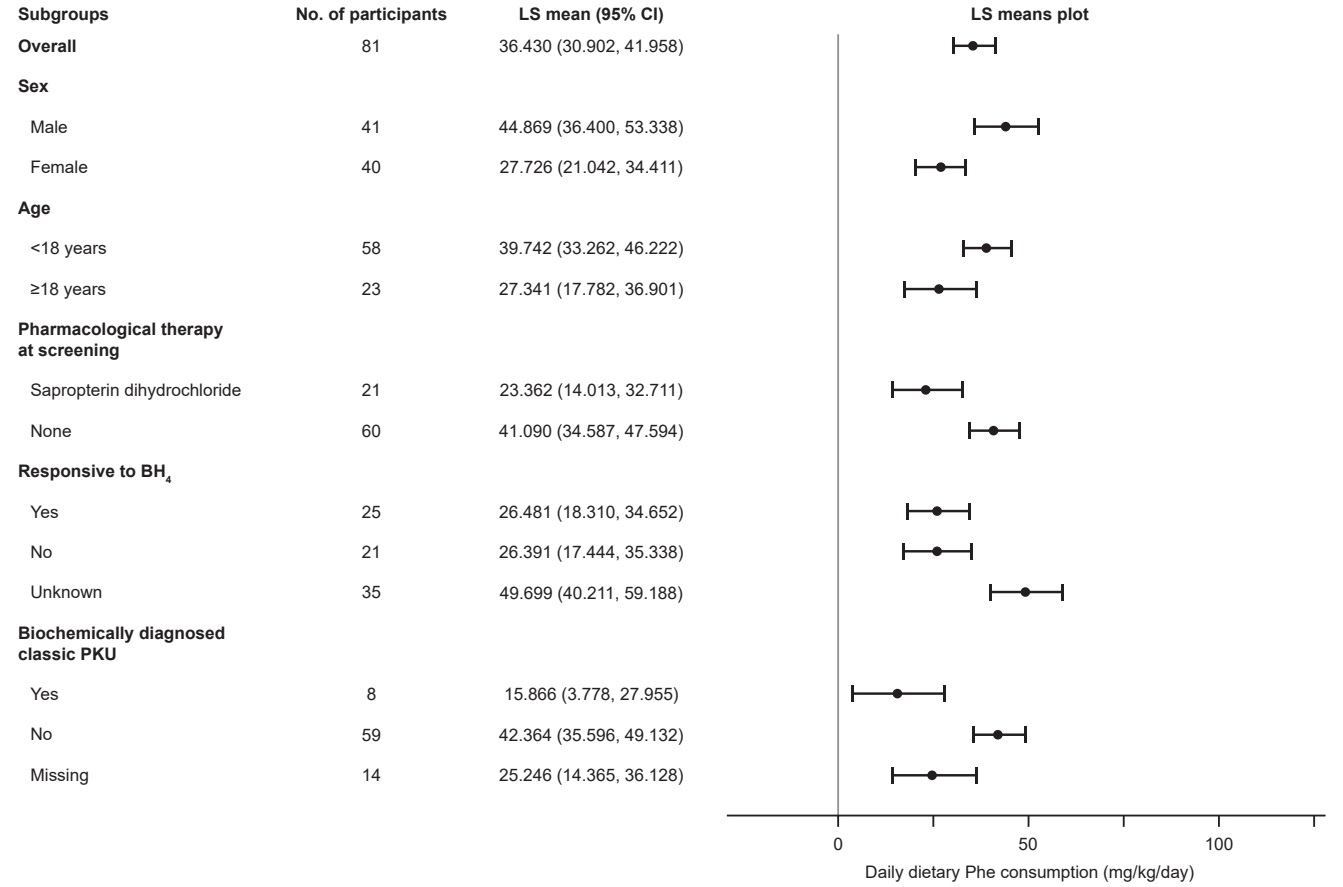

Figure 3 Subgroup analysis of LS mean change in dietary Phe consumed during the dietary Phe tolerance assessment. BH_4, tetrahydrobiopterin; CI, confidence interval; LS, least-squares; Phe, phenylalanine; PKU, phenylketonuria.

symptoms module, sepiapterin treatment resulted in marked reductions in severity of slow thinking (−12.9 [−19.6, −6.2]; $P = .0002$) and lack of concentration (−10.8 [−19.0, −2.7]; $P = .01$). For the PKU in general module, a reduction in emotional impact (−8.3 [−13.5, −3.1]; $P = .0019$) represented a key driver toward reduction in overall PKU impact scores (−5.7 [−9.9, −1.5]; $P = .0079$). Reductions in the impact of protein substitutes on family (−4.8 [−9.2, −0.4]; $P = .0322$) and the social impact of dietary protein restriction (−9.1 [−13.2, −5.0]; $P < .0001$) across 2 modules were especially meaningful, linking a more liberalized diet to improved HRQoL.

