

Treatment of hyperphenylalaninemia with Sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH₄) and its influence on the amino acids and fatty acids patterns from childhood to adulthood (Tratamiento de la hiperfenilalaninemia con dihidrocloruro de Sapropterina [tetrahidrobiopterina, 6r-bh₄] y su influencia en el patrón de aminoácidos y ácidos grasos desde la infancia hasta la edad adulta)

Submission date 31/01/2011	Recruitment status No longer recruiting	<input type="checkbox"/> Prospectively registered
		<input type="checkbox"/> Protocol
Registration date 18/04/2011	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan
		<input type="checkbox"/> Results
Last Edited 18/04/2011	Condition category Nutritional, Metabolic, Endocrine	<input type="checkbox"/> Individual participant data
		<input type="checkbox"/> Record updated in last year

Plain English summary of protocol

Not provided at time of registration

Contact information

Type(s)

Scientific

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Additional identifiers

Protocol serial number
EC81/00474

Study information

Scientific Title

Treatment of hyperphenylalaninemia with Sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) and its influence on the amino acids and fatty acids patterns from childhood to adulthood, a Phase IV, longitudinal, unblinded, controlled, single-centre, retrospective and prospective clinical study

Study objectives

The aim of this study is to compare the response to dietary treatment or pharmacological treatment with Sapropterin in patients with hyperphenylalaninemia secondary to phenylalanine hydroxylase deficiency and to assess the blood profile of long-chain fatty acids and amino acids and its relationship with the metabolic control and other complications such as osteopenia.

Hyperphenylalaninemia (HPA) is a metabolic disorder mainly caused by a defect in the phenylalanine hydroxylase gene, which produces a deficiency of this enzyme resulting in an alteration of the metabolism of phenylalanine (Phe) and consequently its accumulation. Phe is toxic to the central nervous system, therefore an accumulation of Phe leads to an alteration in the psychomotor development. A strict diet can control the Phe blood level enough to avoid most of the serious neurological effects. However, dietary treatment presents some problems, such as difficult adherence, negative impact on the daily life of the patients or nutritional deficiencies. Sapropterin significantly reduces and maintains blood Phe concentrations with the subsequently improving quality of diet.

Sapropterin allows to partially or fully liberalize the diet with limited intake of phenylalanine in certain types of hyperphenylalaninemias. This will improve the quality of life of patients, as well as their neurological / cognitive development. Furthermore, in patients who have a good response to Sapropterin, this treatment is able to maintain certain biochemical parameters (total amino acids and essential fatty acids) equally or better controlled than the dietary treatment.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Clinical Research Ethics Committee of Aragon [Comité Ético de Investigación Clínica de Aragón]
Ref: C.I. EC09/055, 02/09/2009

Study design

Phase IV longitudinal retrospective and prospective unblinded controlled single-centre clinical study

Primary study design

Interventional

Study type(s)

Treatment

Health condition(s) or problem(s) studied

Hyperphenylalaninemia (HPA)

Interventions

1. Male and female patients with hyperphenylalaninemia secondary to phenylalanine hydroxylase deficiency, controlled in the Metabolism Unit at Children's Hospital Miguel Servet, who respond to treatment with Sapropterin being able to leave the phenylalanine free diet completely or partially
2. The drug administered is Kuvan® (tablets of 100 mg) at a dose of 5-20 mg/kg/day orally (PO), in a single dose. Calculated dose will be rounded to the nearest 100 mg
3. Tablets should be dissolved in water (120 ml for children and 240 ml for adults), and solution should be drunk within 15-20 minutes after preparation
4. Control group: patients of both sexes, from birth, diagnosed with classic hyperphenylalaninemia, controlled in the Metabolism Unit at Children's Hospital Miguel Servet, who have not responded to treatment with Sapropterin and are only under dietary treatment.
5. Every four months the following information will be collected:
 - 5.1. Anthropometric variables (weight, height), phenylalanine tolerance by a nutrition survey which collects intakes for the previous three days. F
 - 5.2. In subjects taking Sapropterin, daily dose, adherence to treatment, and adverse effects will also be collected
 - 5.3. Biochemical parameters will be assessed every 4 months during the year following the beginning of the study, they will include: total amino acids, essential (AA) amino acids (phenylalanine, methionine, tryptophan, valine, leucine, isoleucine, histidine, lysine, tyrosine) and essential fatty acids
 - 5.5. An estimation will be made of the ratios total AA/AA essential and Phe/Tyr before and after treatment with Sapropterin.
6. Total duration of treatment: 1 year
7. Total duration of follow-up: 28 days

Intervention Type

Drug

Phase

Phase IV

Drug/device/biological/vaccine name(s)

1. Sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4)
2. Kuvan®

Primary outcome(s)

1. Every four months biochemical analysis of total amino acids and essential fatty acids as indicators of quality
2. Amino acids levels were analyzed by HPLC (cation-exchange high performance liquid chromatography)
3. The levels of essential fatty acids were determined by gas-liquid chromatography

Key secondary outcome(s)

1. Prevalence in our population of patients with hyperphenylalaninemia who respond to Sapropterin
2. Correlation between a type of mutation and the response to Sapropterin
3. Relationship in our population between the response to Sapropterin and the severity of biochemical phenotype and genotype
4. Profile of total and essential amino acids and fatty acids on patients treated with Sapropterin versus patients treated with diet. Liberalization of phenylalanine-free diet as much as possible
5. Diet liberalization will be assessed by increasing the amounts of Phe on the daily diet and controlling at the same time the Phe blood level is within the appropriate limits (less than 240 nmol/ml in children under 6 year-old, less than 360 nmol/ml in children of 6-10 year-old, and less than 500 nmol/ml in older than 10)

Completion date

25/11/2011

Eligibility**Key inclusion criteria**

1. Patients with hyperphenylalaninemia due to phenylalanine hydroxylase deficiency, who respond to treatment with Sapropterin
2. Childbearing women who should have a negative pregnancy test within 7 days prior to start of treatment with Sapropterin and should use reliable contraception during the whole study
3. The control group will include patients with hyperphenylalaninemia due to phenylalanine hydroxylase deficiency that are metabolically well controlled without Sapropterin

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Other

Sex

All

Key exclusion criteria

1. Liver impairment or other underlying chronic disease that may require regular treatment
2. Pregnancy and breastfeeding

Date of first enrolment

12/03/2009

Date of final enrolment

25/11/2011

Locations

Countries of recruitment

Spain

Study participating centre

Servicio de Pediatría. Unidad de Metabolismo. Hospital Universitario Miguel Servet.

Zaragoza

Spain

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Sponsor information

Organisation

Aragon Institute of Health Sciences [Instituto Aragonés de Ciencias de la Salud] (Spain)

ROR

<https://ror.org/05p0enq35>

Funder(s)

Funder type

Government

Funder Name

Aragon Institute of Health Sciences [Instituto Aragonés de Ciencias de la Salud] (Spain)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes