NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sapropterin for treating phenylketonuria [ID1475]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Sapropterin for treating phenylketonuria [ID1475]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from BioMarin Pharmaceuticals

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. British Dietetic Association
   b. British Inherited Metabolic Disease Group
   c. Metabolic Support UK
   d. National Society for Phenylketonuria (NSPKU)
   e. Royal College of Pathologists
   **NB.these submissions were provided when the appraisal first started, in 2018*

4. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group

5. **Evidence Review Group report – factual accuracy check**

6. **Technical engagement response from company**

7. **Technical engagement responses from experts:**
   a. Prof. Anita MacDonald, Consultant Dietitian – clinical expert, nominated by the National Society for Phenylketonuria and the British Dietetic Association
   b. Dr Hugh Lemonde, Consultant Paediatric Inherited Metabolic Disease – clinical expert, nominated by the British Inherited Metabolic Disease Group – *see BIMDG response (item 8b)*
   c. Dr Robin Lachmann, Consultant in Metabolic Medicine – clinical expert, nominated by the Royal College of Physicians
   d. Patient expert, nominated by the National Society for Phenylketonuria
   e. Sharon Buckley, Patient Advocate – patient expert, nominated by the National Society for Phenylketonuria
   f. Claire Foreman, Head of Acute Programmes, Specialised Commissioning - commissioning expert, nominated by NHS England and Improvement

8. **Technical engagement responses from consultees and commentators:**
   a. National Society for Phenylketonuria (NSPKU)
   b. British Inherited Metabolic Disease Group (BIMDG)

9. **Evidence Review Group critique of company response to technical engagement** prepared by Liverpool Reviews and Implementation Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sapropterin dihydrochloride for treating phenylketonuria [ID1475]

Document B

Company evidence submission by BioMarin International Limited

July, 2020

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Glossary

ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-RS	Attention-Deficit Hyperactivity Disorder Rating Scale-IV
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ASRS	Adult ADHD Self-Report Scale
BH4	Tetrahydrobiopterin
BMI	Body Mass Index
BOI	Burden Of Illness
BRIEF	Behavior Rating Inventory of Executive Function
CGI-I	Global Function Evaluation
CI	Confidence Intervals
CNS	Central nervous system
DLA	Disability Living Allowance
EF	Executive Function
EQ-5D-5L	EuroQol – 5 Dimensions – 5 Levels
EMA	European Medicines Agency
ER	Emergency Room
ESPKU	European Society for Phenylketonuria and Allied Disorders
EU	European Union
GEC	Global Executive Composite
GIN	International Guidelines Network Library
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
HPA	Hyperphenylalaninaemia
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
HST	Highly Specialised Technology
ICIEM	International Congress of Inborn Errors of Metabolism
IQ	Intelligence Quotient
ITT	Intention-to-treat
KAMPER	The Kuvan Adult Maternal Paediatric European Registry
KOGNITO	Kuvan's Effect on the Cognition of Children with Phenylketonuria
LTI	Long term illness
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MCID	Minimal Clinically Important Difference
MMRM	Mixed-Effect Model Repeated Measure
MRI	Magnetic Resonance Imaging
NHS	National Health System

NICE	National Institute for Health and Care Excellence
NONMEM	Non-linear mixed-effect modelling
NSPKU	National Society for Phenylketonuria
PAH	Phenylalanine Hydroxylase
PAS	Patient Access Scheme
PedsQL	Paediatric Quality of Life
Phe	Phenylalanine
Phenoptin™	A previous trade name for sapropterin dihydrochloride which is now superseded by Kuvan®
PKU	Phenylketonuria
PKUDOS	The Phenylketonuria Demographics Outcomes and Safety Registry
PKU-MOMS	PKU in the Maternal Phenylketonuria Observational Program
PKU-QoL	Phenylketonuria Quality of life
PODCI	The Pediatric Outcomes Data Collection Instrument
PopPK	Population Pharmacokinetics
PPE	Per Protocol Extension
PRD	Protein-restricted diet
PRO	Patient reported outcomes
QoL	Quality of life
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SLR	Systematic Literature Review
SOC	System Organ Class
SPARK	Safety Paediatric efficAcy phaRmacokinetic with Kuvan
STA	Single Technology Assessment
Tyr	Tyrosine
UK	United Kingdom
6R-BH4	The investigational name for sapropterin dihydrochloride

