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Efficacy and safety of sepiapterin versus sapropterin in patients with phenylketonuria: Results from the Phase 3, randomized, crossover, open-label, active-controlled AMPLIPHY trial

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ABSTRACT

Aim: AMPLIPHY is the first Phase 3 study comparing sepiapterin versus sapropterin in children and adults with phenylketonuria (PKU).
Methods: AMPLIPHY was an international, Phase 3, two-part, open-label study in participants with PKU aged ≥2 years. Participants responsive to sepiapterin (60 mg/kg/day) in Part 1 (≥20% reduction in blood phenylalanine [Phe]) entered Part 2, a crossover treatment period, and were randomized 1:1 to alternative treatment sequences

Abbreviations: BH_4, tetrahydrobiopterin; BMI, body mass index; CI, confidence interval; ETV, early termination visit; FAS, full analysis set; IRB, institutional review board; LEC, local ethics committee; LS, least-squares; MMRM, mixed model for repeated measures; OR, odds ratio; PAH, phenylalanine hydroxylase; PAS, primary analysis set; Phe, phenylalanine; PKU, phenylketonuria; SAS, safety analysis set; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event; Tyr, tyrosine.

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Sapropterin
Sepiapterin

of sepiapterin (60 mg/kg/day, licensed dosage) and sapropterin (20 mg/kg/day, maximum licensed dosage) for 4 weeks each, with a 14-day washout between treatments. The primary endpoint was mean change in blood Phe from baseline to Weeks 3–4 of each treatment period (Part 2).

Results: Of 82 participants enrolled, 67 (81.7%) and 62 (75.6%) had reductions in blood Phe ≥20% and ≥30%, respectively, in Part 1. Sixty-two participants were randomized in Part 2 (mean [SD] age, 15.8 [10.8] years). In the primary analysis set (≥30% reduction in blood Phe in Part 1, $n = 58$), mean (SD) baseline blood Phe before sepiapterin and sapropterin treatment was 725.8 (302.1) and 790.4 (370.0) μmol/L, respectively. Least-squares mean (SE) reduction in blood Phe from baseline was −437.0 (28.0) and −256.6 (28.2) μmol/L, respectively, representing a least-squares mean difference of −180.4 μmol/L (95% CI: −229.5, −131.4; $p < 0.0001$) and a relative 70% greater reduction with sepiapterin versus sapropterin. Both treatments were well tolerated, with safety profiles consistent with previous reports.

Conclusions: Sepiapterin was superior to the highest approved dose of sapropterin in lowering blood Phe. No new safety signals were observed.

The trial was registered in the UK Clinical Study Registry, ISRCTN, on January 29, 2024 (ID number, ISRCTN79102999; https://www.isrctn.com/ISRCTN79102999).

1. Introduction

Phenylketonuria (PKU) is an autosomal-recessive inborn error of metabolism, characterized by deficiency of the phenylalanine hydroxylase (PAH) enzyme [1]. PAH catalyzes the first and rate-limiting step in the conversion of phenylalanine (Phe) to tyrosine (Tyr), which occurs in a tetrahydrobiopterin (BH_4)-dependent manner [2]. In patients with PKU, pathogenic variants of the *PAH* gene affect PAH activity, leading to elevated blood Phe levels [3]. High Phe levels are toxic to the brain and, if left untreated, Phe accumulation may result in progressive neurocognitive impairment, manifesting as developmental delay, memory impairment, epilepsy, and a range of behavioral, psychiatric, and motor disturbances [3–5].

Currently, there is no cure for PKU. Stringent lifelong dietary management is considered the standard of care, with the goal of maintaining blood Phe levels within specific target ranges [6]. In the USA and Canada, American College of Medical Genetics and Genomics guidelines recommend maintaining blood Phe levels ≤360 μmol/L throughout the lifetime of people with PKU, including during pregnancy [7]. European guidelines recommend target Phe levels of 120–360 μmol/L for children aged ≤12 years and women who are pregnant or preparing to conceive, and 120–600 μmol/L for adolescents (aged >12 years) and adults [8]. Australian guidelines recommend Phe levels of 120–360 μmol/L for those aged ≤12 years and ≤360 μmol/L for those aged >12 years; however, they note that >360 μmol/L may be appropriate in some cases [9].

Even with early and continuous dietary management, children and adults with PKU often struggle to maintain Phe levels within the target range and experience cognitive symptoms, as well as emotional and behavioral issues [7]. Moreover, maintaining a strict, lifelong diet is challenging, and there are many barriers to long-term adherence, including its social impact and issues relating to medical formulas and low-protein foods (e.g. cost, lack of access, lack of insurance coverage, and low palatability) [6].

Until recently, only two pharmacological therapies were approved for the treatment of PKU in some countries: sapropterin dihydrochloride (herein referred to as sapropterin) and pegvaliase. However, these therapies have limitations and are not suitable for all patients. Sapropterin is an orally administered synthetic form of BH_4 approved in several countries to treat children and adults with hyperphenylalaninemia due to BH_4-responsive PKU (aged ≥1 month in the USA) [10–12]. However, only 25–50% of patients respond to sapropterin [13], mainly those with mild rather than classic PKU [14]. Among those who do respond, only a minority are able to stop natural protein restriction [15]. Pegvaliase is a Phe-metabolizing enzyme indicated for the treatment of PKU in individuals aged ≥15 years (Japan), ≥16 years (EU, Australia, Canada, and Brazil), and adults (USA) with inadequate control of blood Phe levels (>600 μmol/L) on existing management [16–20]. Pegvaliase is effective in many patients, but can require up to three consecutive subcutaneous injections per day (in those who require the highest dose), can take up to 18 months or longer for patients to respond, and its use is limited to certain age groups and countries [6,19,20]. Furthermore, the risk of hypersensitivity reactions necessitates prolonged titration to an effective dose [19–21], and the risk of anaphylaxis requires patients to carry an epinephrine injection device. An observer may also be required when patients self-inject; in Europe this is mandated for at least the first 6 months of treatment [19,20]. Thus, there is significant unmet need for more effective therapies for individuals living with PKU to enable diet liberalization in a broader population, with limited side effects and minimal additional burden [22].

