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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/P46/027

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 September, 2016, the MAH submitted a completed paediatric study for Kuvan, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that a phase III non-comparative open-label clinical study to evaluate the response to and safety of Kuvan (sapropterin dihydrochloride) after 6 weeks of treatment in in children with PKU from Russia and the Ukraine of 4 to 18 years of age with phenylketonuria who have elevated blood Phenylalanine levels and number EMR 700773_510 is a stand-alone study.

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:

- EMR 700773_510

A phase III non-comparative open-label clinical study to evaluate the response to and safety of Kuvan (sapropterin dihydrochloride) after 6 weeks of treatment in patients of 4 to 18 years of age with phenylketonuria who have elevated blood Phenylalanine levels.

2.3.2. Clinical study

Clinical study number and title

EMR 700773_510

A phase III non-comparative open-label clinical study to evaluate the response to and safety of Kuvan (sapropterin dihydrochloride) after 6 weeks of treatment in patients of 4 to 18 years of age with phenylketonuria who have elevated blood Phenylalanine levels.

Description

Methods

Objective(s)

To study the degree and frequency of response after 8-day Kuvan treatment and assess the safety of 6-week Kuvan treatment in Russian and Ukrainian patients of 4 to 18 years of age with phenylketonuria (PKU) and elevated blood phenylalanine (Phe) level (≥ 450 µmol/l).

To evaluate the frequency of response to Kuvan therapy after 8 days treatment with a daily dose of 20 mg/kg/day as assessed by a reduction in blood Phe level ≥ 30 % among subjects with PKU aged 4-18 years who have elevated blood Phe levels (≥ 450 µmol/l).

To evaluate the degree of response to Kuvan.

To assess Kuvan safety in responsive patients with PKU after 6 weeks of treatment.

Study design

Open-label non-comparative phase III trial to evaluate the degree and frequency of response to and safety of Kuvan.

Study population /Sample size

108 Outpatients of 4 to 18 years of age with hyperphenylalaninaemia due to phenylketonuria and with blood phenylalanine level at screening ≥ 450 µmol/L, screened for a planned participation of 90.

Treatments

Kuvan**,** manufactured by Merck KGaA and Co, Spittal an der Drau, Austria.

100 mg soluble tablets of sapropterin dihydrochloride.

The drug was administered orally once a day in the morning with food. Before administration the tablet is was to be dissolved in 120-240 ml of water and taken within 15-20 minutes after it was dissolved.

Drug dose was 20 mg/kg/day. Dose adjustment was not planned during the treatment course.

Outcomes/endpoints

Efficacy:

Primary endpoint:

Response to Kuvan after 8-day treatment defined as a reduction in blood Phe levels of ≥ 30% compared to beginning of the test prior to dosing.

Secondary endpoints:

Percentage change of blood Phe level after 8-day Kuvan therapy (response test period) compared to Phe level at the beginning of the test prior to dosing

In the overall subject population;

In the sub-population of subjects who responded to Kuvan.

Safety:

Incidence and description of adverse events

In the sub-population of subjects who responded to Kuvan;

In the overall subject population.

Statistical Methods

The primary efficacy analysis was performed for the intention to treat (ITT) population. For qualitative endpoints absolute number, relative frequency (proportion) and exact (Clopper-Pearson) two-sided 95% confidence interval (CI) for proportion were calculated. For quantitative endpoints the arithmetical mean, two-sided 95% CI for the mean value, median, minimum and maximum were calculated.

Safety analysis was performed in the safety population. Adverse events (AE) were classified using the Medical Dictionary for Regulatory Activities (MedDRA), version 16.0. The safety analysis was performed for the entire sample, and for the responders' sub-population.

The analysis of the AEs including the serious AE (SAE), included defining the total number of AEs, total number of subjects with AE, number of treatment-related AEs, number of AEs resulted in treatment discontinuation, number of withdrawals from the trial at the subject's initiative. Results were presented in a descriptive way.

Results

Recruitment/ Number analysed

One hundred eight (110) subjects were screened. The trial included 90 subjects with PKU. 30 subjects responded to treatment and continued participation in the trial. One subject refused to participate in the trial due to a reason not related to AE. No withdrawals due to AE occurred.

Baseline data

Blood Phe level (mean of two measurements) was 782.2 ± 222.6 µmol/L. 43 (47.8%) subjects had blood Phe level ≥ 600 and < 900 µmol/L. There were no clinically significant deviations from normal ranges in haematology, biochemistry; one clinically significant case of red blood cells in urine was revealed at screening visit. Pregnancy test was performed to 8 females; in all cases it was negative.

Efficacy results

Primary efficacy endpoint: **30 (33.3%)** subjects responded to 8-days treatment (95%CI: 23.7; 44.1).

Secondary efficacy endpoints: The mean percentage change in blood Phe level after 8-days response test period compared to baseline was 14.1 ± 28.4% in overall subject population (95%CI: 8.2; 20.1) and 44.3 ± 15.1% in the sub-population of responders (95%CI: 38.6; 49.9).

