Amsterdam, 11 December 2025
EMADOC-1700519818-2426689
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Sephience

International non-proprietary name: Sepiapterin

Procedure no.: EMA/PAM/0000295271

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	17 November 2025	14 November 2025
☐	CHMP comments	01 December 2025	01 December 2025
☐	Updated CHMP Rapporteur AR	04 December 2025	n/a
☒	CHMP outcome	11 December 2025	11 December 2025

Administrative information

Procedure resources	
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EMA Assistant	**Name: Vanessa Moreno**

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1. Introduction

On 2 September 2025, the MAH submitted a completed paediatric study for Sephience, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

The data from PTC923-PKU-301 study has impact on the benefit/risk profile of Sephience™ (**c**) labelling. Information of this study should be added to section 5.1 of the SmPC as it is supportive of the efficacy in the target population.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study PTC923-PKU-301, "A Phase 3, Randomized, Crossover, Open-Label, Active-Controlled Study of Sepiapterin versus Sapropterin in Participants With Phenylketonuria Greater Than or Equal to 2 Years of Age" is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Sepiapterin Powder for Oral Use is a powder for oral use with a yellow to orange colour and intended to be mixed with water, apple juice, or small amount of soft food such as apple sauce and jams prior to administration. Dosing of sepiapterin is based on age and participant body weight.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- PTC923-PKU-301, "A Phase 3, Randomized, Crossover, Open-Label, Active-Controlled Study of Sepiapterin versus Sapropterin in Participants With Phenylketonuria Greater Than or Equal to 2 Years of Age"

2.3.2. Clinical study

PTC923-PKU-301, "A Phase 3, Randomized, Crossover, Open-Label, Active-Controlled Study of Sepiapterin versus Sapropterin in Participants With Phenylketonuria Greater Than or Equal to 2 Years of Age"

Description

Study 301 was a Phase 3, 2-part, open-label, randomised, active-controlled crossover study of sepiapterin *versus* sapropterin in participants with PKU aged ≥2 years. Participants with biochemically diagnosed classic PKU were eligible, but enrollment in this group was capped at 30% of the total study population.

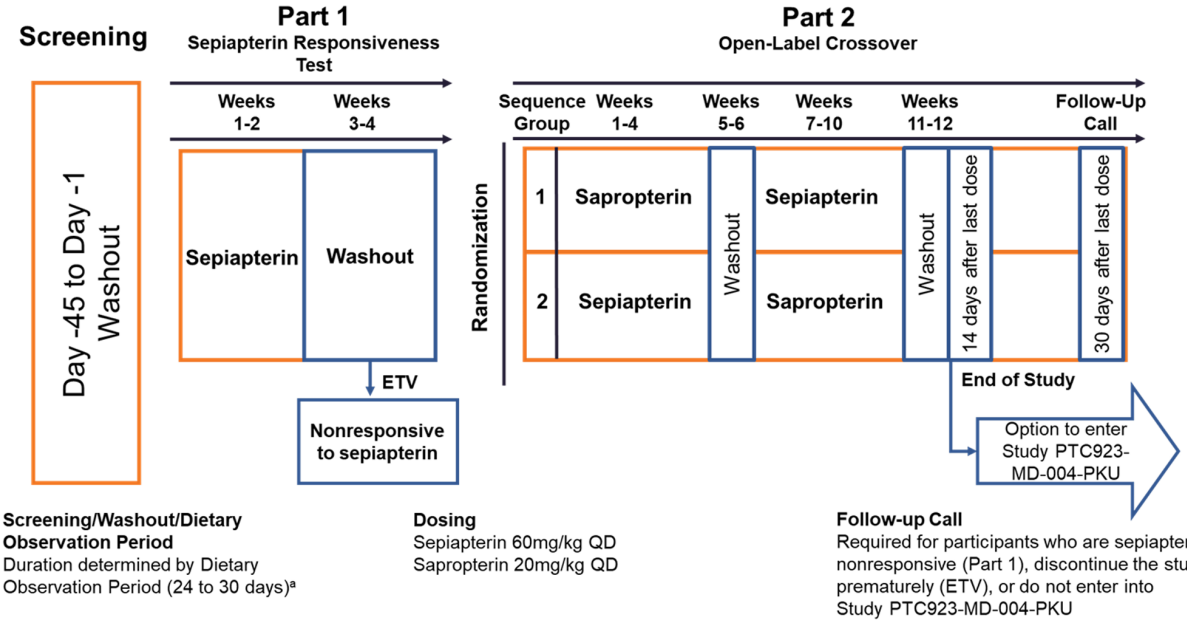
After providing consent and/or assent (as applicable), participants entered the Screening/Washout/Dietary Control Observation Period (up to 45 days in duration). Participants who were receiving exogenous tetrahydrobiopterin supplementation (i.e., sapropterin [KUVAN®]) at the Screening Visit completed a 7-day washout period. During the 24- to 30-day Dietary Control Observation Period, participants continued their usual diet, with no change in total protein, non-Phe protein from medical formula, or daily Phe consumption, and maintained a weekly 3-day diet record for 4 consecutive weeks. Participants with a >20% variance in dietary Phe consumption during the Dietary Control Observation Period were considered screen failures. Eligible participants entered Part 1 at the end of the Dietary Control Observation Period. Throughout the study, participants continued their usual diet without modification (i.e., no change in total protein, non-Phe protein from medical formula, or dietary Phe consumption).

