25 January 2018
EMA/55539/2018
Human Medicines Evaluation Division

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

Kuvan

sapropterin

Procedure no: EMEA/H/C/000943/P46/028

Note

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

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1. Introduction

On 24th October 2017, the MAH (BioMarin International Limited) submitted the final clinical study report (CSR) for the extension phase of the SPARK study for Kuvan, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The SPARK study (Study 2009-015758-33) was a 2-part study called "A phase IIIb comparative open-label clinical study to evaluate the efficacy, safety and pharmacokinetics (PK) of Kuvan after 26 weeks of treatment in patients <4 years of age with phenylketonuria (PKU)".

The initial 26-week part of SPARK was a follow-up measure, FUM005, as well as part of the agreed Paediatric Investigation Plan (PIP) EMA-001476-PIP01-13 for Kuvan. The results of the 26 week treatment phase were submitted to the EMA in September 2014 as part of Type II variation application EMEA/H/C/000943/II/0033.

In this submission, the final CSR of the long-term extension phase of the SPARK study is provided.

This extension phase was not part of the approved PIP for Kuvan.

A short critical expert overview has also been provided.

No changes to the approved product information are proposed by the MAH however the Rapporteur suggests that the results of the 3 year Extension Period should be added to section 5.1 for information to prescribers.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the SPARK STUDY (A Phase IIIb, multicentre, open-label, randomised, controlled study of the efficacy, safety and population pharmacokinetics of sapropterin dihydrchloride (Kuvan) in Phenylketonuria (PKU) patients <4 years old – 2009-015768-33) is a stand-alone study.

The initial 26-week part of SPARK was a follow-up measure, FUM005, as well as part of the agreed Paediatric Investigation Plan (PIP) EMA-001476-PIP01-13 for Kuvan. This study was performed in order to evaluate the response to and safety of Kuvan in patients <4 years of age with PKU.

2.2. Information on the pharmaceutical formulation used in the study

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- 2009-015768-33 - A Phase IIIb, multicentre, open-label, randomised, controlled study of the efficacy, safety and population pharmacokinetics of sapropterin dihydrchloride (Kuvan) in Phenylketonuria (PKU) patients.

2.3.2. Clinical study

2009-015768-33 - A Phase IIIb, multicentre, open-label, randomised, controlled study of the efficacy, safety and population pharmacokinetics of sapropterin dihydrchloride (Kuvan) in Phenylketonuria (PKU) patients.

Description

The purpose of this study was to evaluate efficacy and safety of Kuvan in infants and children with PKU who were <4 years of age at the time of entry into this study and to evaluate the population pharmacokinetics (PopPK), as this age group was not studied in the pre-approval trials.

The main aim of the Extension Period was to evaluate the efficacy over time of Kuvan treatment plus phenylalanine (Phe)-restricted diet therapy in increasing dietary Phe tolerance and also to evaluate long-term safety.

Methods

Objectives

The primary objectives are:

- To evaluate the efficacy after 26 weeks of Kuvan treatment plus Phe-restricted diet therapy in increasing dietary Phe tolerance, as compared to dietary therapy alone in <4 year old infants and children with PKU. Phe tolerance was defined as the amount of dietary Phe (mg/kg per day) ingested while maintaining blood Phe levels within the range of 120 to 360 μ mol/L (defined as $\geq$120 to <360 μ mol/L).
- To evaluate the safety after 26 weeks of Kuvan treatment in <4 year-old infants and children with PKU.
- To evaluate BH4 (tetrahydrobiopterin; sapropterin) blood levels via scheduled PopPK samplings.