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

- The submission focuses on part of the technology's marketing authorisation for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU). The submission is narrower than the marketing authorisation, as the marketing authorisation also includes tetrahydrobiopterin (BH4) deficiency which is clinically distinct from PKU and is an ultra-rare disease. The PKU indication within this submission is in line with the NICE scope.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with phenylketonuria (PKU) whose hyperphenylalaninaemia (HPA) has been shown to be responsive to sapropterin dihydrochloride therapy	Same as final scope	NA
Intervention	Sapropterin in combination with a protein-restricted diet	Same as final scope	NA
Comparator(s)	Established clinical management without sapropterin dihydrochloride	Same as final scope	NA
Outcomes	The outcome measures to be considered include: • phenylalanine concentration in the blood • neuropsychological function • dietary protein intake • nutritional biochemistry (e.g., vitamin B12) • adverse effects of treatment • cognitive and mood symptoms • health-related quality of life	Same as final scope	NA

B.1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Sapropterin dihydrochloride (Kuvan®)
Mechanism of action	Sapropterin dihydrochloride (sapropterin) is a synthetic formulation of tetrahydrobiopterin (BH4), the natural cofactor for the phenylalanine hydroxylase (PAH) enzyme, which stimulates activity of the residual PAH enzyme to metabolise phenylalanine (Phe) into tyrosine.
Marketing authorisation/CE mark status	The European Commission granted a marketing authorisation valid throughout the EU for sapropterin dihydrochloride on 1st December 2008 (1). Sapropterin dihydrochloride also has orphan drug designation until the 4th of December 2020, granted by the European Commission (2).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Sapropterin (Kuvan®) is indicated for the treatment of HPA in adults and paediatric patients of all ages with PKU who have been shown to be responsive to such treatment. Sapropterin is also indicated for the treatment of HPA in adults and paediatric patients of all ages with BH4 deficiency who have been shown to be responsive to such treatment (3). As previously stated, this submission does not include the BH4 deficiency indication.
Method of administration and dosage	Sapropterin is orally administered. The starting dose of sapropterin in adult and paediatric patients with PKU is 10mg/kg body weight once daily. The dose is adjusted, usually between 5 and 20 mg/kg/day, to achieve and maintain adequate blood Phe levels as defined by the physician (3).
Additional tests or investigations	A responsiveness test is required as stipulated within the European Medicines Agency (EMA) licence: "A satisfactory response is defined as a ≥30 percent reduction in blood phenylalanine levels or attainment of the therapeutic blood phenylalanine goals defined for an individual patient by the treating physician. Patients who fail to achieve this level of response within the described one month test period should be considered non-responsive and should not receive treatment with sapropterin" (3).

List price and average cost of a course of treatment	The NHS list price per package for sapropterin 100mg (30 x 100mg tablets) is £597.22. Sapropterin is a weight and dose-based treatment. The starting dose of sapropterin in adult and paediatric patients with PKU is 10mg/kg body weight once daily. This submission assumes an average daily dose of 10 mg/kg per day for paediatric patients (0-17 years of age) and 12.5mg/kg per day adult patients (≥18 years of age). These doses were informed by the dosages used in the clinical trial programme and aligns with the content of an integrated impact assessment (IIA) report produced by NHS England (4)The cost per patient per year based on these doses would be: 30kg patient = £21,799; 75kg patient = £65,396 based on the NHS list price (5).
Patient access scheme (if applicable)	A simple patient access scheme PAS application form has been submitted to PASLU. The proposed discount off the NHS list price is [redacted]*. The proposal is awaiting confirmation.