Oral sepiapterin was approved for the treatment of PKU in the EU in June 2025, the USA and Australia in July 2025, Switzerland in August 2025, and Canada in October 2025. It is a novel formulation of endogenous sepiapterin with a dual mechanism of action (Fig. 1), allowing it to address patients with both BH_4-responsive and non-BH_4-responsive genetic variants [23]. It is a natural precursor to BH_4, the essential cofactor of the PAH enzyme [24–26], and following administration, is rapidly absorbed into target cells and extensively converted intracellularly to BH_4 [25]. Sepiapterin also exerts an independent chaperone effect on PAH by binding directly to misfolded variant PAH tetramers. This results in stabilization of the correct protein conformation and a subsequent increase in enzymatic activity, even in non-BH_4-responsive genetic variants [23,24]. In a Phase 2, open-label, active-controlled, all-comers study (ACTRN12618001031257), oral sepiapterin (60 mg/kg/day) led to statistically significant, dose-related reductions in blood Phe levels from baseline to Day 7, and was more efficacious in reducing blood Phe levels than sapropterin (20 mg/kg/day) [27]. In the pivotal Phase 3 APHENITY trial (NCT05099640), oral sepiapterin (20–60 mg/kg/day) significantly reduced blood Phe levels from baseline to Week 6 versus placebo in a broad population of patients with PKU, inclusive of BH_4-responsive and non-responsive children and adults. Sepiapterin was also generally well tolerated in APHENITY [24].

Here, we report results from the Phase 3 AMPLIPHY trial, which directly compared the efficacy and safety of sepiapterin (60 mg/kg/day) versus the maximum approved dose of sapropterin (20 mg/kg/day) in participants with PKU aged ≥2 years.

2. Methods

2.1. Study design

AMPLIPHY (ISRCTN79102999; https://www.isrctn.com/ISRCTN79102999; date of registration, January 29, 2024) was an international, Phase 3, two-part, randomized, crossover, open-label, active-controlled study of sepiapterin compared with sapropterin in participants aged ≥2 years with PKU (Fig. 2). The screening period was up to 45 days and included a dietary control observation period (see

Supplement). Participants with a >20% variance in dietary Phe consumption during the dietary control observation period were considered screen failures. Following the initial screening visit, eligible participants who were taking sapropterin had to discontinue the medication and undergo a 7-day washout.

Part 1 was an open-label sepiapterin responsiveness test, in which all participants received sepiapterin 60 mg/kg/day for 14 days. Participants were eligible for inclusion in Part 1 irrespective of whether they had previously responded to sapropterin or not. This was based on learnings from the Phase 2 study (ACTRN12618001031257), which showed efficacy in an all-comers population (which included participants who were BH_4 non-responsive), and the Phase 3 APHENITY study, which demonstrated a sepiapterin response in participants who were documented as BH_4 non-responsive [24,27]. Participants who completed Part 1 and were responsive to sepiapterin (defined as a reduction from baseline of ≥20% in blood Phe levels) underwent a sepiapterin washout period of ≥14 days before starting randomized treatment in Part 2. Participants with <20% reduction in blood Phe levels were classified as non-responsive and discontinued the study.

Part 2 was a randomized, active-controlled, open-label, crossover treatment period. Participants were randomly assigned (1:1), using a central randomization process, to one of two treatment sequences: 60 mg/kg sepiapterin followed by 20 mg/kg sapropterin, or 20 mg/kg sapropterin followed by 60 mg/kg sepiapterin, both taken orally, once daily (see Supplement for details on randomization and administration of study drugs). Each treatment period lasted 4 weeks, with a 14-day washout period in between. Dose modifications were not permitted during the study. Adherence to medication administered at home was assessed at study visits by direct questioning, review of completed dosing diaries, and counting returned study drug. Given the clear physical differences between sepiapterin and sapropterin, full blinding was not possible. The study sponsor was blinded to treatment sequences until after database lock.

AMPLIPHY was conducted at 18 hospital clinics across Australia, Canada, Czechia, Denmark, France, Germany, Italy, the Netherlands, Poland, Slovenia, Spain, and the United Kingdom. The study protocol was approved by local ethics committees (LECs) or institutional review boards (IRBs) before study initiation (see Supplement for list of LECs and IRBs). The LECs and IRBs also had to re-approve the protocol following protocol amendments. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, with periodic inspection of all case report forms, study documents, and research/clinical laboratory facilities. There were no important protocol amendments that affected the conduct of the study (see Supplement for details).

2.2. Participants

Part 1 of the study allowed for an all-comer population. Participants were aged ≥2 years with a clinical diagnosis of PKU, hyperphenylalaninemia and blood Phe levels ≥360 μmol/L on current therapy (based on the mean of the last three Phe levels from the participant's medical history, inclusive of the screening value). Exclusion criteria included the following: participants unwilling to undergo sapropterin washout; those using pegvaliase concurrently or in the 60 days before screening; and participants with >20% variance in dietary Phe consumption for 4 consecutive weeks. See Supplement for full inclusion and exclusion criteria.

During the study, participants continued their usual diet without modification (i.e. no change in total protein, low-Phe protein from medical formula, or daily Phe consumption). Participants (or their caregivers) recorded all food intake for 3 consecutive days on a weekly basis throughout the study. Dietary protein intake from natural food sources, low-protein foods, and glycomacropeptide-based and free amino acid-based protein substitutes, as well as total dietary Phe consumption, was calculated by dietitians, and participants were counseled on the necessity of maintaining their usual intake.

Participants with biochemically diagnosed classic PKU (one or more blood Phe level ≥1200 μmol/L in their medical history) were capped at 30% of the total study population to ensure proportionate enrollment across disease severities. No other caps relating to disease severity were applied.

All participants provided written informed consent or assent (by the participant or their parents, guardians, or legal representatives as applicable) before enrollment, based on country regulations.

