A Phase IIIb, Multicentre, Open-Label, Randomized, Controlled Study of the Efficacy, Safety, and Population Pharmacokinetics of Sapropterin Dihydrochloride (KuvanÂ®) in Phenylketonuria (PKU) Patients <4 Years Old

Published: 23-11-2010
Last updated: 04-05-2024

Primary objectives of this study:1. Evaluate the efficacy after 26 weeks of Kuvan® treatment + Phe-restricted diet therapy in increasing dietary Phe tolerance, as compared to dietary therapy alone in

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON36625

Source
ToetsingOnline

Brief title
SPARK (Safety Paediatric efficAcy phaRmacokinetic with KuvanÂ®)

Condition

- Other condition

Synonym
Phenylketonuria (PKU)

Health condition

Phenylketonuria (PKU)

Research involving
Human

Sponsors and support

Primary sponsor: Merck Serono S.A. – Geneva
Source(s) of monetary or material Support: Industry; Merck Serono

Intervention

Keyword: Phenylketonuria (PKU)

Outcome measures

Primary outcome

Dietary Phe tolerance after 26 weeks (6 months) of treatment with Kuvan® + a

Phe-restricted diet, as compared to just a Phe-restricted diet alone.

Secondary outcome

1. Levels of blood Phe during the Study Period;

2. Change from Baseline (prior to enrolment) in dietary Phe tolerance after 26

weeks (6 months) treatment with Kuvan® + a Phe-restricted diet vs. just a

Phe-restricted diet;

3. Blood pressure during the 26-week Study Period and the 3-year Extension

Period;

4. Growth parameters (length or height, weight and maximal occipital-frontal

head circumference) during the 26-week Study Period and the 3-year Extension

Period;

5. Neuromotor developmental milestones and standardized neurodevelopment test

results during the 26-week Study Period and the 3-year Extension Period;

6. Safety, including attention to age group-specific safety concerns (see

Sections 3.12 and 7.5.1):

* Nature, incidence and severity of adverse events;

* Long-term safety for patients enrolled into the Extension Period.

* Incidence of hypophenylalaninemia (a blood Phe level <120 *mol/L); and

* Changes from baseline in vital signs and clinical laboratory parameters.

7. PopPK endpoints will include:

* CL/f (apparent clearance);

* V/f (apparent volume of distribution);

* AUC0-* (area under the plasma concentration curve, time 0 to infinity);

* Cmax (maximum observed plasma concentration);

* Tmax (time to maximum plasma concentration); and

* t1/2 (terminal elimination half-life);

8. PAH genotype.

Study description

Background summary

Phenylketonuria (PKU), an autosomal recessive condition, is a rare metabolic disease caused by a mutation in the gene coding for phenylalanine hydroxylase (PAH), a hepatic enzyme that converts the essential amino acid phenylalanine (Phe) to tyrosine. Defects in the gene for PAH can lead to decreased conversion of Phe to Tyr, progressive accumulation of Phe in the blood, and consequent hyperphenylalaninemia (HPA) (8). Severe HPA is associated with neurotoxicity, leading to neurodevelopmental delay in infants and young children and decreased neurocognitive function in older children and adults. Clinically significant, severe HPA due to defects in the PAH gene is referred to as PKU.
Virtually all cases of clinically significant HPA are detected in routine

newborn screening programs. In the neonatal period, concurrent with the process for confirmation of the diagnosis of PKU, dietary Phe restriction is instituted by limiting whole protein intake and providing Phe-free protein supplements to meet nutritional needs for protein (9). Phe intake is limited to maintain blood Phe levels within a clinically defined therapeutic target range that is above normal blood Phe levels. Although dietary treatment has been proven to be successful for prevention of severe neurodevelopmental delay, non-adherence to treatment is very high in older children, adolescents and adults due to limited practical feasibility of the often-severe protein restriction and poor palatability of the Phe-free protein supplements (10).
Normal Phe levels in children vary with age and assay methodology. Reference ranges for serum Phe determined by ion exchange chromatography at Mayo Medical Laboratories (Rochester, MN, USA), a commonly used reference laboratory for PKU, are 38-137 *mol/L for newborns (0-1 month old), 31-75 *mol/L for infants (1 to 24 months old) and 26-91 *mol/L for older children and adolescents (2 to 18 years old) (11). Circulating Phe levels in untreated infants and children with PKU following a normal diet are >360 *mol/L and can range to >2000 *mol/L. Since low Phe levels can also be detrimental for growth and development, and good clinical outcomes can be obtained even with blood Phe levels that are slightly supranormal (12), therapeutic targets for treatment of children with PKU do not aim for achievement of normal serum Phe levels. Instead, a usual therapeutic target for children with PKU <4 years old is to maintain blood Phe levels within a range of 120-360 *mol/L (defined as *120 to < 360 *mol/L) (8).

Study objective

Primary objectives of this study:
1. Evaluate the efficacy after 26 weeks of Kuvan® treatment + Phe-restricted diet therapy in increasing dietary Phe tolerance, as compared to dietary therapy alone in <4 year-old infants and children with phenylketonuria (PKU). Phe tolerance will be defined as the amount of dietary Phe (mg/kg/day) ingested while maintaining blood Phe levels within the range of 120-360 *mol/L (defined as *120 to < 360 *mol/L).
2. Evaluate the safety after 26 weeks of Kuvan® treatment in <4 year-old infants and children with PKU.
3. Evaluate BH4 (tetrahydrobiopterin; sapropterin) blood levels via scheduled PopPK samplings.