Blood Phe and Tyr

Blood Phe, Tyr, and the Phe:Tyr ratio at baseline and month 12 in the Full Analysis Set are summarized in Supplemental Table 6. In participants undergoing dietary Phe tolerance assessment, mean (SD) blood Phe was 186.6 (71.9) µmol/L (3.08 [1.19] mg/dL) at baseline ($n = 102$) and 360.1 (241.7) µmol/L (5.95 [3.99] mg/dL) at week 26 ($n = 84$) (Supplemental Figure 8). Corresponding values for blood Tyr were 53.8 (15.5) µmol/L (0.97 [0.28] mg/dL) at baseline and 54.4 (17.8) µmol/L (0.99 [0.32] mg/dL) at week 26. Mean (SD) blood Phe:Tyr ratio was 4.0 (2.0) at baseline and 7.3 (4.8) at week 26.

In participants receiving sapropterin dihydrochloride at study entry, mean (SD) blood Phe levels at baseline and week 26 were 189.3 (61.3) µmol/L (3.13 [1.01] mg/dL) and 304.3 (157.9) µmol/L (5.03 [2.61] mg/dL), respectively.

Discussion

Results from APHENITY, a phase 3 study evaluating oral sepiapterin in children and adults with PKU, showed significant reductions in blood Phe levels in participants across a wide age range and with varying disease severities.[3] Based on interim results from the ongoing extension study (median sepiapterin exposure, 72.9 weeks), sepiapterin allowed for meaningful diet liberalization in children and adults with PKU, and the long-term safety profile of sepiapterin was consistent with the initial APHENITY study.

Nearly all participants undergoing dietary Phe tolerance assessment were able to increase their dietary Phe intake, and mean blood Phe levels were maintained around 360 µmol/L (5.95 mg/dL). The corresponding average increase

Table 2 Overall safety profile of sepiapterin during the extension study (Safety Analysis Set, $n = 169$)

Adverse Event Category	Total ($n = 169$) n (%) [m]
TEAEs[a]	
Any	130 (76.9) [742]
Treatment-related[b]	49 (29.0) [124]
TEAEs grade 3 or higher[c]	
Any	8 (4.7) [10]
Treatment-related[b]	1 (0.6) [1]
Serious AEs	
Any	3 (1.8) [4]
Treatment-related[b]	0
TEAEs with an outcome of death	0
TEAEs leading to discontinuation of study drug	
Any	3 (1.8) [4]
Treatment-related[b]	3 (1.8) [4]
TEAEs leading to discontinuation from the study	
Any	3 (1.8) [6]
Treatment-related[b]	3 (1.8) [6]

m, number of events; *MedDRA*, Medical Dictionary for Regulatory Activities; *TEAE*, treatment-emergent adverse event.

All TEAEs reported are coded using MedDRA version 26.0, and the number and proportion of participants reporting TEAEs are summarized by system organ class and preferred term.

[a]TEAEs were defined as adverse events that occurred or worsened after the first dose of the study drug on month 1, day 1.

[b]Adverse events assessed by the investigator to be "probably related" or "possibly related" to the study drug.

[c]Adverse events with missing severity were analyzed as grade 3 (severe).

in natural protein intake was 30 g (1.07 oz) daily, which should allow individuals to eat more "regular" food at home and socially, eg, in restaurants and when traveling, and to rely less on specialty products. Among participants previously treated with sapropterin dihydrochloride, more than half doubled their Phe intake beyond that achieved with sapropterin dihydrochloride, and mean blood Phe levels remained within target range. This highlights the potential benefit of sepiapterin compared with sapropterin dihydrochloride, particularly considering that these individuals may already have had higher natural protein intake than untreated individuals and therefore had less scope to increase their natural protein intake with sepiapterin. Results in participants shown to be nonresponsive to BH_4 and in participants with biochemically defined classic PKU were consistent with the primary analysis, highlighting the potential of sepiapterin to address unmet needs in these populations. During the Phe tolerance assessment, approximately 50% of participants were able to reduce their intake of low-Phe protein substitutes. Adjustments to these substitutes were not stipulated in the algorithm, suggesting that additional reductions could be implemented in real-world practice to increase natural protein intake further. There was also a subgroup of participants who were not taking any low-Phe protein substitutes at baseline, suggesting they already had a fairly liberalized diet; nevertheless, these participants were able to more than double their daily protein intake, demonstrating that sepiapterin can enable even further diet liberalization among these patients.