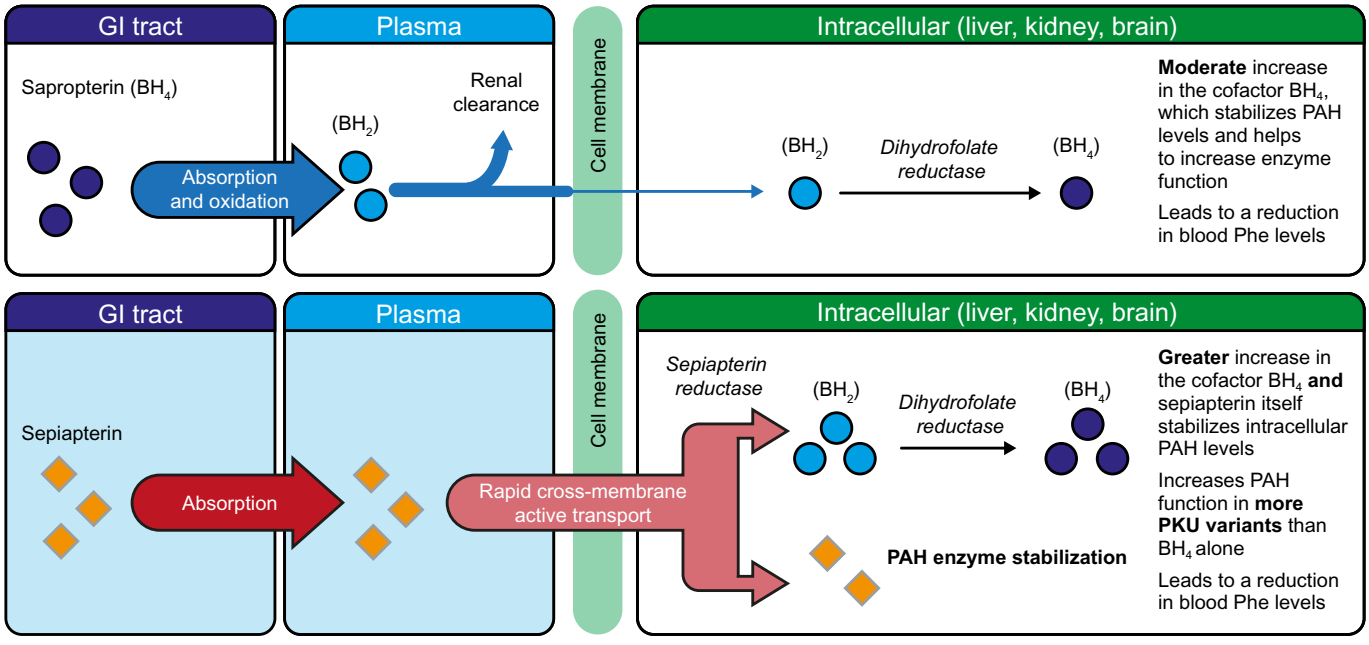

Fig. 1. The dual mechanism of action of sepiapterin [38].
BH_2: dihydrobiopterin; BH_4: tetrahydrobiopterin; GI: gastrointestinal; PAH: phenylalanine hydroxylase; Phe: phenylalanine; PKU: phenylketonuria.
Figure reproduced from MacDonald A, et al. Mol Gent Metab 2026;147:109705 [38].

2.3. Endpoints

The primary endpoint was the mean change in blood Phe levels from baseline to the end of each 4-week treatment period in Part 2. Baseline blood Phe levels were calculated as the mean levels on Day −1 and Day 1 (pre-dose) of each treatment period. Post-treatment concentrations were calculated as mean levels from at least three samples per participant, collected on Days 19, 24, and 28 (i.e. during Weeks 3–4 of each treatment period). Dried blood Phe levels were measured using a validated high-performance liquid chromatography–tandem mass spectrometry method [28].

Secondary endpoints included the proportion of participants with baseline blood Phe levels ≥600 μmol/L or ≥360 μmol/L who reached levels <600 μmol/L or <360 μmol/L, respectively, at the end of each 4-week treatment period in Part 2. Post hoc analyses were conducted to evaluate the proportion of participants who achieved age-appropriate blood Phe levels according to European guidelines [8] at the end of each 4-week treatment period in Part 2 (<600 μmol/L for participants aged ≥12 years and <360 μmol/L for participants aged <12 years).

Exploratory outcomes included changes in blood Tyr over time, including the Phe:Tyr ratio. Blood samples for Phe and Tyr evaluation were collected after fasting or ≥3 h postprandial and at approximately the same time each day.

The safety and tolerability of sepiapterin were evaluated through treatment-emergent adverse events (TEAEs) and treatment-related TEAEs (see Supplement for details).

2.4. Statistical analysis

2.4.1. Sample size

The study was designed to have 90% power to detect a treatment difference between sepiapterin and sapropterin of 115 μmol/L for the reduction in blood Phe levels. See Supplement for details.

2.4.2. Analysis populations

The primary analysis set (PAS) comprised participants with mean percentage reductions in blood Phe levels of ≥30% in Part 1, who were randomized and received at least one dose of study drug in Part 2. The full analysis set (FAS) comprised all participants who were randomized and received at least one dose of study drug in Part 2. For both PAS and FAS, participants were analyzed according to randomized treatment. The safety analysis set (SAS) comprised all participants who received at least one dose of study drug, including in Part 1; participants were analyzed according to actual treatment received.

2.4.3. Analysis of endpoints

A mixed model for repeated measures (MMRM) was used to analyze mean change in blood Phe levels from baseline to each of the 2-week post-baseline assessment intervals within the two treatment periods for each participant (see Supplement for details on the MRMM). The least-squares (LS) mean estimate for the change in blood Phe levels from baseline to the average of Weeks 3–4 was used for treatment comparisons. For the primary analysis, the MMRM was used on the available data assuming the missing assessments were missing at random; no explicit imputation was involved.

All efficacy analyses were performed based on the PAS and FAS. For the primary endpoint, a gatekeeping procedure was used to control for family-wise error rate. First, the endpoint was tested at the significance level of 0.05 (two-sided) on the PAS; if this was statistically significant, the FAS was also tested at the 0.05 significance level.

Change in blood Phe levels in Part 1 was analyzed according to the following subgroups: BH_4 responsive (based on information from medical record: yes [≥20%/≥30% reduction in blood Phe levels], no [<20%/<30% reduction], or missing); and receiving sapropterin at screening (yes or no). Data for the primary endpoint in Part 2 were analyzed according to the following subgroups: sex (male or female); BH_4 responsive (yes [≥20% reduction in blood Phe levels], no [<20% reduction], or missing); receiving sapropterin at screening (yes or no); and classic PKU (yes or no).

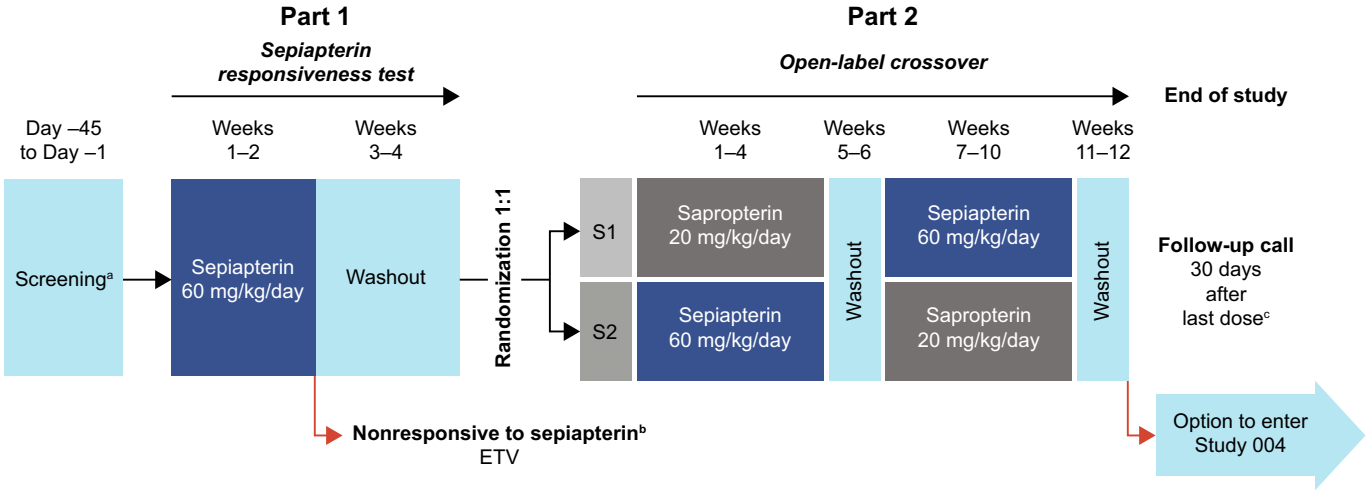

Fig. 2. AMPLIPHY study design.