Part 1 consisted of an open-label assessment of responsiveness to sepiapterin wherein all participants received 14 days of oral sepiapterin treatment. Participants who experienced a ≥20% reduction in blood Phe levels were classified as responsive and progressed to Part 2. Nonresponsive participants did not enter Part 2 of the study.

Part 2 was a 2-period crossover study wherein each participant was randomised 1:1 to 1 of 2 treatment sequences: 20 mg/kg sapropterin-60 mg/kg sepiapterin (Sequence 1) or 60 mg/kg sepiapterin-20 mg/kg sapropterin (Sequence 2). Randomisation was stratified based on mean percent reduction in blood Phe levels from Part 1 (i.e., participants with mean percent reduction in Phe levels of ≥20% to <30% and participants with mean percent reduction in Phe levels of ≥30%). Participants received each open-label treatment for 4 weeks. Each 4-week treatment period was followed by a 14-day washout.

After completing the study, eligible participants had the option to continue treatment in an open-label Study PTC923-MD-004-PKU.

Figure 1: Study Design



Abbreviations: ETV, Early Termination Visit
Source: PTC923-PKU-301 Clinical Study Report, Figure 1

Methods

Study participants

Planned:

- Part 1: approximately 100 participants
- Part 2: 42 participants analysed:
- Part 1: 82 participants enrolled and treated with sepiapterin
- Part 2: 62 participants randomized and treated (30 participants to Sequence 1 sapropterin/sepiapterin] and 32 participants to Sequence 2 [sepiapterin/sapropterin])

This study enrolled male and female participants aged ≥2 years with a confirmed clinical diagnosis of PKU. Participants were required to have had blood Phe levels ≥360 µmol/L while on current therapy at any time during Screening or when taking the average of the 3 most recent Phe levels from the participant's medical history (inclusive of the Screening value). Enrolment of participants with biochemically defined classic PKU was capped at 30% of the total study population.

Treatments

Part 1 All participants received sepiapterin 60 mg/kg for 14 days starting on Day 1. Part 2 Participants who experienced a ≥20% reduction in blood Phe following therapy were classified as responsive and were randomized to 1 of 2 treatment sequences:

- Sequence 1: Sapropterin 20 mg/kg daily for 4 weeks followed by sepiapterin 60 mg/kg daily for 4 weeks (each treatment period followed by a 14-day [+3-day window] washout period)
- Sequence 2: Sepiapterin 60 mg/kg daily for 4 weeks followed by sapropterin 20 mg/kg daily for 4 weeks (each treatment period followed by a 14-day [+3-day window] washout period)