Overall, 26 of 156 (16.6%) participants in the APHENITY study were documented as nonresponsive to BH_4 and did not respond to sepiapterin with a >15% reduction in blood Phe levels, indicating that there may be a patient population that is not responsive to either treatment.[3] However, sepiapterin has been demonstrated to be effective at reducing blood Phe levels in a large proportion of BH_4-nonresponsive patients.[3] In the initial APHENITY study, there was a prespecified cap of 20% of participants with classic PKU (those who typically do not respond to BH_4), to ensure a proportionate enrolment across disease severities.[3] Therefore, real-world data are necessary to provide realistic sepiapterin response rates in BH_4-nonresponsive patients.

In this study, long-term sepiapterin treatment was well tolerated in a wide range of participants, including those aged <2 years. The most common treatment-related TEAEs were headache, diarrhea, discolored feces, vomiting, and fatigue (see Supplemental Table 4). With the exception of discolored feces, TEAEs were similar to those reported for sapropterin dihydrochloride, in terms of types of events and their low severity.[3,14] Furthermore, there were no concerning trends in height and weight, with pediatric participants being largely within the 5th and 95th percentiles throughout the study.

PK data from this study confirmed results of an earlier phase 1 study, showing that sepiapterin is quickly absorbed after oral administration and rapidly and extensively converted to BH_4.[25]

Long-term HRQoL data in sepiapterin-treated participants aged ≥9 years who underwent the dietary Phe tolerance assessment demonstrated improvements in PKU-QOL scores across all 4 modules and most domains, with consistent and durable improvements for key domains relating to PKU symptom burden and impact severity. These results likely reflect the high proportion of participants able to liberalize their diet.

In the Full Analysis Set, blood Phe remained relatively constant over time, indicating durability of the effect of sepiapterin. Fasting blood Tyr levels were normal at study entry (reference fasting values: 35-102 μmol/L [0.63-1.85 mg/dL]),[27] which was expected as most participants were taking supplements that included sufficient amounts of Tyr. Blood Tyr levels remained stable throughout the study. This is consistent with the results of a phase 1 sepiapterin study, in which there was a transient and early increase in Tyr levels (as expected based on the normal physiologic response at the start of treatment), followed by rapid normalization in approximately 24 hours and maintenance within normal limits during continued treatment.[28] Among participants undergoing the dietary Phe tolerance assessment, blood Phe gradually increased to the target threshold

of 360 μmol/L (5.95 mg/dL), as expected given the design of the algorithm, which aimed to maximize dietary protein intake. These results demonstrate that daily sepiapterin may allow participants to increase their dietary Phe intake while maintaining optimal blood Phe levels, consistent with recommendations in the American College of Medical Genetics and Genomics and European guidelines.[2,4]

Currently, the standard of care for PKU is a lifelong Phe-restricted diet.[11] This is associated with reduced HRQoL, nutritional deficiencies, obesity, cardiovascular comorbidities, and low bone mineral density.[29] Furthermore, adherence can be challenging owing to poor palatability of protein substitutes, the restrictive and socially isolating nature of the diet, and its financial and time-consuming impact.[7,8] Most adult patients do not achieve effective blood Phe control with dietary management alone or with sapropterin dihydrochloride, thereby leading to suboptimal outcomes and substantial neurocognitive sequelae in all ages, further affecting HRQoL.[1,8,11,30-32] Notably, growing evidence suggests that patients with PKU who can consume more natural dietary protein may have improved dietary adherence and improved outcomes, including HRQoL, growth and development, and reduced risk of certain chronic diseases (eg, osteoporosis).[8,33-35] Importantly, the meaningful and significant increases in dietary Phe intake and decreases in supplemental low-Phe protein substitutes observed in this study have the potential to improve HRQoL for patients with PKU in real-world settings. This is supported by the HRQoL enhancements reported here.

Although diet liberalization can lead to a range of benefits, in the real world, patients with PKU sometimes find it challenging to increase their natural protein intake[11] because they might be unfamiliar with how to prepare high-protein food (which may lead to poor food choices). Some patients can have issues with the smell, taste, and texture of high-protein food, and in some countries, the cost of high-quality protein sources may be a barrier.[36] Furthermore, patients can have food neophobia, thus continuing to eat foods they are accustomed to as they are anxious about introducing higher-protein food. However, in this study, participants were successfully able to increase dietary Phe intake. Importantly, participants received regular support from a dietitian throughout the study, who helped to monitor their diet and calculate total protein and Phe intake. It is important that patients undergoing protein liberalization in the real world receive adequate support from a dietitian to ensure this process improves the nutritional quality of the diet and to ensure they learn about the composition of a healthy diet from a young age. It is also important to manage patients' expectations in case of the need to reduce natural protein intake after an initial increase, in the event of increased blood Phe levels above the target range.