[a]The screening period included a dietary observation period of 2430 days, during which participants continued their usual diet without modification (i.e. no change in total protein, non-Phe protein from medical formulas, or daily Phe consumption) and maintained a weekly 3-day diet record for 4 consecutive weeks; those with a variance of >20% in dietary Phe consumption were considered screen failures. Following the initial screening visit, eligible participants who were taking sapropterin had to discontinue the medication and undergo a 7-day washout period.

[b]Sepiapterin responsiveness was defined as a reduction from baseline of ≥20% in blood Phe levels.

[c]A follow-up call was also required for participants who were sepiapterin non-responsive (in Part 1), those who discontinued the study prematurely (ETV), and those who did not enter into Study 004.

Baseline blood Phe levels were calculated as the mean of blood Phe levels on Day −1 and Day 1 (pre-dose) of each treatment period.

Dosing of sepiapterin and sapropterin was based on the participant's weight; the weight obtained on Day 1 of each treatment period was used to calculate the exact amount (in mg) of treatment required for each participant's daily dose.

ETV: early termination visit; Phe: phenylalanine.

A sensitivity analysis of the primary endpoint was conducted using both the PAS and FAS; this involved a completer analysis with an analysis of covariance model, which included only the participants who had assessments at Weeks 3–4 in each treatment period of Part 2.

Post hoc analyses were carried out using Kaplan–Meier estimates to assess median time to achieve blood Phe levels <600 μmol/L and <360 μmol/L in participants who had baseline blood Phe levels ≥600 μmol/L and ≥360 μmol/L, respectively, during each treatment period of Part 2. A log-rank test was used to determine the treatment difference between sepiapterin and sapropterin. All statistical analyses were performed using SAS (version 9.4).

3. Results

3.1. Participant disposition and baseline demographics and clinical characteristics

Participants were recruited between January 2024 and September 2024. Overall, 82 participants enrolled in Part 1; of these, 15 were non-responsive to sepiapterin (i.e. <20% reduction in blood Phe levels) and five violated the exclusion criteria. Sixty-two participants were therefore randomized in Part 2 (sequence 1, $n = 30$; sequence 2, $n = 32$) and 60 completed the study. Reasons for discontinuation were participant decision ($n = 1$) and withdrawal of consent ($n = 1$; Fig. 3); of note, both participants were considered responders in Part 1 and withdrew after completing the sepiapterin treatment period in Part 2, before switching to sapropterin. The numbers of participants in the PAS, FAS, and SAS were 58, 62, and 82, respectively.

Baseline demographic and clinical characteristics are shown in Table 1 (overall population and participants in Part 2) and Table S1 (by randomized treatment sequence). In the overall population, 52.4% of participants ($n = 43/82$) were female and the mean age at screening was 15.3 years (range, 2–66 years); 86.6% of participants ($n = 71/82$) had previously received BH_4 treatment and 46.3% ($n = 38/82$) were receiving BH_4 treatment at screening and had to undergo the 7-day washout period. None of the participants had previously received pegvaliase. Mean blood Phe at baseline was 578.6 μmol/L in the overall population. Baseline characteristics of participants in Part 2 were similar

Table 1
Baseline demographics and clinical characteristics at screening (Safety Analysis Set).

Parameter	Overall population ($n = 82$)	Participants in Part 2 ($n = 62$)
Age, years		
Mean (SD)	15.3 (10.63)	15.8 (10.84)
Median (range)	14.0 (2, 66)	14.0 (2, 66)
Age group (years), *n* (%)		
2–5	8 (9.8)	4 (6.5)
6–11	20 (24.4)	16 (25.8)
12–17	38 (46.3)	29 (46.8)
≥18	16 (19.5)	13 (21.0)
Female, *n* (%)	43 (52.4)	30 (48.4)
Race, *n* (%)		
White	71 (86.6)	53 (85.5)
Asian	2 (2.4)	1 (1.6)
Other	8 (9.8)	7 (11.3)
Multiple	1 (1.2)	1 (1.6)
Weight, kg, mean (SD)	54.2 (22.45)	55.9 (21.31)
BMI, kg/m^2, mean (SD)	21.8 (5.11)	21.99 (4.85)
Blood Phe level, μmol/L		
Overall, mean (SD)	578.6 (172.64)	585.1 (166.18)
Overall, median (min, max)	557.3 (348, 1332)	561.1 (348, 1332)
2–5 years, mean (SD)	545.0 (114.00)	585.0 (74.41)
6–11 years, mean (SD)	497.7 (103.77)	503.1 (109.33)
12–17 years, mean (SD)	579.5 (164.85)	566.6 (131.43)
≥18 years, mean (SD)	694.3 (224.90)	727.2 (228.23)
Classic PKU, *n* (%)[a]	15 (18.3)	10 (16.1)
Prescribed total daily dietary protein, g[b]		
Mean (SD)	50.5 (31.54)	52.1 (31.97)
Median (min, max)	51.0 (1, 118)	52.0 (1, 118)
Treatment with sapropterin, *n* (%)		
Previous	71 (86.8)	53 (85.5)
Current	38 (46.3)	32 (51.6)

BH_4: tetrahydrobiopterin; BMI: body mass index; Phe: phenylalanine; PKU: phenylketonuria; SD: standard deviation.
[a] Blood Phe levels just after birth ≥1200 μmol/L or historical evidence of Phe levels ≥1200 μmol/L in their medical history.
[b] 53 participants from the overall population and 41 who participated in Part 2 were prescribed dietary protein.