The secondary objectives are:

- To evaluate blood Phe levels for all subjects during the 26-week Study Period.
- To evaluate the effectiveness of Kuvan treatment in increasing dietary Phe tolerance, as compared to pre-Kuvan treatment during the 26-week Study Period in <4 year-old infants and children with PKU.
- To assess neurodevelopmental function during Kuvan treatment, as compared to dietary treatment alone, during the 26-week Study Period in < 4 year-old infants and children with PKU.
- To investigate the predictive value of the phenylalanine hydroxylase (PAH) genotype in BH4 responsive individuals.
- To assess potential effects on blood pressure during the 26 week Study Period and the 3-year Extension Period.
- To assess potential effects on growth during the 26 week Study Period and the 3-year Extension Period.
- To evaluate long-term safety, neurodevelopmental outcomes, dietary Phe tolerance, and blood Phe levels in the 3-year Extension Period.

Study design

This study is a multicentre, open-label, randomised, controlled study.

Following Screening, eligible subjects were randomized 1:1 to receive either (a) 10 mg/kg per day Kuvan plus a Phe-restricted diet, or (b) just a Phe-restricted diet over a 26-week Study Period. It was intended that all subjects would maintain blood Phe levels within a range of 120 to 360 µmol/L (defined as ≥120 to <360 µmol/L) through monitored dietary intake during the 26-week Study Period. If after approximately 4 weeks, a subject's Phe tolerance had not increased by >20% versus baseline, the Kuvan dose could have been increased in a single step to 20 mg/kg per day. A PopPK trial was included in the Study Period, with collection of baseline (pre-treatment) blood samples for measurement of endogenous BH4 levels. PopPK samplings were also to be obtained during trial Weeks 5 to 12, inclusive.

After completing the 26-week Study Period, subjects were then eligible for enrolment in the Extension Period, in which all subjects who continued in the trial were to receive Kuvan treatment plus a Phe-restricted diet. For those subjects randomized to the Phe-restricted diet alone during the 26-week Study Period, they were commenced on Kuvan at a same starting dose of 10 mg/kg per day in the Extension Period. At the discretion of the Investigator, a dose increase up to a maximum of 20 mg/kg per day was to be allowed during the Extension Period. A subject's treatment during the Extension Period was to continue for 3 years or until commercial product was approved for <4 year-old subjects with PKU.

Subjects who achieved their 4th birthday during the Extension Period had the option of remaining in the study or exiting the study and obtaining commercial product, while those subjects who had their 4th birthday during the Study Period had to complete the 26-week phase, unless prematurely discontinued from the study.

Study population /Sample size

One hundred and nine (109) subjects were screened. The intention-to-treat (ITT) population included all randomised subjects. The trial enrolled 56 subjects with phenylketonuria (PKU) and aged <4 years of age at the scheduled Day 1 visit of the 26-week Study Period. 27 subjects received Kuvan plus Phe-restricted diet and 29 subjects received Phe-restricted diet only. All randomised subjects in the Kuvan plus Phe-restricted diet group received at least one dose of study drug in this study. In total, 51 out of the 56 subjects completed the primary 26-week Study Period and continued on to the Extension Period of the study.

The efficacy population consisted of all subjects who were randomised at the start of the Study Period and analysed according to the group allocated. For the primary analysis, the efficacy population was the ITT population.

The safety population consisted of all subjects who had some safety assessment data available (at least one visit in vital signs, adverse event [AE] or laboratory results) in the Study Period and:

- who received at least one dose of Kuvan in the Study Period, or
- who were randomised to Phe-restricted diet alone.

Overall, 54 subjects were included in the safety population (27 subjects in each treatment group).

At the end of the 26- week Study Period, 51 subjects were eligible and entered the Extension Period. No withdrawals due to AE occurred.

The sample size analysed in the Extension Period was small, and a total of 18 out of 51 subjects (35.3%) discontinued the study prematurely. The reason for the majority of the subjects who discontinued prematurely, was due to the subject having reached an age where they could be taken off study, per the protocol, and switched to commercial drug.

Two populations were defined for the Extension Period, the intention-to-treat Extension (ITTE) population and the per-protocol Extension (PPE) population:

i. The intention-to-treat Extension (ITTE) population included all subjects randomised in the Study Period who continued in the Extension Period. All randomised subjects who continued in the Extension Period received at least one dose of study drug in the Extension Period. In total, 33 out of the 51 subjects completed the study.

ii. The per-protocol Extension (PPE) population comprised all subjects in the ITTE population without any major protocol deviations.