B.1.3 Health condition and position of the technology in the treatment pathway

Disease overview

PKU, also referred to as phenylalanine hydroxylase (PAH) deficiency, is an autosomal recessive inborn error of phenylalanine (Phe) metabolism caused by a deficiency in the enzyme PAH. This enzyme is responsible for converting Phe into tyrosine (Tyr).

This lack of enzyme activity results in elevated blood Phe levels which are toxic to the central nervous system and cause severe neurological complications, brain abnormality and cognitive impairment (6, 7). Indeed, if left untreated, PKU can lead to irreversible intellectual disability (approximately 98% of individuals with untreated PKU fall within the range of global intellectual disability (8)), as well as microcephaly, motor deficits, eczematous rash, autism, seizures, developmental problems, aberrant behaviour and psychiatric symptoms (9).

The basis for neurological dysfunction and subsequent complications (such as microcephaly, motor deficits, seizures etc.) is twofold. Firstly, elevated Phe competes at the blood-brain barrier with Tyr causing a reduction in Tyr and subsequently a

reduction in dopamine and other neurotransmitters. Secondly, elevated Phe compromises myelination of white matter in the brain (10). The prevalence of these white matter abnormalities tends to be higher and more severe in older children, those who are off treatment, or those with high Phe levels (11) and the picture emerging from the literature of the last 20 years is that over 90% of all PKU patients suffer from white matter abnormalities (11). These white matter abnormalities are common in early diagnosed and treated patients (11) and are reversible following a reduction in blood Phe levels (12).

There is currently no cure for PKU and sapropterin was the first pharmaceutical treatment licensed to help manage it. PKU is a lifelong condition. Given the severity of disease, neonatal screening is commonplace in most European countries including the UK (13).

Elevated Phe in children and adolescents

Children 0-11 years old

Blood Phe concentration during childhood is the major determinant of cognitive outcome. If blood Phe levels remain uncontrolled, children with PKU can suffer severe mental retardation and loss of IQ, microcephaly, seizures and tremors, psychological, behavioural and social problems, stunted growth, delayed speech and difficulties with executive thought processes (14, 15).

Children 12-17 years old

Early dietary management to control blood Phe levels is effective in the prevention of severe and irreversible damage to the grey matter of the brain and the resulting mental disabilities caused by high Phe concentrations during brain development in childhood. However, high Phe concentrations in adolescence and adulthood can lead to a number of reversible complications. Good Phe control during childhood thus allows forpatients with PKU to have normal/near normal intellectual ability but, with progressive loss of Phe control, patients develop the following complications (6, 16):

- Neurocognitive deficits, largely related to poor executive function (EF), including attention deficits, reduced inhibitory control and reduced speed of

response over multiple domains (17, 18).

- Neuropsychiatric symptoms, including high levels of depression, anxiety and inattention (17, 19)
- Psychosocial impairments, including lack of autonomy, social maturity deficits and difficulties forming relationships (16, 20).

Elevated Phe in adults

The effect of high blood Phe is also detrimental to adults; higher Phe is associated with an increased prevalence of neuropsychiatric symptoms and EF deficits (17). European PKU guidelines state that deficits in EF, attention problems, decreased verbal memory and social and emotional difficulties are observed in adults with PKU, even when treated early (7).

EF refers to higher order cognitive abilities, which encompasses planning, organisation, cognitive flexibility, inhibitory control and working memory. These are considered as EF because they require the integration and processing of information across a range of cognitive domains, sensory modalities and response modalities (8).

Poor EF may also impact treatment adherence and, therefore, lead to psychosocial deficits that are not always visible. These psychosocial aspects include social difficulties and psychosocial problems, such as forming interpersonal relationships, achieving autonomy, attaining educational goals, maintaining steady employment and having healthy emotional development. The key to reducing the risks associated with PKU is improved metabolic control throughout life (20).

The neurological complications observed due to elevated Phe are well documented (6, 7). Untreated PKU can lead to irreversible intellectual disability (approximately 98% of individuals with untreated PKU fall in the range of global intellectual disability (8) as well as microcephaly, motor deficits, eczematous rash, autism, seizures, developmental problems, aberrant behaviour and psychiatric symptoms (9). Furthermore, neuropsychiatric symptoms such as depression, anxiety and attention deficit disorder are higher in PKU patients than the general population (17).