Safety results

Safety analysis included 90 subjects. Thirty four AEs occurred in 24 (26.7%) subjects. In the sub-population of responders 25 AEs occurred in 16 (53.3%) subjects.

Two (5.9%) AEs were related to the investigational drug based on the Investigator's judgment in the overall population and 2 (8.0%) AEs were related to the investigational drug in the subpopulation of responders. Other AEs were not related to the investigational drug.

Most AEs, 30 (88.2%) in overall population and 21 (84.0%) AEs in the sub-population of responders, were mild; other AEs were moderate.

Eighteen (52.9%) AEs required concomitant medications administration, one (2.9%) AE required surgical treatment and 15 (44.1%) AEs did not require any intervention. In the subpopulation of responders, 9 (36.0%) AEs required medications administration, one (4.0%) AE required surgical treatment and 15 (60.0%) AEs did not require any intervention.

Seven (20.6%) AEs in overall population and 7 (28.0%) AEs in the sub-population of responders were ongoing at the termination of a subject's participation in the trial. Other AEs (79.4% and 72.0%) terminated before the end of subjects' participation in the trial.

Twenty five (73.5%) AEs in overall population and 19 (76.0%) AEs in the sub-population of responders did not require changing the dose of Kuvan.

In the overall population 27 (79.4%) AEs completely resolved; 5 (14.7%) AEs not resolved and 2 (5.9%) AEs resolved with sequelae. In the sub-population of responders 19 (76.0%) AEs completely resolved; 5 (20.0%) AEs not resolved and 1 (4.0%) AEs resolved with sequelae.

Overall rate of SAE in this trial was 1.1%. This one SAE was not related to the investigational drug. There were no cases of early withdrawal from the trial due to AE. One subject refused to participate in the trial due to a reason not related to AE.

Most common systems of organs with AEs were respiratory, thoracic and mediastinal disorders (13.3% in overall population and 20.0% in responders), gastrointestinal disorders (3.3% and 10.0%); renal and urinary disorders (4.4% and 13.3%); vascular disorders (3.3% and 10.0%).

Most common AEs were respiratory tract infection viral (10.0% in overall population and 13.3% in responders), retinal vascular disorder (2.2% and 6.7%), phenylalaninaemia (2.2% and 6.7%).

No clinically significant changes in the parameters of complete blood count and blood chemistry test were observed. One case of clinically significant red blood cells in urine was revealed at screening visit; one such case of white blood cells in urine was revealed at Follow-up visit. There were no clinically significant changes in other parameters of urinalysis.

2.3.3. Discussion on clinical aspects

For the primary **efficacy** endpoint, **30 (33.3%)** subjects responded to 8-days treatment (95%CI: 23.7; 44.1). For Secondary efficacy endpoints, the mean percentage change in blood Phe level after 8-days response test period compared to baseline was 14.1 ± 28.4% in overall subject population (95%CI: 8.2; 20.1) and 44.3 ± 15.1% in the sub-population of responders (95%CI: 38.6; 49.9).

The **safety** of Kuvan in Study EMR700773_510 was assessed by the type, frequency and intensity of adverse events (AEs), AEs leading to discontinuation, total number of AEs, total number of subjects with AE, number of treatment-related AEs, number of AEs resulting treatment discontinuation, number of withdrawals from the trial.
Safety analysis included 90 subjects. Thirty four AEs occurred in 24 (26.7%) subjects. In the sub-population of responders 25 AEs occurred in 16 (53.3%) subjects.

Kuvan was **generally well-tolerated** in subjects 4-18 years (inclusive). There were no deaths during the study and no subjects withdrew from the study or permanently discontinued treatment due to an AE.
Two (5.9%) AEs were related to the investigational drug based on the Investigator's judgement in overall population and 2 (8.0%) AEs were related to the investigational drug in the subpopulation of responders. Other AEs were not related to the investigational drug.
Most AEs, 30 (88.2%) in overall population and 21 (84.0%) AEs in the sub-population of responders, were mild; other AEs were moderate.
Eighteen (52.9%) AEs required concomitant medications administration, one (2.9%) AE required surgical treatment and 15 (44.1%) AEs did not require any intervention. In the subpopulation of responders, 9 (36.0%) AEs required medications administration, one (4.0%) AE required surgical treatment and 15 (60.0%) AEs did not require any intervention.
Overall rate of SAE in this trial was 1.1%. This one SAE was not related to the investigational drug.

3. Rapporteur's CHMP overall conclusion and recommendation

This trial results showed that Kuvan is effective in lowering hyperphenylalaninaemia and that Kuvan is safe and well tolerated in children with PKU from Russia and the Ukraine. The results

obtained in this trial confirm the efficacy and safety of Kuvan administration previously demonstrated in other multinational clinical trials.

☒ **Fulfilled:**

No regulatory action required.