In total, 6 subjects had a major protocol deviation during the Extension Period and were thus excluded from the PPE population; all were related to adherence to Kuvan (<80% or >125%).

The safety extension population consisted of all subjects who received at least one dose of Kuvan and had some safety assessment data available (at least one visit with vital signs, adverse event [AE] or laboratory results).

Baseline data

The primary 26-week efficacy analysis included 56 subjects. Thirty (53.6%) were males; 96.4% were Caucasians. The overall mean ± SD age was 21.2 ± 12.1 months.

The mean ± SD age at PKU diagnosis was 27.2 ± 79.8 days for subjects in the Kuvan plus Phe-restricted diet group and 32.6 ± 72.2 days for subjects in the Phe-restricted diet alone group.

The mean ± SD blood Phe level at baseline was 287.3 ± 166.6 µmol/L in the Kuvan plus Phe-restricted diet group and 352.9 ± 219.9 µmol/L in the Phe-restricted diet alone group. Most subjects had either mild (46.4%) or moderate (32.1%) PKU disease severity. Six subjects (22.2%) in the Kuvan plus Phe-restricted diet group and 5 subjects (17.2%) in the Phe-restricted diet alone group had at least one medical history condition on entry to the study.

The majority of subjects received a concomitant medication during the Study Period (88.9% in the Kuvan plus Phe-restricted diet group and 93.1% in the Phe-restricted diet alone group) and in the Extension Period (100% in the Kuvan continuous group and 92.3% in the Kuvan Extension only group).

The overall mean ± SD adherence to Kuvan during the Study Period was 100% ± 4.4%, ranging from 82% to 107%. The overall mean ± SD adherence to diet in the Kuvan plus Phe-restricted diet was 94.6% ± 9.4%, ranging from 69% to 111%. The overall mean (SD) adherence to Phe-restricted diet alone was 92.1% ± 23.8%, ranging from 65% to 183%.

The overall mean ± SD adherence to Kuvan during the Extension Period was 106.8% ± 25.5%, ranging from 74% to 240%. The mean ± SD study treatment duration period was slightly longer in the Kuvan continuous group compared with the Kuvan Extension only group (181.4 ± 50.6 weeks and 136.6 ± 40.7 weeks, respectively). A shorter treatment duration was expected in the Kuvan Extension only group as the subjects started receiving Kuvan at the start of the Extension Phase only (expected treatment duration 3 years), whereas the Kuvan continuous group started Kuvan treatment at the beginning of the Study Period (expected treatment duration 3.5 years).

Treatments

The test product was Kuvan 100 mg soluble tablets (sapropterin dihydrochloride).

Eligible subjects were randomized 1:1 to receive either (a) 10 mg/kg per day Kuvan plus a Phe-restricted diet, or (b) just a Phe-restricted diet over a 26-week Study Period. If after approximately 4 weeks, a subject's Phe tolerance had not increased by >20% versus baseline, the Kuvan dose could have been increased in a single step to 20 mg/kg per day.

For those subjects randomized to the Phe-restricted diet alone during the 26-week Study Period, their starting Kuvan dose in the Extension Period was to be 10 mg/kg per day. A dose increase up to a maximum of 20 mg/kg per day was to be allowed during the Extension Period at the discretion of the Investigator.

Outcomes/endpoints

The primary endpoint of the study was the dietary Phe tolerance after 26 weeks (6 months) of treatment with Kuvan plus Phe-restricted diet as compared to a Phe-restricted diet alone, where Phe tolerance was defined as the amount of dietary Phe (mg/kg/day) ingested while maintaining overall control of PKU (assessed by mean blood Phe levels within target range, analysis of diet and Kuvan treatment compliance). The dietary Phe tolerance (mg/kg/day) was described using summary statistics at each visit of the Study Period, according to treatment group (Kuvan plus Phe-restricted diet; Phe-restricted diet alone) and to age group (<12 months; ≥12 months to <24 months; ≥24 months to <48 months).