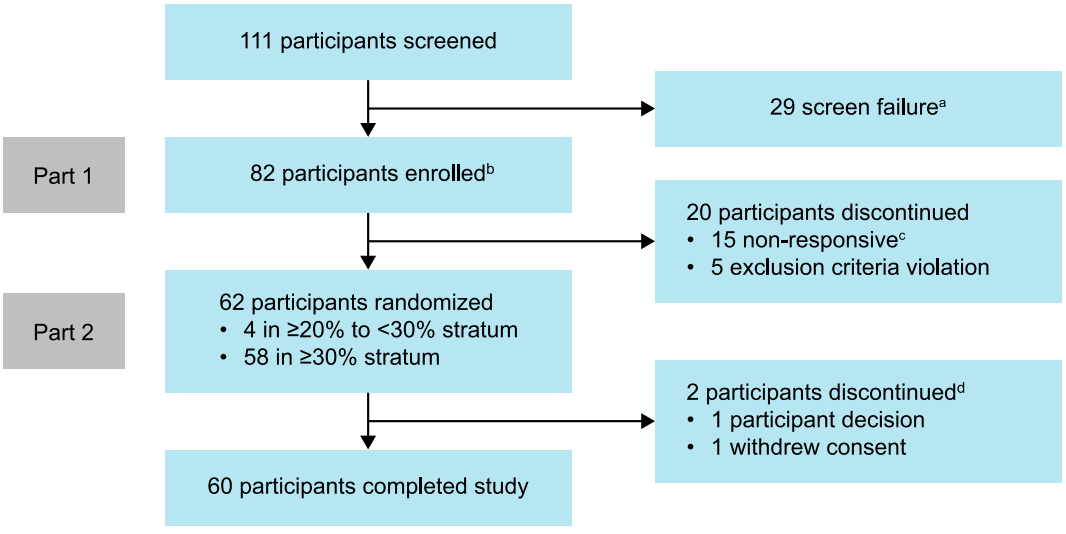

Fig. 3. Participant disposition.
[a]13 patients failed screening because of >20% variance in dietary Phe consumption during the dietary control observation period.
[b]Australia ($n = 21$), Canada ($n = 9$), Czechia ($n = 8$), Denmark ($n = 8$), France ($n = 3$), Germany ($n = 2$), Italy ($n = 3$), the Netherlands ($n = 5$), Poland ($n = 10$), Slovenia ($n = 2$), Spain ($n = 3$), and the United Kingdom ($n = 8$).
[c]Sepiapterin responsiveness was defined as a reduction from baseline of ≥20% in blood Phe levels.
[d]Both participants withdrew after completing the sepiapterin treatment period in Part 2, before switching to sapropterin.
Phe: phenylalanine.

to those of the overall population. See Supplement for details on concomitant medications.

3.2. Responsiveness to sepiapterin

During Part 1, 81.7% of participants (n = 67/82) demonstrated a reduction from baseline in blood Phe levels of ≥20% with sepiapterin and 75.6% (n = 62/82) demonstrated a reduction of ≥30%. Subgroup results are summarized in Table S2.

3.3. Primary endpoint (change in blood Phe levels)

During Part 2, the reduction in blood Phe levels between baseline and Weeks 3–4 in the PAS was significantly greater with sepiapterin (n = 58) than sapropterin (n = 56); the LS mean difference was −180.4 μmol/L (95% CI: −229.5, −131.4; $p < 0.0001$), representing a relative 70% greater reduction with sepiapterin versus sapropterin (Fig. 4). Results were similar in the FAS and the completer sensitivity analyses, with significant treatment differences of approximately 180 μmol/L ($p <$ 0.0001 for all; Table S3).

Treatment differences numerically favored sepiapterin in all subgroups analyzed (Fig. 5). Statistical significance was shown in many subgroups, including those who were previously BH_4 responsive and those receiving sapropterin at study entry (both $p < 0.0001$).

3.4. Secondary endpoints

At baseline, blood Phe levels were ≥600 μmol/L in 37 participants treated with sepiapterin and 39 treated with sapropterin. During Weeks 3–4 of treatment, 89.2% of sepiapterin-treated participants achieved Phe levels <600 μmol/L, compared with 51.3% of sapropterin-treated participants (odds ratio [OR]: 12.5 [95% CI: 2.57, 60.56; p = 0.0028]). The median (min, max) time to reach blood Phe levels <600 μmol/L was 7 (7, 43) days with sapropterin and 7 (1, 14) days with sepiapterin (p = 0.0008).

At baseline, blood Phe levels were ≥360 μmol/L in 52 participants treated with sepiapterin and 51 treated with sapropterin. During Weeks 3–4 of treatment, 69.2% of sepiapterin-treated participants achieved Phe levels <360 μmol/L, compared with 39.2% of sapropterin-treated participants (OR: 3.95 [95% CI: 1.56, 10.04; p = 0.0048]). The median (min, max) time to reach blood Phe levels <360 μmol/L was 30 (1,30) days with sapropterin and 7 (1, 43) days with sepiapterin ($p <$ 0.0001).

In participants aged ≥12 years with baseline blood Phe levels ≥600 μmol/L, a significantly higher proportion achieved Phe levels <600 μmol/L with sepiapterin than sapropterin (88.5% [n = 23/26] versus 44.0% [n = 11/25]; p = 0.0108). In participants aged <12 years with baseline blood Phe levels ≥360 μmol/L, the proportion achieving Phe levels <360 μmol/L was numerically higher with sepiapterin than sapropterin (76.5% [n = 13/17] versus 47.4% [n = 9/19]; p = 0.0594).

3.5. Exploratory endpoints

Mean blood Tyr levels were in the normal range (30–120 μmol/L [29]) at baseline and remained stable during administration of both treatments; see Supplement for blood Tyr levels and Phe:Tyr ratio (Figs. S1 and S2).

3.6. Safety

Mean (SD) overall duration of exposure to sepiapterin in Parts 1 and 2 was 42.3 (3.35) days. During Part 2, mean (SD) exposure was 28.4 (3.21) days for sepiapterin and 28.5 (1.95) days for sapropterin. Adherence rates during Part 2 were 99.3% and 98.4% for sepiapterin and sapropterin, respectively.

During Part 2, the incidence of TEAEs was similar for sepiapterin and sapropterin (61.1% and 66.7%, respectively; Table 2); for both treatments, the majority of events (>95%) were mild or moderate in severity. No serious TEAEs, TEAEs leading to death, or TEAEs leading to treatment discontinuation were reported. Most common TEAEs (reported by >5% participants in either treatment group) were upper respiratory tract infection, nasopharyngitis, diarrhea, nausea, and headache. The overall incidence of treatment-related TEAEs was 14.5% (n = 9) with sepiapterin and 6.7% (n = 4) with sapropterin. The only treatment-related TEAEs that occurred in more than one participant were diarrhea and nausea, reported in five (8.1%) and three (4.8%) participants, respectively (all during sepiapterin treatment). The incidence of TEAEs and treatment-related TEAEs in Part 2 by age and sex are presented in Table S4; the incidence of treatment-related TEAEs was similar in male and female participants during sepiapterin treatment.