Duration of Treatment:

Observation Period: 24 to 30 days

Part 1: 28 to 35 days

Part 2: 84 days

Objective(s)

Primary:

- To compare the efficacy of sepiapterin to sapropterin in reducing blood phenylalanine (Phe) levels in participants with phenylketonuria (PKU)

Secondary:

- To evaluate the efficacy of sepiapterin in reducing blood Phe levels
- To assess the safety and tolerability of sepiapterin

Exploratory

- To evaluate changes in blood tyrosine (Tyr) over time, including the Phe:Tyr ratio
- To assess the taste, palatability, and acceptability (<18 years) of sepiapterin
- To evaluate sepiapterin effect on quality of life (QOL) using the Phenylketonuria Quality of Life questionnaire (PKU-QOL) in the subset of participants who are able to complete the PKU-QOL (ie, participants whose primary language is English, Turkish, Dutch, German, Spanish, Italian, Portuguese, or French) (ages 6 to 8 years, Parent PKU-QOL; ages 9 to 11 years, Child PKU-QOL; ages 12 to 17 years Adolescent PKU-QOL; and ages ≥18 years Adult PKU-QOL)
- To evaluate sepiapterin effect of QOL using the EQ-5D (EQ-5D-Y Proxy Version 1 [3 to 7 years]; EQ-5D-Y [8 to 15 years]; and EQ 5D-5L ([≥16 years])

Outcomes/endpoints

The primary efficacy endpoint was mean change in blood Phe level from baseline to Weeks 3 and 4 of each treatment period (the average of the last 2 weeks of each treatment period) in Part 2.

The primary analysis was performed on Primary Analysis Set (PAS), which was defined as the stratum of participants with a mean percent reduction in Phe level of ≥30% during Part 1.

Secondary

- Proportion of participants with baseline blood Phe levels ≥600 µmol/L who achieve Phe levels <600 µmol/L after each treatment period in Part 2
- Proportion of participants reaching blood Phe <360 µmol/L after each treatment period in Part 2
- Adverse events (AEs), physical examinations, vital sign assessments, 12-lead electrocardiograms (ECGs), and routine clinical laboratory assessments

Exploratory

- Changes in blood Tyr over time, including the Phe:Tyr ratio
- Taste, palatability, and acceptability scores (<18 years)
- Changes from baseline in QOL using PKU-QOL questionnaire in the subset of participants that are able to complete the PKU-QOL (ie, participants whose primary language is English, Turkish, Dutch, German, Spanish, Italian, Portuguese, or French) (ages 6 to 8 years, Parent PKU-QOL; ages 9 to 11 years, Child PKU-QOL; ages 12 to 17 years, Adolescent PKU-QOL; and ages ≥18 years Adult PKU-QOL)
- Changes from baseline in QOL using the EQ-5D (EQ-5D-Y Proxy Version 1 [3 to 7 years]; EQ-5D-Y [8 to 15 years]; and EQ-5D-5L ([≥16 years])

Sample size

82 patients were enrolled in the study.

Randomisation and blinding (masking)

Statistical Methods

The following datasets were defined for this study:

- Primary Analysis Set (PAS): All participants who achieved a ≥30% reduction in blood Phe concentrations in Part 1, were randomized, and took at least 1 dose of study drug in Part 2 were included in the PAS. Participants were analysed according to their randomized treatment.
- Full Analysis Set (FAS): All participants who were randomized and took at least 1 dose of study drug in Part 2 were included in the FAS. Participants were analysed according to their randomized treatment. All efficacy analyses were based on the FAS.
- Per Protocol (PP) Analysis Set: The PP Analysis Set included all participants in the FAS who met the study eligibility requirements and had no major protocol deviations that affected the validity of the efficacy measurements. The PP Analysis Set was used for sensitivity analysis of the primary efficacy endpoint. The criteria for inclusion in the PP Analysis Set were detailed in the statistical analysis plan (SAP) and finalized prior to study unblinding.
- Safety Analysis Set: All participants who received at least 1 dose of study drug, including during Part 1, were included in the Safety Analysis Set. Participants were analysed according to actual treatment received.