Elevated Phe in women of childbearing age

Maternal PKU syndrome refers to the teratogenic effects of elevated maternal blood Phe on the developing foetus. These high blood Phe levels during pregnancy can lead to growth retardation, microcephaly, intellectual disabilities and birth defects, including congenital heart defects (CHD) (9).

Signs of maternal PKU may be evident at birth, but other signs can be delayed and only observed over the course of an individual's growth and development.

Tight Phe control before conception and continually throughout pregnancy is therefore critically important. Cognitive outcomes in children whose mothers had good Phe control pre-conception are better than in children whose mothers began or resumed dietary Phe restriction after conception (21).

The European PKU guidelines (7) recommend the following for maternal PKU:

- Women with untreated Phe level >360 micromol/L must be treated to bring Phe level to 120-360 micromol/L;
- Blood Phe levels before and during pregnancy should be maintained at 120-360 micromol/L;
- Significant effort should be taken to avoid any unplanned pregnancies in PKU women; and
- Education and effective contraceptive methods are key elements.

Co-morbidities

PKU patients have increased comorbidities compared to the general population. Specifically, PKU adults have higher rates of chronic ischaemic disease, obesity, asthma, renal insufficiency (with and without hypertension), eczema, alopecia, osteoporosis, gall bladder disease etc. (22, 23). These increased comorbidities have been attributed to high Phe and are shown to be associated with biological mechanisms that are related to increased risk of other chronic diseases (24-27), as well as the consequences of the Phe-restricted diet and medical food nutrition (28, 29).

Current management

Current management of PKU involves reducing dietary Phe intake by adhering to a diet that is low in protein Phe for life. This involves avoiding foods rich in protein (e.g. meats, fish, eggs, standard bread, most cheeses, nuts and seeds), foods and drinks that contain aspartame, flour, soya, beer, or cream liqueurs. This effectively means that 85% of 'normal' food is harmful to patients and should be avoided or consumed in extremely small and controlled quantities. A range of Phe-free foods and protein supplements are available in the UK and are reimbursed by NHS England. Nevertheless, most patients are unable to achieve or maintain good overall Phe control through dietary control alone (30, 31) and suffer from significant disease burden (16) which impacts on their ability to function in society. The impact of a strict diet is a key determinant of the progressively poorer Phe control in PKU patients as they age. These patients, therefore, require additional support.

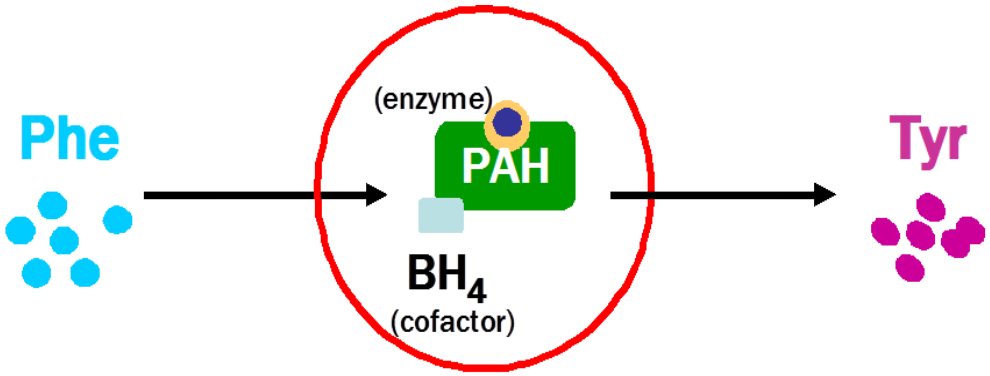
PKU may have a significant impact on the quality of life of patients (both paediatric and adult), affecting their educational and work performance, social and family relationships and imposes a substantial burden on caregivers and families (32). An indirect relationship also exists between quality of life and EF impairment (20).