This extension study has strengths and limitations. A key strength is its design, which incorporated a variety of meaningful mid-term and long-term outcomes, including dietary Phe tolerance, HRQoL, and safety. Other strengths include the long duration of the study, the broad study population, and the robust nature of the dietary tolerance assessment, which allowed participants to optimize their diets while managing blood Phe levels. A key limitation of the study is the open-label design, meaning subjective endpoints may be subject to bias; however, this is mitigated by the fact that the dietary Phe tolerance assessment was based on participants maintaining blood Phe levels <360 μmol/L (<5.95 mg/dL), which is a biochemical endpoint that is less subject to bias. On a practical level, delays in receiving blood Phe results from the central laboratory sometimes meant that dietary adjustments were delayed. Another limitation is that protein intake was self-reported, which might result in inaccuracies because protein content on food labels may be incomplete or inaccurate, or it can fluctuate based on cooking methods, storage temperature, and environmental factors.[37,38] Self-reported protein intake is also subject to under- or overreporting, and accuracy might decline over time as caregivers and patients can find self-reporting onerous.[39,40] To mitigate this, dietitians and other staff members were highly involved in monitoring participants' food intake and assisted with calculating total protein intake and corresponding Phe intake, to ensure that the reporting was as accurate as possible. Another limitation of diary records is the potential for missing data; however, emphasis was placed on key dietary record time points (baseline and week 26 in the dietary Phe tolerance assessment). If records for either or both time points were missing, this was taken into account by assessing all such instances as major deviations, which have been minimal to date. Limitations associated with self-reports for some HRQoL assessments (eg, slow thinking and lack of concentration) are also acknowledged, as well as the lack of an objective measure of cognitive or behavioral performance in the study. Finally, the heterogeneous nature of the population means that baseline Phe intake may have been inflated, potentially masking some of the effects of sepiapterin. However, subgroup results show that across different populations (eg, participants not taking low-Phe protein substitutes at study entry, patients on sapropterin dihydrochloride at study entry), participants were able to meaningfully increase their natural protein intake. The inclusion of participants across a wide age range could also affect the interpretation of the overall increase in dietary Phe intake, but data on the proportion of participants reaching age-adjusted RDA for protein intake mitigate this.

In summary, interim results from the APHENITY Extension Study demonstrate that sepiapterin treatment allowed a broad spectrum of patients with PKU to meaningfully increase their dietary Phe intake, including some BH_4-nonresponsive participants, participants previously treated with sapropterin dihydrochloride, and participants with classic PKU, in turn, leading to improvements in several elements of HRQoL. Sepiapterin was well tolerated in infants, children, and adults, with no safety concerns emerging with long-term use, extending past 2 years for the majority of participants. These data provide further

evidence of the clinical benefit and consistent safety profile of sepiapterin, which may allow patients with PKU to have a more normal diet while maintaining blood Phe levels within guideline-recommended ranges. The study is ongoing and will provide additional long-term data on the safety profile of sepiapterin and its effect on diet, Phe levels, and HRQoL.

Data Availability

The information developed during the conduct of this clinical study is considered confidential by the study sponsor, and individual deidentified participant data, the study protocol, or the statistical analysis plan will not be shared. This information may be disclosed as deemed necessary by the study sponsor. Additional requests for information should be directed to the corresponding author. The study sponsor intends that the data from this study will be presented and published in collaboration with the investigators.

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Ethics Declaration

The study protocol was approved by the relevant independent ethics committees and institutional review boards before study initiation. The main institutional review board was the Medical Ethical Committee of the University Medical Center Groningen; a full list of institutional review boards and ethics committees is provided in the Supplemental Methods. The study was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), the Declaration of Helsinki, and other applicable regulatory requirements. Before study initiation, informed consent was obtained from all study participants, or their legal representatives, in accordance with current regulations.

Conflict of Interest

Francjan van Spronsen: The University Medical Center Groningen (Groningen, Netherlands) received financial compensation for activities including advisory boards for Alltrna, Arla Foods International, BioMarin Pharmaceutical, Illumina, Moderna, Jnana Therapeutics, Origin Biosciences, Pluvia Biotech, PTC Therapeutics, Sentynl Therapeutics, and Travere Therapeutics; grants from BioMarin Pharmaceutical, E.S.PKU, NPKUA, N.P.K.U.V, Nutricia, and the Tyrosinemia Foundation; consultancy for APR, BioMarin Pharmaceutical, Pluvia Biotech, and PTC Therapeutics; clinical trial support for PTC Therapeutics; member of the Data Safety Monitoring Board for Sanofi; lectures/chair for BioMarin Pharmaceutical, Nutricia, PTC Therapeutics, and Vitaflo.

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Additional Information

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