Primary Efficacy Analysis: The primary endpoint was the mean change in blood Phe levels from baseline to Weeks 3 and 4 of each treatment period (the average of the last 2 weeks of each treatment period) in Part 2, with baseline defined as the average of Day -1 and Day 1 predose blood Phe concentration of each respective treatment period in Part 2. Phe level after each treatment period refers to the average of blood Phe concentration collected during the Week 3-4 analysis visit window of each treatment period. Mean level at Weeks 3 and 4 was calculated as the average of blood Phe concentration collected during the Week 3-4 analysis visit window of each treatment period. The null hypothesis was that the mean change in blood Phe levels from baseline to Weeks 3 and 4 was the same between sepiapterin and sapropterin, *versus* the alternative that they were different, at the 2-sided 0.05 significance level. For the primary efficacy endpoint, a gatekeeping procedure was used to control the familywise error rate. The stratum of participants with mean percent reduction in Phe level of ≥30% during Part 1 (i.e., PAS) was tested at the significance level of 0.05 (2-sided). If p was <0.05, then the study was to be declared positive; otherwise, the study would be declared negative. Only if the test based on the PAS was statistically significant at the 0.05 level would the FAS be tested, also at the 0.05 significance level. A mixed-model repeated measures (MMRM) model was fitted on the calculated mean change in blood Phe from baseline to Weeks 3 and 4 of each treatment period in Part 2 for each participant. The model included fixed effects for treatment group, sequence, period, visit (Weeks 1 and 2 and Weeks 3 and 4), treatment-by-visit interaction, and the baseline blood Phe (for each period) as a covariate. In addition, participant nested within sequence was included as a random effect. The MMRM model was used on available data assuming the missing assessments were missing at random; no explicit imputation was involved. An unstructured within-participant covariance structure was assumed. If the model did not converge under the unstructured covariance matrix, the following covariance structures were to be employed in order until convergence is reached: heterogeneous Toeplitz, heterogeneous Compound Symmetry, heterogeneous first-order autoregressive, Toeplitz, Compound Symmetry, and first-order autoregressive. The least squares (LS) mean estimate for the change in blood Phe levels from baseline to Weeks 3 and 4 was used to perform treatment group comparisons. For the analysis on FAS, an additional fixed-effect term, the randomization stratum (mean percent reduction in Phe levels of ≥20% to <30% or ≥30% in Part 1), was included in the model.

The following sensitivity analyses were performed:

1. The MMRM model described above for the primary endpoint on the FAS was also performed on the PP Analysis Set.

2. Completer analysis with an analysis of covariance (ANCOVA) model: only the completers who had the assessments at Weeks 3 and 4 in each period of Part 2 were included in the ANCOVA model.

For the analysis on PAS, the model included fixed effects for treatment group, sequence, and period; the baseline blood Phe (for each period) was used as a covariate. The randomization stratum was also added to the analysis on FAS.

The following subgroup analyses were performed for the change in blood Phe levels from baseline to Weeks 3 and 4 for both PAS and FAS:

- Sex (male, female)
- Age: (<18 years, ≥18 years; 2 to 5 years, 6 to 11 years, 12 to 18 years, ≥18 years)
- Response to sapropterin challenge (yes, no)
- Participants who were receiving supplementation treatment (pegvaliase pqpz, sapropterin, or none) at study entry
- Classic PKU (yes, no)
- Baseline Phe level of Part 2 (≥600 µmol/L, <600µmol/L; ≥360 µmol/L, <360µmol/L; ≥120 µmol/L, <120µmol/L)

(the protocol includes statistical plan for secondary endpoints)