Aetiology of disease

PKU is a general term for a wide spectrum of disease-causing genotypes - more than 1083 PAH gene variants (33) have been identified that result in a mild deficiency in PAH activity to a total inactivation of PAH enzyme function (34).

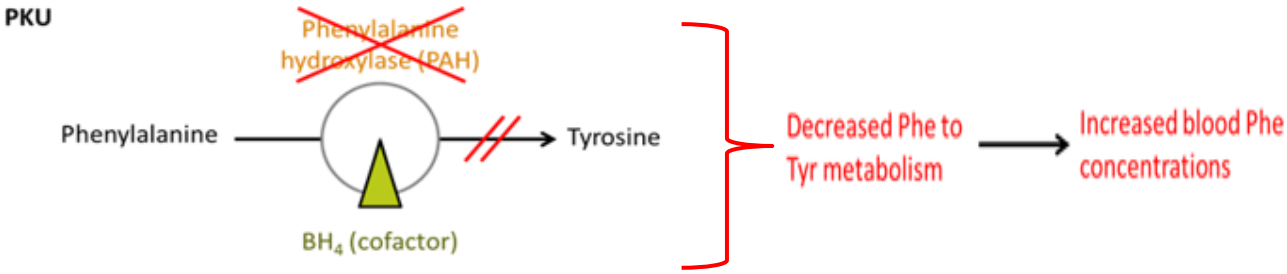
Phe is an essential amino acid required for protein synthesis. It cannot be synthesised de novo in the body and needs to be provided through food. Phe is metabolised into Tyr by the enzyme PAH using tetrahydrobiopterin (BH4) as a cofactor (Figure 1).

Figure 1. PAH metabolises Phe into Tyr using BH4 as a cofactor



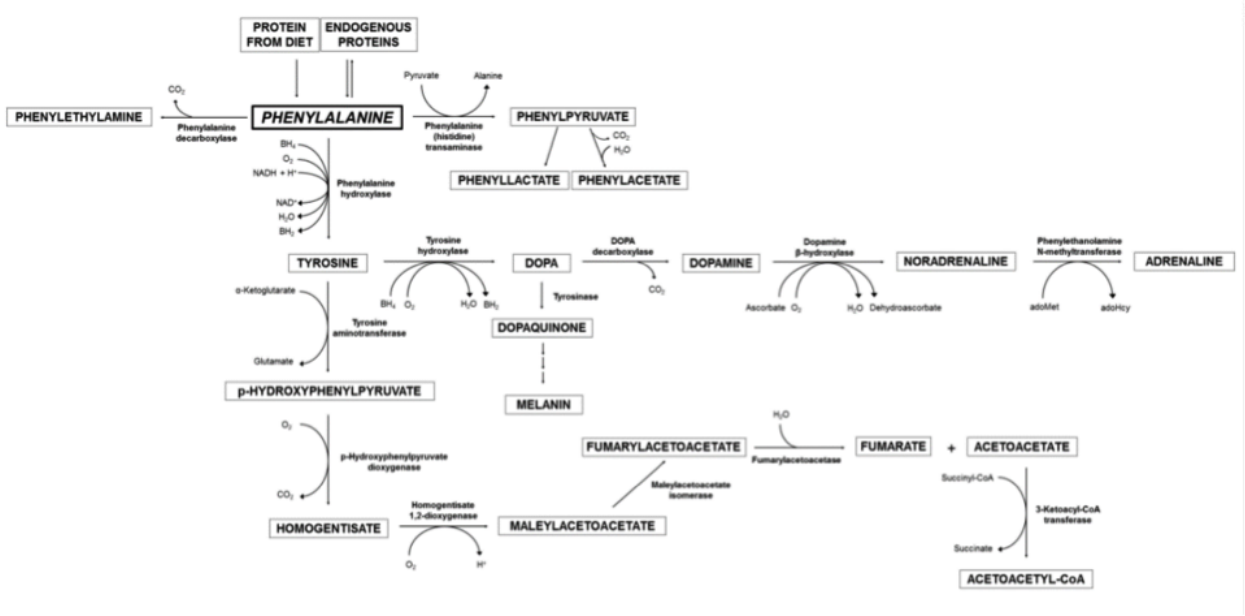
In PKU patients, the absence or reduced availability of PAH results in Phe not being converted into Tyr and, therefore, in an increased blood Phe concentration, which is illustrated in Figure 2.