Secondary objectives of the study:
1. Evaluate blood Phe levels for all subjects during the 26-week Study Period.
2. 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.
3. 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.
4. Assess potential effects on blood pressure during the 26-weeks Study Period

and the 3-year Extension Period.
5. Assess potential effects on growth during the 26-weeks Study Period and the 3-year Extension Period.
6. Evaluate long-term safety, neurodevelopmental outcomes, dietary Phe tolerance, and blood Phe levels in the 3-year Extension Period.
7. Investigate in BH4-responsive individuals the predictive value of the phenylalanine hydroxylase (PAH) genotype.

Study design

Following Screening, eligible subjects will be randomized 1:1 to receive either: (a) 10 mg/kg/day Kuvan® + a Phe-restricted diet or (b) just a Phe-restricted diet over a 26-week Study Period.
It is intended that all subjects will maintain blood Phe levels within a range of 120-360 *mol/L (defined as *120 to <360 *mol/L) through monitored dietary intake during the 26-week Study Period. If after approximately 4 weeks, a patient*s Phe tolerance has not increased by >20% vs. Baseline, the Kuvan® dose will be increased in a single step to 20 mg/kg/day. A population pharmacokinetics (PopPK) study is included in the Study Period, with collection of baseline (pre-treatment) blood samples for measurement of endogenous BH4 levels. PopPK samplings will also be obtained during study Weeks 5-12, inclusive.
After completing the Study Period, subjects will be eligible for enrolment in the Extension Period, in which all subjects who continue in the study will receive Kuvan® treatment + a Phe-restricted diet. For those patients randomized to the Phe-restricted diet alone during the 26-week Study Period, their starting Kuvan® dose in the Extension Period will be 10 mg/kg/day. A subject*s treatment during the Extension Period will continue for 3 years or until commercial product is approved and becomes available for <4 year-old patients with PKU.

Intervention

Measuring Phe levels in blood (at the hospital + at home)
blood sampling for PopPK
BH4 responsiveness test

Study burden and risks

-

Contacts

Public

Merck Serono S.A. – Geneva

9, Chemin des Mines
CH-1201 Geneva
CH
Scientific
Merck Serono S.A. – Geneva

9, Chemin des Mines
CH-1201 Geneva
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Male or female PKU infants and young children <4 years of age at the scheduled Day 1 visit of the 26-week Study Period (taking into consideration the maximum of 42 days in the Screening Period).;2. At least two previous blood Phe levels * 400 *mol/L obtained on 2 separate occasions.;3. Previously responded, as assessed by the Investigator, to a BH4 test, if all 3 of the following criteria are satisfied:
a) The BH4 dose was 20 mg/kg/day.
b) The duration of the test was at least for 24 hours.
c) A 30% decrease in blood Phe levels.
NOTE: If a patient has not undergone a BH4 test prior to Screening, such a test must be performed, (Please refer to the note , section 7.1.1 bullet point #7).;4. Defined level of dietary Phe tolerance consistent with the diagnosis of PKU;;5. Good adherence to dietary treatment, including prescribed dietary Phe restriction and prescribed amounts of Phe-free protein supplements and low-Phe foods.;6. Maintenance of blood Phe levels within the therapeutic target range of 120-360 *mol/L (defined as *120 to < 360 *mol/L) over a 4-month period prior to Screening, as assessed by the Investigator. At least, the last 4 values of phenylalanine (either from venous blood or dry blood
spot) should be assessed, out of which 75% should be within the above therapeutic range.;7.

Parent(s) and/or guardian(s) willing to comply with all study procedures, maintain strict adherence to the diet, and willing and able to provide written, signed informed consent after the nature of the study has been explained and prior to any study procedures.

Exclusion criteria

1. Use of Kuvan®, Biopten®, or any unregistered preparation of tetrahydrobiopterin within the previous 30 days, unless for the purposes of a BH4 responsiveness test.
2. Previous exposure to Kuvan®, Biopten®, or any unregistered preparation of tetrahydrobiopterin for >30 days.
3. Known hypersensitivity to Kuvan® or its excipients.
4. Known hypersensitivity to other approved or non-approved formulations of tetrahydrobiopterin.
5. Previous diagnosis of BH4 deficiency.
6. Current use of methotrexate, trimethoprim, or other dihydrofolate reductase inhibitors.
7. Current use of medications that are known to affect nitric oxide synthesis, metabolism or action.
8. Current use of levodopa.
9. Current use of experimental or unregistered drugs that may affect the study outcomes.
10. Inability to comply with study procedures.
11. Inability to tolerate oral intake.
12. History of organ transplantation.
13. Concurrent disease or condition that would interfere with study participation or increase the risk for adverse events, including seizure disorders, corticosteroid administration, active malignancy, diabetes mellitus, severe congenital heart disease, renal or hepatic failure.
14. Other significant disease that in the Investigator*s opinion would exclude the subject from the trial.
15. Any condition that, in the view of the Principal Investigator renders the subject at high risk for failure to comply with treatment or to complete the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-06-2011
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sapropterin
Generic name:	Kuvan
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-11-2010
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-05-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-08-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-08-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-10-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-01-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-01-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-03-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-015768-33-NL
ClinicalTrials.gov	NCT01376908
CCMO	NL32785.068.10