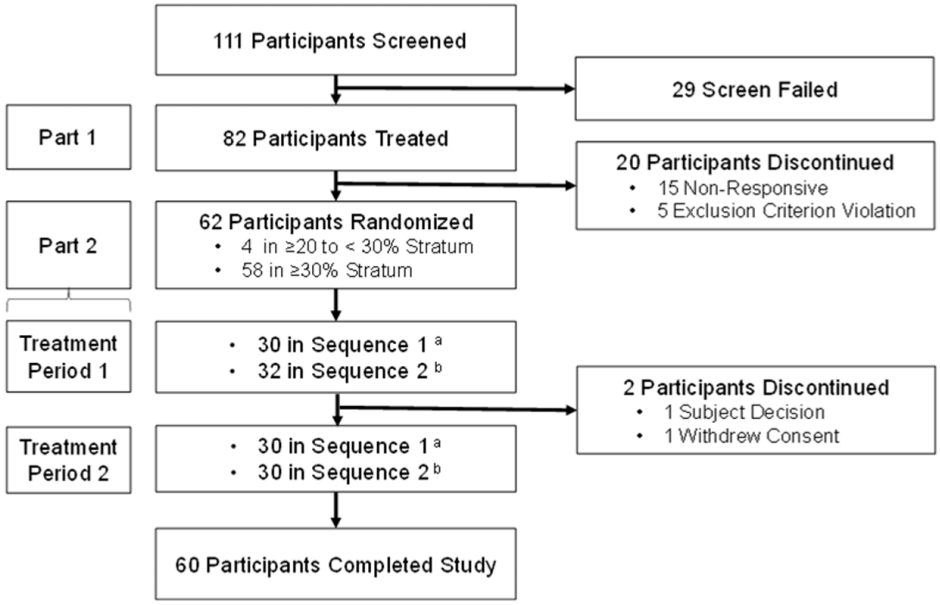
Results

Participant flow

Eighty-two participants were tested for responsiveness in Part 1. Of those 82 participants, 67 participants (81.7%) demonstrated a ≥20% reduction in blood Phe in response to sepiapterin during Part 1. Five of these 67 participants were not randomised to Part 2 because it was discovered that these participants did not meet the study eligibility criteria.

Thus, 62 participants were randomised to receive either Sequence 1 (sapropterin-sepiapterin) (subsample size [n]=30) or Sequence 2 (sepiapterin-sapropterin) (n=32) during Part 2.

Figure 2: Participant Disposition



Recruitment

Baseline data

The median age of the Part 2 participants (i.e., the PAS) at Screening was 14.0 years (range: 2 to 66 years) with the majority (79.0%) of the study population being children or adolescents (<18 years). In terms of race, participants were predominantly white (85.5%). Relatively equal proportions of men and women were enrolled in Part 2 of the study. Most (96.8%) participants in Part 2 had PKU diagnosed at newborn screening, and the majority (83.9%) presented with phenotypically defined non-classic PKU. In Part 2, disease characteristics were similar between participants in Sequence 1 and Sequence 2.

Number analysed

Efficacy results

Part 1

In Part 1, 70 of 82 participants (85.4%) achieved a Phe value < 600 µmol/L, 56 of 82 participants (68.3%) achieved a Phe value < 360 µmol/L, and 6 of 82 participants (7.3%) achieved a Phe value < 120 µmol/L at Weeks 1 and 2.