Figure 2. Aetiology of PKU and BH4 deficiency



There is also a complex interaction of Phe with other neurotransmitters, which is illustrated below in Figure 3. This shows the reduced peripheral production of Tyr and subsequently dopamine, noradrenaline and adrenaline. Most of Phe obtained from diet or endogenous proteolysis is hydroxylated, producing Tyr by PAH; however, this is deficient in PKU. Additional routes include transamination to phenylpyruvate and decarboxylation in order to synthesise phenylethylamine (35).

Figure 3. Phenylalanine metabolism



Since Phe shares a common transport system across the blood-brain barrier with Tyr and tryptophan, elevated Phe levels limit the entry of Tyr and tryptophan into the central nervous system (36).

Tyr and tryptophan are precursors to the neurotransmitters dopamine, noradrenaline and serotonin; therefore, low tyrosine and tryptophan levels in the CNS can impact the critical regulation of mood, anxiety, and cognition provided by these neurotransmitters (37-39). As such, neuropsychiatric symptoms such as inattention, hyperactivity, depression and anxiety are higher in PKU patients than the general population (17) and high Phe levels adversely affect information processing in the brain (such as impaired executive function) caused by reduced brain dopamine.

Treatment Guidelines

European guidelines for the diagnosis and treatment of PKU were published in 2017 (7). These guidelines were developed by over 19 medical specialists in the field of PKU throughout Europe under the auspices of the European Society for Phenylketonuria and Allied Disorders (ESPKU) (9).

The guidelines include recommendations for the following:

Treatment initiation

- All patients with untreated blood Phe levels >360 micromol/L should be treated.
- For patients with untreated Phe levels between 360-600 micromol/L treatment is recommended until 12 years of age.

Lifelong treatment

Lifelong treatment is recommended for any patient with PKU whose blood Phe levels are greater than 600micromol/L.

Lifelong follow up

All adults with PKU should have life-long, systematic follow up in specialised metabolic centres due to specific risks which may occur during adulthood.

Target blood Phe levels

Table **3** below details the target Phe levels for PKU patients according to their age.

Neurocognitive assessments

The guidelines also recommend that neurocognitive evaluations should be performed at 12 and 18 years of age in all patients.

Table 3: Target Phe levels by subgroup.

Population	Target range	Source
Treated PKU patients up to the age of 12 years	120 – 360 micromol/L	European PKU guidelines published 2017 (9)
Treated PKU patients aged >12 years	120 - 600 micromol/L	European PKU guidelines published 2017 (9)
Treated pregnant PKU women	120-360 micromol/L	European PKU guidelines published 2017 (9)

Clinical Pathway

The aim of the current management strategy is to reduce circulating blood Phe levels below which they are associated with harm to the brain, whilst at the same time ensuring sufficient quantities of Phe are available to support optimal growth, development, and mental functioning while providing a nutritionally balanced diet.

A lifelong Phe-restricted diet, applied immediately on diagnosis, is the mainstay of the management of PKU. Natural sources of protein are substituted with Phe-free “medical foods” (40). People with PKU typically use special nutritional products (41), where foods are categorised according to their Phe content, to design their diet according to their daily Phe tolerance. The diet is very strict on protein intake (10 to 20% of a normal diet) (42). The diet excludes many natural protein sources and so, to support normal growth and development, synthetic protein substitutes, often supplemented with vitamins and minerals, are added to the diet along with proprietary low protein foods. Compliance with a diet that is low in Phe can help protect the brain from the neurotoxic effects of elevated Phe and, if blood Phe levels can be reduced to less toxic levels (as suggested by the European Guidelines (9)), patients can lead more fulfilling lives. However, subtle neuropsychological defects remain, on average, relative to their non-PKU peers, and periodic evaluations of executive, emotional, behavioural and other neuropsychological functions are recommended, in addition to nutritional status (40).