The secondary endpoints comprised: blood Phe-levels and the change from baseline in blood Phe-levels, change from baseline (prior to enrolment) in dietary Phe tolerance after 26 weeks (6 months) of treatment with Kuvan, blood pressure and the change from baseline in blood pressure, physical growth parameters (height or length, weight and maximal occipital-frontal head circumference), and age-related neuromotor developmental milestones and standardised neurodevelopment test results.

Statistical Methods

Primary analysis

The primary endpoint of the study was the dietary Phe tolerance after 26 weeks (6 months) of treatment with Kuvan plus Phe-restricted diet as compared to a Phe-restricted diet alone, where Phe tolerance was defined as the amount of dietary Phe (mg/kg/day) ingested while maintaining overall control of PKU (assessed by mean blood Phe levels within target range, analysis of diet and Kuvan treatment compliance). The dietary Phe tolerance (mg/kg/day) was described using summary statistics at each visit of the Study Period, according to treatment group (Kuvan plus Phe-restricted diet; Phe-restricted diet alone) and to age group (<12 months; ≥12 months to <24 months; ≥24 months to <48 months). The dietary Phe tolerance during the Study Period was analysed using repeated measures Analysis of Covariance (ANCOVA) on the observed records.

The secondary efficacy endpoints comprised: blood Phe-levels and the change from baseline in blood Phe-levels, change from baseline (prior to enrolment) in dietary Phe tolerance after 26 weeks (6 months) of treatment with Kuvan, blood pressure and the change from baseline in blood pressure, physical growth parameters (height or length, weight and maximal occipitalfrontal head circumference), and age-related neuromotor developmental milestones and standardised neurodevelopment test results, all during the Study Period. The secondary endpoints were analysed using descriptive and inferential statistics to compare the two treatment groups (Kuvan plus Phe-restricted diet and Phe-restricted diet alone) during the Study Period.

Final analysis

The main aim of the Extension Period was to evaluate the efficacy over time of Kuvan treatment plus Phe-restricted diet therapy in increasing dietary Phe tolerance. Phe tolerance was defined as the prescribed amount of dietary Phe (mg/kg/day) while maintaining the mean filter-paper blood Phe levels within the target ranges (≥120 to <360 μmol/L). The dietary Phe tolerance (mg/kg/day) was described using summary statistics at each time point of the Extension Period, according to age group (<12 months, ≥12 months to <24 months, ≥24 months to <48 months). The dietary Phe tolerance during the Extension Period was analysed using a linear mixed model for repeated measures on the observed records applying the likelihood method.

Results

Efficacy:

Primary Efficacy Analysis – 26-week Study Period

The primary endpoint was the dietary Phe tolerance defined as the prescribed amount of dietary Phe (mg/kg/day) while maintaining the mean filter-paper blood Phe levels within the target ranges. After 26 weeks of treatment with Kuvan plus Phe-restricted diet, dietary Phe tolerance was significantly increased compared with dietary therapy alone. At Week 26, the adjusted mean Phe tolerance was higher in the Kuvan plus Phe-restricted diet group (80.6 mg/kg/day) compared with the Phe-restricted diet alone group (50.1 mg/kg/day). The adjusted difference between the two treatment groups was 30.5 mg/kg/day (95% CI: 18.7; 42.3) and was statistically significant (p<0.001).

Overall, BMI SDS, height SDS, max occipital-frontal head circumference SDS and weight SDS were maintained along the appropriate growth curves and considered to be normal in subjects in both treatment groups with minimal changes noted from baseline. The majority of subjects had normal neuromotor development. Statistically, there was no difference between treatment groups for each development milestone. During the 26-week Study Period, there were small increases in the number of subjects with abnormal findings for some neurodevelopment milestones (assessment gross motor, assessment language, assessment personal social).