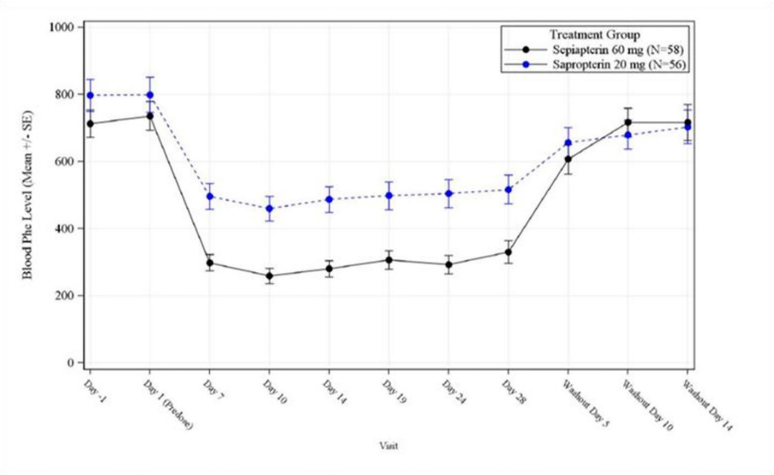
For the 38 participants who were on sapropterin at study enrolment, blood Phe decreased by 449.8 µmol/L from a mean baseline of 766.9 µmol/L to a mean of 317.2 µmol/L at Weeks 1 and 2. This change represents a 54.1% decrease in blood Phe from baseline after only 2 weeks of sepiapterin treatment. Among these participants, 27 (71.1%) participants achieved a blood Phe of < 360 µmol/L and 35 (92.1%) participants achieved a blood Phe <600 µmol/L at Weeks 1 and 2 of Part 1.

Part 2

In the PAS, mean (standard deviation [SD]) baseline blood Phe concentrations for participants entering treatment were 790.4 µmol/L (370.01) and 725.8 µmol/L (302.09) for sapropterin and sepiapterin, respectively. Least square (LS) mean (SE) changes from baseline in blood Phe concentrations were -256.6 µmol/L (28.22) and -437.0 µmol/L (27.95) for sapropterin and sepiapterin, respectively. The LS

mean difference between sepiapterin and sapropterin was -180.4 µmol/L, p< 0.0001, indicating that sepiapterin was superior to sapropterin at lowering blood Phe in patients with PKU.

Figure 2: **Mean Blood Phenylalanine Levels (µmol/L) Over Time – Part 2 (Primary Analysis Set)**



Abbreviations: N, number of participants who received the respective treatment; Phe, phenylalanine
Source: PTC923-PKU-301 Clinical Study Report, Figure 3

The same test was performed on the Full Analysis Set (FAS), which was defined as all participants who were randomised and took at least 1 dose of study drug in Part 2. Sepiapterin had a statistically significant (p< 0.0001) greater treatment effect than sapropterin on mean change in blood Phe levels from baseline to Weeks 3 and 4 when the analysis was repeated on the FAS.

Results of the subgroup analyses (sex, age group, response to sapropterin challenge, participants receiving sapropterin supplementation at study entry, biochemically diagnosed classic PKU, baseline Phe level of Part 2) on the primary efficacy endpoint were generally consistent with the results of the primary analysis showing treatment benefit favouring sepiapterin relative to sapropterin across all subgroups.

Across all secondary efficacy endpoints, sepiapterin 60 mg/kg had a statistically significant treatment effect that was superior to sapropterin 20 mg/kg. Treatment with sepiapterin 60 mg/kg resulted in consistently greater proportions of participants in the PAS who achieved reductions in Phe levels <120, <360, <600 µmol/L compared with sapropterin 20 mg/kg. At Weeks 3 and 4 in Part 2, the proportion of participants treated with sepiapterin achieving a Phe level <120, <360, <600 µmol/L was 6.9%, 72.4%, and 89.7% *versus* 1.8%, 44.6%, and 64.3% in the sapropterin group.

The proportion of participants with baseline Phe≥600 µmol/L who achieved Phe levels <600 µmol/L in Part 2 was significantly greater (p=0.0028) following treatment with sepiapterin (89.2%) compared with sapropterin (51.3%) in the PAS. Similar results were observed when the analysis was repeated on the FAS.

Among participants who were ≥12 years in the stratum of participants with a baseline blood Phe of ≥600 µmol/L, a statistically significantly greater proportion of participants achieved the age-appropriate European target blood Phe level of <600 µmol/L at Weeks 3 and 4 with sepiapterin (88.5%) *versus* sapropterin (44.0%) in the PAS and FAS.

The proportion of participants with baseline Phe ≥360 µmol/L in the PAS who achieved Phe levels < 360 µmol/L in Part 2 was significantly greater (p=0.0048) following treatment with sepiapterin (69.2%) compared with sapropterin (39.2%) in the PAS. Consistent results were observed when the analysis was repeated on the FAS.