Despite recent developments, the standard of care for PKU treatment in the NHS remains this low-protein diet, that completely avoids high-protein foods (such as meat, eggs and dairy products) with controlled intake of many other foods, such as potatoes and cereals.(44) In addition, people with PKU must take an amino acid supplement to ensure they receive all the nutrients required for normal growth and good health. The Phe restricted diet is divided into three components: synthetic protein substitute, Phe free foods and natural protein. The dietary products used in the management of PKU are prescribed by GPs and the expense is born by the primary care budget. (45)

There are many challenges in adhering to a severe Phe-restricted diet in adolescence and adulthood including the time required for dietary management, poor palatability of medical food and the difficulty of maintaining diet in work and social situations. Dietary management can also be difficult to achieve due to neurocognitive deficits associated

with elevated Phe. Additionally, the limited range of foods that can be eaten can lead to social isolation. Following a Phe-restricted diet requires patients to plan their meals, take nutritional supplements appropriately throughout the day and record dietary Phe and protein intake.

Therefore, adherence to a Phe-restricted diet is extremely challenging with as many as 75% of adolescents being unable to keep blood their Phe levels within the recommended target range (30).

As children become older, adherence to the restrictive diet wanes, as demonstrated across multiple studies. For example, Walter et al, 2002 showed that 79% of 15-19-year olds had Phe levels above the EU recommended range (30). Similar evidence has been shown from van Spronsen et al (7) and Ahring et al (43)that 60% and 35% respectively of > 16 years olds had Phe levels in excess of the EU recommended range (7, 16, 30, 43). Transition to adulthood is a challenging period for PKU patients as along with their PKU, they are also faced with challenges in maturation including a desire for increased independence and peer pressure. These difficulties are augmented by the necessity to adhere to dietary therapy for their chronic disease (44).

Due to the challenges presented above, Ford et al. reported that only 57% of adult patients said they were following a prescribed low Phe diet. Seventy-three per cent of both adults and caregivers of children said they found dietary management difficult. The top 5 issues affecting the ability to follow diet in adults were: 1) limited food choices 2) diet being too time-consuming to manage, 3) unpleasant protein substitutes, 4) unpleasant food choices and 5) inconvenience. Additionally, 44% of adult patients described social exclusion because of their diet. Inability to access suitable food in restaurants, at work and related social activities was also common (32).

Although data related to the impact of treatment on adult patients with PKU off therapy for prolonged periods of time are limited, there is some evidence of improvement in the quality of life. Furthermore, white matter changes in the brain may be reversible with improved metabolic control. Given the negative impact of a poorly controlled diet, it is important to monitor metabolic control in PKU throughout the individual's lifetime

and allocate aggressive efforts to encourage patients with PKU to remain in regular follow-up control (45).

Phe-free supplements have poor palatability and maintaining metabolic control becomes more difficult with age, as patients enter adolescence and endure more pressure from school, peers and their carers control loosens (30). Depending upon their age, it is estimated that between 30% and 80% of patients by the age of 15 are unable to achieve or maintain good overall Phe control in spite of dietary limitations.

A similar picture emerges from a study by Cazzorla 2018. Italian PKU patients' adherence to their PKU diet was found to be unsatisfactory, with increased consumption of natural protein sources and reduced daily use of amino-acid supplements with compliance affected by increased social pressure and poor palatability of the supplements (46).

Sapropterin is currently under consideration by NHSE Clinical Priorities Advisory Group for routine commissioning in England, for the treatment of phenylketonuria (all ages). As stated in the Clinical Commissioning Policy proposition, NHS England has recognised the unmet need in treatment for PKU patients and has concluded that there is enough evidence to consider making sapropterin available. (47).