Final Efficacy Analysis – 3-year Extension Period

The main aim of the Extension Study was the dietary Phe tolerance defined as the prescribed amount of dietary Phe (mg/kg/day) while maintaining the mean filter-paper blood Phe levels within the target ranges. Over 36 months of treatment with Kuvan plus Phe-restricted diet, dietary Phe tolerance was significantly increased compared to baseline (first pre-dose visit in the 26-Week Study Period) in the Kuvan continuous group. At the End of Study visit the estimate of the difference compared to baseline in dietary Phe tolerance was 38.74 mg/kg/day (95% CI: 28.9; 48.6) and was statistically significant (p<0.0001), thus demonstrating that the significant increase in dietary Phe tolerance was sustained over 3.5 years. In the Kuvan Extension only group, a less pronounced effect was observed, with significant differences versus baseline (last visit in the Study Period prior to starting Kuvan) observed at Months 9 and 21 only. At the end of the Extension Period, the estimate of the difference compared to baseline in dietary Phe tolerance was 5.48 mg/kg/day (95% CI: -2.8; 13.8), and was not statistically significant (p=0.1929).

The results in the PPE population for the Kuvan continuous group were consistent with those observed in the ITTE population. In the Kuvan Extension only group, the analysis of the PPE population showed that the estimate of the difference compared to baseline was significant at the majority of time points, with the exception of Months 3, 24 and 36 (End of Extension Period) only. Therefore, by excluding 2 subjects from the analysis with major protocol deviations (1 subject with >125% adherence to Kuvan

and 1 subject with <80% adherence to Kuvan), the dietary Phe tolerance had improved significantly compared to baseline.

In the Kuvan continuous group, blood Phe levels remained stable over time, with no significant changes observed in blood Phe level from baseline to any visit during the Extension Period. In the Kuvan Extension only group, decreases in blood Phe level were observed at all visits compared with baseline during the Extension Period, with statistically significant decreases in blood Phe level from baseline to Months 21, 30, and 33. This indicates that in this group of subjects the dietary phenylalanine supply could have been increased leading to a higher dietary phenylalanine tolerance. Due to the study protocol with less frequent adjustments during the Extension Period this did not always take place. This observation underscores the need for thorough biochemical and dietary monitoring of patients under Kuvan treatment to optimize the benefit for the patient. No differences between the age groups were observed for the change in blood Phe levels during the Extension Period. The results for the PPE population analysis were consistent with the results observed for the ITTE population.

The proportion of subjects maintaining mean filter-paper blood Phe levels both $\leq$360 μmol/L and within the range $\geq$120 μmol/L to <360 μmol/L was greater in the Kuvan Extension only group compared with the Kuvan continuous group. However, it was expected that there would be variance outside of these ranges during the course of the 3-year Extension Period.

During the 3-year Extension Period, weight SDS, max occipital-frontal head circumference SDS and weight SDS were maintained along the same growth curves and considered to be normal in subjects in both treatment groups and only small and non-statistically significant changes were noted from baseline. This indicates that long-term treatment with Kuvan plus Phe restricted diet does not impact growth parameters and subjects were able to grow normally.

The majority of subjects had normal neuromotor development and there were no differences between treatment groups for any development milestone. The number of subjects with abnormal findings in neurodevelopment milestones decreased in all areas across both treatment groups by the end of the study.

Safety:

The safety of Kuvan in Study EMR700773-003 (BMN 162-503) was assessed by the type, frequency and intensity of AEs, AEs leading to discontinuation, total number of AEs, total number of subjects with AE, number of treatment-related AEs, number of AEs resulting in treatment discontinuation, number of withdrawals from the trial, and physical examination findings including vital signs and laboratory tests.

The safety analysis included 54 subjects. All subjects experienced at least one AE. Thirty-one out of 282 events (11.0%) were classified as related to Kuvan and were experienced by 8 out of 27 subjects (29.6%).

Kuvan was generally well-tolerated in subjects <4 years. There were no deaths during the study and no subjects withdrew from the study or permanently discontinued treatment due to an AE during the 26-week Study Period or the 3-year Extension Period.