In the subset of participants <12 years of age who had a baseline blood Phe of ≥360 µmol/L, a greater proportion of participants who were treated with sepiapterin achieved the age-appropriate European target blood Phe level of <360 µmol/L at Weeks 3 and 4 compared with sapropterin treatment (76.5% *versus* 47.4%, respectively). The treatment difference favouring sepiapterin was numerically superior, approaching statistical significance (p=0.0594) in the PAS and the FAS.

The proportion of participants with baseline Phe ≥120 µmol/L who achieved Phe levels <120 µmol/L in Part 2 was greater following treatment with sepiapterin (6.9%) compared with sapropterin (1.8%) in the PAS, but the p value was not estimable. Consistent results were observed when the analysis was repeated on the FAS.

The Phe:Tyr concentration ratio followed a similar pattern of change as blood Phe after treatment with sepiapterin and sapropterin. Both treatments elicited a rapid reduction in the Phe:Tyr ratio from baseline that was sustained throughout the 28-day treatment period, but sepiapterin had a more profound effect. The Phe:Tyr ratio was approximately 17 at baseline and decreased by a mean of -10.1 after 28 days of sepiapterin treatment compared with -5.7 with 28 days of sapropterin treatment. Minimal changes in blood Tyr concentration were observed in Part 1 or Part 2.

Palatability of sepiapterin was favourable in 5 (83.3%) of 6 participants <5 years of age, and taste was rated as "good" or "really good" in more than half of the participants of ≥5 to <18 years of age (39/60 [65%]). Acceptability or ease of administration of the first dose of sepiapterin was considered unfavourable or difficult by 22 (88%) of 25 parents or caregivers of children <12 years of age. Considering acceptability was assessed at the first dose only, in young children, ease of administration of drug product is expected to improve with repeat dosing, and there were no participants who discontinued from the study due to difficulty in administering the study drug.

Safety results

All participants who received at least 1 dose of study drug, including during Part 1, were included in the Safety Analysis Set.

There were no unanticipated safety findings in this study. Sepiapterin 60 mg/kg/day was well tolerated in this study population of participants with PKU ≥2 years of age.

There were no deaths, serious treatment-emergent adverse events (TEAEs), or discontinuations due to TEAEs in the study. The majority of TEAEs were mild (Grade 1) or moderate (Grade 2) in severity. No severe (Grade 3) TEAEs were considered related to study drug in either part of the study.

In Part 1, 44 participants (53.7%) had at least 1 TEAE, and 17 participants (20.7%) had at least 1 treatment-related TEAE. The most frequent treatment-related TEAEs by System Organ Class (SOC) were diarrhoea (5 participants [6.1%]), abdominal pain (3 participants [3.7%]), and headache (3 participants [3.7%]).

In Part 2, 41 participants (66.1%) experienced at least 1 TEAE while receiving sepiapterin, and 37 participants (61.7%) experienced at least 1 TEAE while receiving sapropterin. The most frequent treatment-related TEAEs by SOC during sepiapterin treatment were Gastrointestinal disorders (sepiapterin 11.3%, sapropterin 1.7%). The most frequent treatment-related TEAEs by SOC during sapropterin treatment were nervous system disorders (sepiapterin 1.6%, sapropterin 3.3%). Treatment-emergent adverse events preferred terms reported in ≥5% of participants during sepiapterin treatment and at rates of at least 2% higher compared with during sapropterin treatment were diarrhoea (sepiapterin 9.7%, sapropterin 1.7%) and nausea (sepiapterin 9.7%, sapropterin 3.3%), which are consistent with the known safety profile of sepiapterin. Treatment emergent adverse events preferred

terms reported in ≥5% of participants during sapropterin treatment and at higher rates compared with during sepiapterin treatment were upper respiratory tract infection (sepiapterin 12.9%, sapropterin 15.0%) and headache (sepiapterin 8.1%, sapropterin 13.3%), which are consistent with the known safety profile of sapropterin.

Clinical laboratory values were generally stable and within the normal range throughout Part 1 and Part 2. There were no participants with any postbaseline abnormal liver function results meeting the criteria of Hy's Law. All abnormal electrocardiogram results were not clinically significant, and the proportion of abnormal not clinically significant results was similar between the sepiapterin and sapropterin treatment periods.

2.3.3. Discussion on clinical aspects

Study 301 was designed to demonstrate superiority of sepiapterin treatment over sapropterin treatment in patients with PKU aged ≥2 years. Results of this study showed that sepiapterin imparted clinically significant and highly statistically significant greater magnitude of mean blood Phe reduction compared with sapropterin in patients with PKU ≥2 years of age. By Day 28 of treatment, the LS mean change in blood Phe levels from baseline to Weeks 3 and 4 was -437.0 µmol/L with sepiapterin and -256.6 µmol/L with sapropterin for an LS mean treatment difference of -180.4 µmol/L ($p<0.0001$).

The superior treatment benefit of sepiapterin relative to sapropterin was demonstrated across all subgroups, including subpopulations nonresponsive to sapropterin therapy and those with classic PKU, supporting its use in a broad patient population. Considering the study population comprised a larger proportion of patients who were responsive to sapropterin (>50%) than typically observed in clinical practice, the treatment difference measured in this study likely underestimates what may be observed in a general population, including patients who are treatment-naive. The substantial reduction in Phe level with sepiapterin treatment allowed a greater proportion of participants to achieve the targeted European guidelines (<600 µmol/L in participants ≥12 years of age) for blood Phe levels in PKU compared with sapropterin. Among participants who were ≥12 years in the stratum of participants with a baseline blood Phe of ≥600 µmol/L, a statistically significantly greater proportion of participants achieved the target blood Phe level of <600 µmol/L at Weeks 3 and 4 with sepiapterin (88.5%) versus sapropterin (44.0%).

There were no unanticipated safety findings in this study. The majority of TEAEs were mild or moderate in severity and consistent with the known safety profiles of both sepiapterin and sapropterin. Data from this study indicate consistency of the safety profile of sepiapterin in children ≥2 years of age with that of adults with PKU in Studies PTC923-MD-003-PKU and PTC923-MD-004-PKU. The data from Study 301 has no impact on the benefit/risk profile of Sephience™ (c) labelling; therefore, no changes were proposed to the current approved sepiapterin Summary of Product Characteristics.

3. CHMP's overall conclusion and recommendation

The study provides further insight on the response to Sephience (sepiapterin) in different subgroups, including subpopulations non-responsive to sapropterin therapy and those with classic PKU, supporting its use in a broad patient population. No new safety data was generated.

The results obtained from Study 301 indicate that its primary endpoint was met. It was demonstrated that sepiapterin treatment is superior to sapropterin treatment in patients with PKU above 2 years with statistically significant reduction of the mean blood Phe by day 28 in all subgroups studied, including patients that were reported as non-responsive to sapropterin (> 50% population of the study) and

patients treatment-naïve as well as patients with different Phe values at baseline (≥600 µmol/L, Phe ≥360 µmol/L, and Phe ≥120 µmol/L). The reduction in plasma Phe levels was accompanied by an increase in Phe:Tyr ratio that was maintained during the 28-day treatment. This has been along with a favourable acceptability of the treatment and not compromising safety. Facing this, it is not agreed with the MAH in that the data from Study 301 has no impact on the benefit/risk profile of Sephience (**c**) labelling. Information of this study should be added to section 5.1 of the SmPC as it is considered supportive of the efficacy in the target population and of relevance to the prescriber.

☒ Fulfilled:

In view of the available data regarding Study 301 the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided ***no later than 60 days after the receipt*** of these conclusions. The scope of the variation should be the update of section 5.1 of the SmPC as information of the outcome of Study 301 is considered supportive of the efficacy in the target population and of relevance to the prescriber.