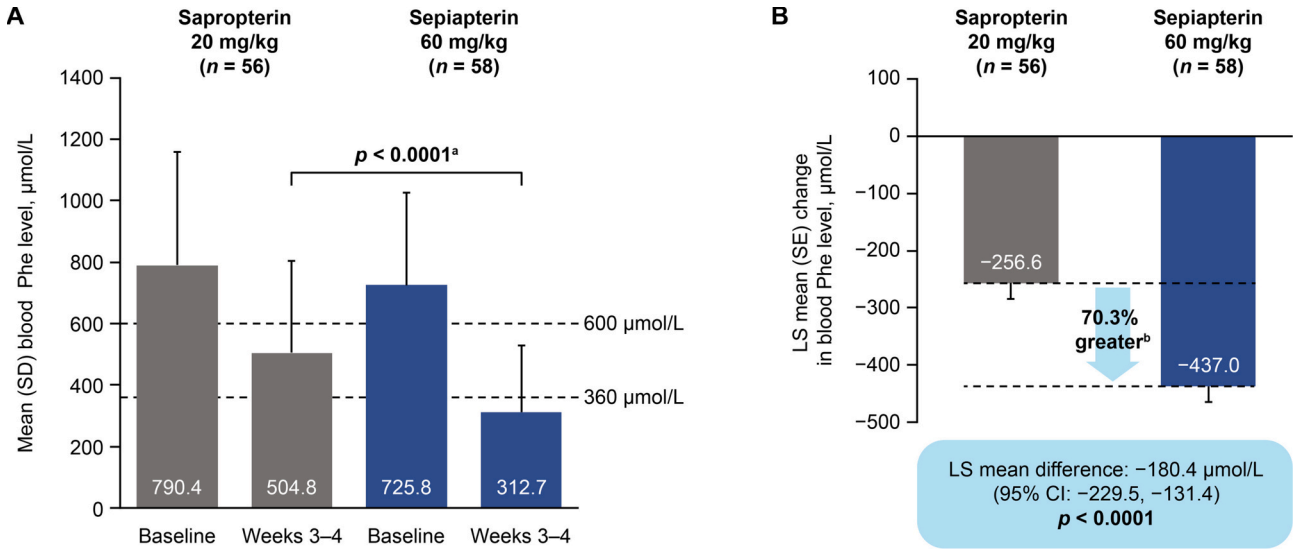

Fig. 4. (A) Mean blood Phe level and (B) LS mean change in blood Phe level between baseline and Weeks 3–4 with sepiapterin and sapropterin (PAS).
[a]p value is for LS mean difference.
[b]Relative reduction in LS mean with sepiapterin versus sapropterin.
CI: confidence interval; LS: least-squares; PAS: primary analysis set; Phe: phenylalanine; SD: standard deviation; SE: standard error.

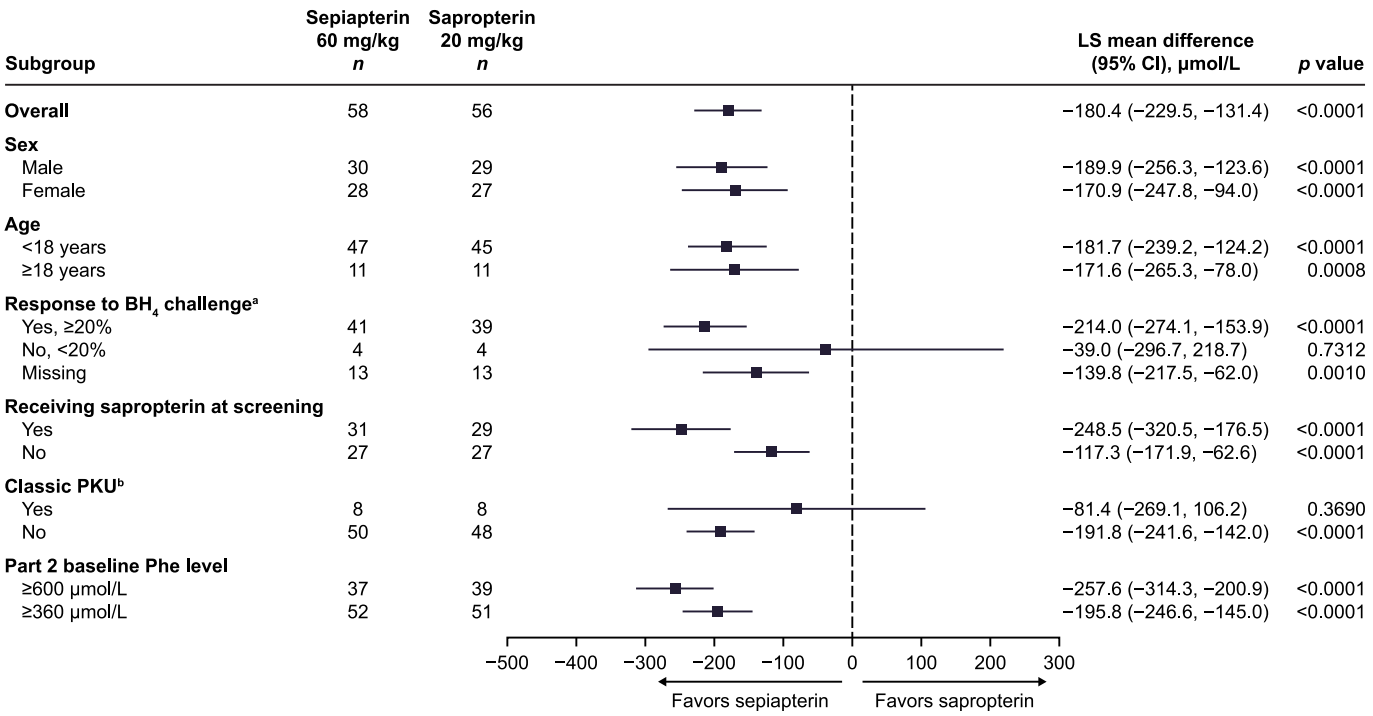

Fig. 5. Subgroup analyses of treatment differences for the change in blood Phe levels between baseline and Weeks 3–4 (PAS).
[a]Based on information in participants' medical records.
[b]Defined as blood Phe levels just after birth ≥1200 µmol/L or historical evidence of Phe levels ≥1200 µmol/L in their medical history. In total, 10 patients with classic PKU participated in Part 2 of the study; two of these patients had blood Phe levels reduced by >20% but <30% in Part 1, so were not included in the PAS.
BH_4: tetrahydrobiopterin; CI: confidence interval; LS: least-squares; PAS: primary analysis set; Phe: phenylalanine; PKU: phenylketonuria.

Table 2
Safety profile of sepiapterin and sapropterin in Part 2 (Safety Analysis Set).

	Sepiapterin (*n* = 62) *n* (%)	Sapropterin (*n* = 60) *n* (%)
Any TEAE	41 (66.1)	37 (61.7)
Any serious TEAE	0	0
Any TEAE leading to death	0	0
Any TEAE grade 3 or above	2 (3.2)	1 (1.7)
Any treatment-related TEAE	9 (14.5)	4 (6.7)
Any TEAE leading to treatment discontinuation	0	0
Most common TEAEs[a]		
Upper respiratory tract infection	8 (12.9)	9 (15.0)
Nasopharyngitis	5 (8.1)	4 (6.7)
Diarrhea	6 (9.7)	1 (1.7)
Nausea	6 (9.7)	2 (3.3)
Headache	5 (8.1)	8 (13.3)

TEAE: treatment-emergent adverse event.
[a] Incidence >5% during either treatment.