During the 26-week Study Period, 8 out of 27 subjects (29.6%) in the Kuvan plus Phe-restricted diet group experienced 31/282 (11.0%) events that were classified as related to Kuvan. All other AEs were not related to the investigational drug. Most AEs, 273 (96.8%) in the Kuvan plus Phe-restricted diet group and 260 (93.5%) in the Phe-restricted diet alone group, were mild; all other AEs were moderate.

Serious adverse events (SAEs) were reported for 3 subjects in the Kuvan plus Phe-restricted diet group (gastroenteritis, rash, stomatitis and Kuvan overdose) and 1 subject in the Pherestricted diet alone

group (bronchiolitis and bronchopneumonia). All SAEs were unrelated to study drug. There were no cases of early withdrawal from the trial due to AE.

The treatment-emergent AEs (TEAEs) reported with the highest incidence (≥ 30% of subjects in either group by System Organ Class [SOC]) in the Kuvan plus Phe-restricted diet group and the Phe-restricted diet alone group were in the following SOCs, respectively: infections and infestations (81.5% and 81.5%), general disorders and administration site conditions (63.0% and 66.7%), gastrointestinal disorders (63.0% and 59.3%), respiratory, thoracic and mediastinal disorders (51.9% and 59.3%) and investigations (44.4% and 40.7%).

The most common (≥ 40% of subjects in either group by preferred term [PT]) TEAEs in the Kuvan plus Phe-restricted diet group and the Phe-restricted diet group alone, respectively were: pyrexia (63.0% and 66.7%), cough (48.1% and 48.1%) and nasopharyngitis (48.1% and 40.7%). Differences were observed between the treatment groups for the following PTs: rhinorrhoea (7.4% and 29.6%) and upper respiratory tract infection (3.7% and 22.2%).

Analysis of clinical laboratory data and vital signs did not reveal any adverse effects from treatment with Kuvan.

There were no clinically significant changes in height, height standard deviation score (SDS), weight, weight SDS, BMI, BMI SDS, heart rate, diastolic blood pressure (DBP), systolic blood pressure (SBP), temperature, max occipital-frontal head circumference, max occipital-frontal head circumference SDS and respiratory rate during the trial.

Extension Period:

During the 3-year Extension Period, 9 out of 25 subjects (36.0%) in the Kuvan continuous group experienced 40/838 (4.8%) events that were classified as related to Kuvan. In the Kuvan Extension only group, 4 out of 26 subjects (15.4%) experienced 7/563 (1.2%) events that were classified as related to Kuvan. All other AEs were classified as not related to the investigational drug. The majority of AEs, 795 events (94.9%) in the Kuvan continuous group and 533 events (94.7%) in the Kuvan Extension only group, were mild. Two subjects (8.0%) experienced 2 TEAEs considered to be severe in the Kuvan continuous group and 2 subjects (7.7%) experienced 3 TEAEs considered to be severe in the Kuvan Extension only group. Ten subjects (40.0%) experienced 41 TEAEs considered to be moderate in severity in the Kuvan continuous group and 11 subjects (42.3%) experienced 27 TEAEs considered to be moderate in severity in the Kuvan Extension only group.

Serious adverse events were reported for 13 subjects, none of which were assessed as related to study drug by the Investigator. Six subjects (24.0%) had SAEs in the Kuvan continuous group and 7 subjects (26.9%) had SAEs in the Kuvan Extension only group. All subjects recovered from the SAEs. In addition, 1 subject in the Kuvan Extension only group had 2 events of bronchiolitis that occurred pre-treatment. There were no cases of early withdrawal from the trial due to AE.

The TEAEs reported with the highest incidence (>60% of subjects in either group by System Organ Class [SOC]) in the Kuvan continuous group and the Kuvan Extension only group were in the following SOCs, respectively: infections and infestations (100% and 92.3%), general disorders and administration site conditions (92.0% and 84.6%), gastrointestinal disorders (84.0% and 73.1%) and respiratory, thoracic and mediastinal disorders (84.0% and 61.5%).