4. Discussion

AMPLIPHY is the first study to directly compare the efficacy and safety of sepiapterin and sapropterin in both children and adults with PKU. Results demonstrate a superior treatment efficacy with sepiapterin over sapropterin; the reduction in blood Phe levels was significantly greater, representing a relative 70% greater reduction with sepiapterin versus sapropterin in the PAS. The treatment difference for the change in blood Phe levels was also significant in the FAS and among participants who completed the study, as well as in almost all participant subgroups analyzed, including male and female participants, children and adults, and those treated with sapropterin at the start of the study. In addition, the proportions of participants with high baseline blood Phe levels (≥600 and ≥360 µmol/L) whose blood Phe levels were reduced to below these levels after treatment was significantly greater with sepiapterin than sapropterin. The median time to reach these levels was also significantly shorter with sepiapterin than sapropterin. As per current USA and European PKU guidelines, individuals who maintain Phe levels below target levels are likely to exhibit better intellectual outcomes, executive functioning, mental health, and social skills than those who do not [7,8]. Therefore, these results suggest the potential for sepiapterin to improve patient outcomes; studies assessing the effect of sepiapterin on quality of life are ongoing.

Before entering Part 2, participants received sepiapterin for 2 weeks in Part 1 to assess responsiveness, defined as a reduction from baseline of ≥20% in blood Phe levels. Results show that over 80% of participants were responsive to sepiapterin. This ≥20% threshold was based on results from APHENITY [24], in which the majority of participants who were in the 15–30% response category had a reduction of ≥20%. This threshold also aligns with that used in the pegvaliase registration studies [30]. Furthermore, in patients with high Phe levels, a ≥20% reduction is likely to be considered clinically meaningful. Because the threshold was lower than that specified in the European PKU guidelines and EU sapropterin label, the primary analysis in AMPLIPHY included participants who had a ≥30% reduction in blood Phe levels during Part 1; results were consistent with the FAS. Not all participants who were enrolled in the study had previous exposure to sapropterin, yet from a mechanistic perspective, those responsive to sepiapterin would overlap with sapropterin-responsive participants, as sepiapterin has a dual mechanism of action, and higher BH_4 levels are achieved with sepiapterin administration [25]. Response to sapropterin is defined as a ≥30% reduction in blood Phe levels [11,12], therefore using a lower threshold for sepiapterin responsiveness would likely capture participants who are responsive to sapropterin. The assumption that sapropterin-responsive patients will also respond to sepiapterin was confirmed in the completed Phase 3 APHENITY study [24]. Therefore, Part 1 of this study allowed for an all-comer population to be tested for responsiveness to sepiapterin only. Furthermore, as the purpose of this study was to

evaluate sepiapterin (the test treatment) against sapropterin (the control treatment) at the highest possible doses, patients known to be non-responsive to sapropterin and those with unknown responsiveness were not excluded, given the potential to receive treatment benefits from sepiapterin. This was based on results from the Phase 2 study (ACTRN12618001031257), which showed significant reductions in blood Phe levels with sepiapterin versus sapropterin in an all-comers population (which included participants who were BH_4 non-responsive), as well as results from the Phase 3 APHENITY study, which demonstrated significant decreases in blood Phe levels versus placebo in the subgroup of participants who were documented as BH_4 non-responsive [24,27]. To confirm this, an additional analysis was carried out comparing treatment efficacy in participants who had a ≥30% reduction in blood Phe levels with sapropterin (i.e. the participants who were demonstrably BH_4 responsive), with sepiapterin-responsive participants; the results were consistent with the primary analysis ($p < 0.0001$; data not shown). To minimize any bias toward sepiapterin, the highest approved dose of sapropterin was used as the comparator, and a 4-week treatment period was used. This duration is in line with the recommended time for assessing sapropterin responsiveness [11,12], although it differs from common clinical practice in Europe, where an initial 48-h BH_4 loading test is often carried out [8,31]. Additionally, subgroup analyses show that the treatment difference between sepiapterin and sapropterin was significant, irrespective of whether participants were receiving sapropterin at screening, mitigating any potential bias.

The safety profiles of sepiapterin and sapropterin in AMPLIPHY were generally similar. The rate of treatment-related TEAEs was higher during sepiapterin treatment, but there were no serious TEAEs or TEAEs leading to treatment discontinuation in either group. Both treatments were well tolerated, with safety profiles consistent with those previously reported and no new safety signals observed.

Differences in the clinical effects between sepiapterin and sapropterin are driven by their distinct pharmacokinetic profiles and mechanisms of action; sepiapterin is actively transported into target cells more efficiently than sapropterin, leading to a greater increase in intracellular BH_4 [32–34]. It also has an independent chaperone effect that stabilizes PAH against thermal unfolding, further enhancing its function and enabling enzymatic activity even in non-BH_4-responsive genetic variants, which often lead to the most severe forms of PKU [35]. Results of this study are consistent with a Phase 2 randomized crossover study comparing 1 weeks' treatment with sepiapterin (20 mg/kg/day and 60 mg/kg/day) with the maximum licensed dosage of sapropterin (20 mg/kg/day) in adults with PKU (ACTRN12618001031257) [27]. Unlike in AMPLIPHY, participants in the Phase 2 study did not undergo responsiveness testing before treatment commenced. The results showed that, compared with sapropterin 20 mg/kg/day, sepiapterin 20 mg/kg/day was associated with a numerically greater reduction in blood Phe levels, while the reduction with the higher sepiapterin dose (60 mg/kg/day) was even significantly greater. Furthermore, in the Phase 2 study, sepiapterin 60 mg/kg/day resulted in a significant reduction in Phe levels in participants with classic PKU. In the current study, the magnitude of the reduction in Phe in those with classic PKU was numerically greater with sepiapterin than with sapropterin; however, only eight participants had classic PKU, limiting the ability to detect a statistically significant difference. As stated in the Methods, enrollment of participants with classic PKU was capped at 30% to ensure a broad representation of PKU severities. Appropriate representation of classic and mild/moderate PKU in the study ensured that the results are applicable across a broad spectrum of patients with PKU. It is well established that sapropterin has limited efficacy in patients with classic PKU, with 90% or more failing to respond to pharmacological doses [1]; therefore, these results demonstrate that sepiapterin has the potential to address unmet needs in this population.