The most common (≥ 40% of subjects in either group by PT) TEAEs in the Kuvan continuous group and the Kuvan Extension only group were: diarrhoea (48.0% and 42.3%), vomiting (68.0% and 61.5%), pyrexia (92.0% and 84.6%), nasopharyngitis (68.0% and 46.2%), pharyngitis (52.0% and 11.5%), rhinitis (52.0% and 23.1%), amino acid level decreased (44.0% and 11.5%), and cough (76.0% and

57.7%). Differences were observed between the treatment groups for the following PTs: pharyngitis (52.0% and 11.5%), rash (28.0% and 11.5%), and amino acid level decreased (44.0% and 11.5%).

Analysis of clinical laboratory data and vital signs did not reveal any adverse effects from treatment with Kuvan.

There were no clinically significant changes in height, height SDS, weight, weight SDS, BMI, BMI SDS, heart rate, DBP, SBP, temperature, max occipital-frontal head circumference, max occipital-frontal head circumference SDS and respiratory rate during the trial.

Overall, the results of the safety analysis demonstrated the good safety profile for Kuvan in subjects >4 years old from the first 26-week Study Period which is maintained in the 3-year Extension Period and is in-line with information included in the currently approved product information.

Efficacy results

The results of this trial showed that the addition of Kuvan to a phenylalanine (Phe)-restricted diet in patients <4 years old significantly improved Phe tolerance over 26 weeks compared with Phe-restricted diet alone.

The results of this 3-year Extension Period demonstrated that long-term treatment with Kuvan plus a Phe-restricted diet maintained dietary Phe tolerance over 3.5 years.

Safety results

The results of this trial showed that Kuvan is safe and well tolerated in the investigated population with oral administration.

The results of this 3-year Extension Period demonstrated that the long-term safety profile of Kuvan during the Extension Period also continued to be favourable.

2.3.3. Discussion on clinical aspects

The results of this trial were submitted to the EMA in September 2014 as part of a Type II variation application EMEA/H/C/000943/II/0033. They showed that the addition of Kuvan to a phenylalanine (Phe)-restricted diet in patients <4 years old significantly improved Phe tolerance over 26 weeks compared with Phe-restricted diet alone, and that Kuvan is safe and well tolerated in the investigated population with oral administration. The variation application was approved on 22 June 2015, broadening the indication to include children of all age ranges.

This 3-year Extension Period demonstrated that long-term treatment with Kuvan plus a Phe-restricted diet maintained dietary Phe tolerance over 3.5 years. The long-term safety profile of Kuvan during the Extension Period also continued to be favourable.

3. Rapporteur's overall conclusion and recommendation

The initial Study Period of this trial showed that the addition of Kuvan to a Phe-restricted diet in PKU patients <4 years old significantly improved Phe tolerance compared with Phe-restricted diet alone over a 26-week Study Period. The newly available results from the Extension-Period demonstrates that long-term treatment with Kuvan plus a Phe-restricted diet in subjects <4 years old maintained dietary Phe tolerance over 3.5 years. The long-term safety profile of Kuvan during the Extension Period continued to be favourable. Data from this Extension study continue to support the favourable risk/benefit profile for Kuvan in paediatric PKU patients. Results from this study are in agreement with those observed in the studies the Sponsor conducted in subjects >4 years old.

The data collected in this study are consistent with the data reflected in the EU Product Information, and no update to any of the components is proposed at this time.

This is agreed by the Rapporteur.

Based on the review of the submitted data, this application regarding the submission of the final clinical study report (CSR) for the extension phase of the SPARK study for Kuvan, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended,

is approvable subject to satisfactory response to the additional clarification requested in section 4.

(Supported by MSs)

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

No changes to the approved product information are proposed by the MAH however the Rapporteur suggests that the results of the 3 year Extension Period should be added to section 5.1 for information to prescribers.

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 without any delay and no later than 60 days after the receipt of these conclusions.