The efficacy and safety of sepiapterin in patients with PKU have also been evaluated in the Phase 3, randomized, double-blind, placebo-controlled APHENITY study [24] and in the ongoing long-term extension (NCT05166161) [36,37]. During the placebo-controlled period, the reduction in blood Phe levels from baseline to Week 6 was significantly greater in the sepiapterin group than placebo in the overall population ($p < 0.0001$), as well as in subgroups taking sapropterin at study entry ($p < 0.0001$) and in those documented as being responsive or unresponsive to BH_4 ($p < 0.0001$ and $p = 0.001$, respectively). Furthermore, APHENITY included a larger number of participants with classic PKU ($n = 19$) than AMPLIPHY, and results showed a highly significant reduction in blood Phe levels versus placebo in this subgroup ($p < 0.0001$) [24]. Interim analyses from the ongoing extension showed that long-term sepiapterin treatment was well tolerated and demonstrated the potential for meaningful liberalization of the highly restrictive PKU diet. Collectively, these data add to the body of evidence for the clinical value of sepiapterin as a potential therapeutic option for patients with PKU.

Limitations of this study include the short treatment duration. However, this is being addressed through the ongoing long-term APHENITY Extension Study, in which participants will receive sepiapterin for up to 4 years [37]. Another limitation is the open-label design; given the clear physical differences between sepiapterin and sapropterin, it was not feasible to blind the study. However, this was mitigated by the objective nature of the efficacy endpoints. In addition, the small number of participants in some subgroups (those with classic PKU and those who were BH_4 non-responsive) limited the ability to detect statistically significant treatment differences.

Strengths of the study include the following: the dietary control observation period which excluded participants with a >20% variance in dietary Phe consumption ($n = 13$) and use of 3-day diet diaries, to confirm that there were no changes in diet that could affect the overall conduct and results of the study; the inclusion of a wide range of participants aged ≥2 years, ensuring the generalizability of the results; and the use of a comparator highly relevant to clinical practice (sapropterin). It is also important to note that most of the population had previously been treated with sapropterin and only four participants were non-responsive to BH_4. Despite the population having a high proportion of sapropterin responders, a significant treatment difference in Phe reductions was seen with sepiapterin versus sapropterin, providing evidence of the potential for sepiapterin to enhance outcomes, beyond those seen with sapropterin.

In conclusion, the AMPLIPHY study results demonstrate the superiority of the approved dosage of sepiapterin (60 mg/kg/day) in lowering blood Phe levels compared with the approved maximum dosage of sapropterin (20 mg/kg/day) in a broad range of children and adults with PKU. There were no new safety signals and no serious TEAEs or TEAEs leading to treatment discontinuation in either group. These findings add to the growing body of evidence on the efficacy and safety of sepiapterin, providing further evidence of its clinical value as a potential therapeutic option for a broad spectrum of patients with PKU and representing an advancement in the pharmacological management of this condition.

CRediT authorship contribution statement

Maria Giżewska: Writing – review & editing, Investigation. **Anita Inwood:** Writing – review & editing, Investigation. **Renáta Tyčová:** Writing – review & editing, Investigation. **Suresh Vijay:** Writing – review & editing, Investigation. **Olivia Fjellbirkeland:** Writing – review & editing, Investigation. **Francjan van Spronsen:** Writing – review & editing, Investigation. **Eva Maria Venegas-Moreno:** Writing – review & editing, Investigation. **Laura Guilder:** Writing – review & editing, Investigation. **Alberto Burlina:** Writing – review & editing, Investigation. **Heidi Peters:** Writing – review & editing, Investigation. **Murray Potter:** Writing – review & editing, Investigation. **Urh Grošelj:** Writing – review & editing, Investigation. **Anupam Chakrapani:** Writing – review & editing, Investigation. **Amaya Bélanger-Quintana:** Writing – review & editing, Investigation. **François Maillot:** Writing – review &

editing, Investigation. **Frank Rutsch:** Writing – review & editing, Investigation. **Jean-Baptiste Arnoux:** Writing – review & editing, Validation, Investigation. **Michel Tchan:** Writing – review & editing, Investigation. **Kim Ingalls:** Writing – review & editing, Supervision, Investigation. **Zhenming Zhao:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Catalina Hughes:** Writing – review & editing, Investigation. **Neil Smith:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ania C. Muntau:** Writing – review & editing, Investigation.

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Declaration of competing interest

MG: honoraria as a speaker or travel support from Applied Pharma Research, BioMarin Pharmaceutical, Mead Johnson, Nutricia, PTC Therapeutics, and Vitaflo; investigator in clinical trials sponsored by PTC Therapeutics; participation in advisory boards for BioMarin Pharmaceutical, Nutricia, and PTC Therapeutics.

AI: participation in advisory boards and clinical trial support for PTC Therapeutics.

RT: investigator in clinical trials sponsored by PTC Therapeutics; participation in advisory boards for PTC Therapeutics.

SV, LGu, AB, FM, UG, and MT: no conflicts of interest.

OF: participation in advisory board for and fees for lectures from PTC Therapeutics; principal investigator for a PTC Therapeutics clinical trial.

FvS: the University Medical Center Groningen (Groningen, Netherlands) received financial compensation for activities including advisory boards for AlltRNA, Arla Foods International, BioMarin Pharmaceutical, Illumina, Jnana Therapeutics, Moderna, 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 Applied Pharma Research, 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.

EMV-M: investigator in clinical trials sponsored by PTC Therapeutics; participation in advisory boards for PTC Therapeutics.

HP: investigator in clinical trials sponsored by PTC Therapeutics; travel support and consulting fees from PTC Therapeutics; participation in advisory boards and presentations from PTC Therapeutics.

MP: investigator in clinical trials sponsored by PTC Therapeutics; participation in advisory boards and presentations for PTC Therapeutics.

AC: institutional research support from PTC Therapeutics.

AB-Q: honoraria as an adviser and speaker, and travel funding from PTC Therapeutics; honoraria or funding from BioMarin Pharmaceutical, Danone, Grand Fontaine, Nutricia, Recordati Rare Diseases, Sanofi, and Takeda.

FR: consultancy fees from BioMarin Pharmaceutical, Immedica, Inozyme, and PTC Therapeutics.

J-BA: investigator in clinical trials sponsored by PTC Therapeutics; travel support and consulting fees from PTC Therapeutics; participation in advisory boards for PTC Therapeutics.

KI, ZZ, CH, and NS: employees of and may own stocks or shares in PTC Therapeutics.

ACM: clinical trial support for BioMarin Pharmaceutical and PTC Therapeutics; participation in advisory boards for BioMarin Pharmaceutical, Jnana Therapeutics, Maze Therapeutics, Pluvia Biotech, PTC Therapeutics, and Synlogic Therapeutics; consulting and lecturing for BioMarin Pharmaceutical, Jnana Therapeutics, Maze Therapeutics, and PTC Therapeutics.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2026.156513.

Data availability

The information developed during the conduct of this clinical study is considered confidential by the study sponsor, and individual de-identified participant data, the study protocol, or 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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