The introduction of sapropterin into the clinical pathway can help PKU patients maintain their Phe levels within the EU guideline targets and increase their ability to consume natural protein (48), while at the same time decreasing the need to take protein supplements. Furthermore, the maintenance of Phe levels within normal parameters will help deal with the detrimental effects on children and adults living with PKU.

Burden of PKU

Detrimental effects of elevated blood Phe in children and adults

Blood Phe levels consistently above EU guidelines, as discussed above, have been associated with suboptimal outcomes in children, adults, and in pregnant women with PKU. Uncontrolled PKU causes blood Phe to stay chronically elevated.(44, 49, 50) Some of the outcomes associated with uncontrolled Phe have been captured by Enns,

2010(16) who undertook a systematic review of the literature and found a range of sub-optimal outcomes. These fall into the following categories:

- Neurological outcomes;
- Quality of life outcomes;
- Growth / nutritional deficiencies;
- Bone pathology issues;
- Associated co-morbidities

These outcomes are observed in patients who have been unable to control their blood Phe levels despite current management with diet.

- **Neurological outcomes (neurocognitive and neuropsychiatric)**

The main effects of PKU are on the neurological function of patients. The abnormally high blood Phe levels are toxic to the brain and lead to severe, irreversible neurophysiologic damage including microcephaly (decreased brain and skull size) and defects in the myelin sheaths that surround nerves and aid neurotransmission. The brains of PKU patients who have not managed to reduce their Phe show evidence of hypomyelination and gliosis, arrest in cerebral development and, in some cases, white matter degeneration (11, 12, 15, 51). The resulting non-physical symptoms of high blood Phe concentration can be severe. This white matter degeneration has been observed in magnetic resonance imaging (MRI) of the brain of PKU patients (11, 12).

Cognitive and motor functions are dependent on both the structural integrity of specific brain regions as well as the tracts connecting these brain structures. These deficits can lead to impaired speed of neural transmission, impaired cognitive and motor deficits which manifests as poor co-ordination, visual functioning, processing speed, language, memory and learning and attention and executive function (11).

Cleary et al, 1995 demonstrated that adolescent and adult patients with white matter abnormalities (as demonstrated through MRI scans) who maintained a strict Phe-free diet had greater improvements in their MRI score (indicating improvement) compared

to patients who did not follow a strict diet. Indeed, the largest change in MRI was seen in patients who returned to a strict diet and lowered blood Phe to <400microol/L (12).

Elevated Phe in the brain impacts mood, causes impaired executive function (which interferes with the ability to perform basic cognitive tasks such as focusing, memory, planning and impulse control) and leads to a range of co-morbidities including anxiety and depression (52). These tasks play a critical role in fulfilling responsibilities of adolescence and adulthood such as schooling, acquiring and maintaining employment, forming relationships, managing money, raising a family, and driving. Bilder's 2016 systematic review and meta-analysis highlights the significant lifelong disability caused by the toxic effects of excess blood Phe and identifies 26 comorbidities associated with PKU, including severe neurological complications, psychiatric disorders including anxiety, depression and attention deficit hyperactivity disorder (ADHD), cognitive deficits and intellectual impairment (17).

High blood Phe concentration during childhood is the major determinant of neurological disease and cognitive outcomes. If children and parents do not manage to reduce the blood Phe, children with PKU, especially below the age of 11 years old, can suffer severe mental retardation, intellectual disability and loss of IQ, microcephaly, seizures, ataxia and tremors, motor deficits, psychological, behavioural stunted growth, and, in many cases, features of autism. From an age of about 6 months, these children exhibit developmental problems, such as delayed speech, which may be accompanied by aberrant behaviours including self-harm, aggression, impulsivity, and psychosis (6, 14, 15).

This is especially detrimental for paediatric and adolescent PKU patients, being at risk for multiple neuropsychiatric impairments, as it can adversely affect their educational performance. Academic difficulties in patients with PKU may be a function of the ADHD symptoms, executive functioning deficits, verbal memory and learning, vision-motor coordination and processing speed deficits that PKU patients experience, all of which are known to affect academic performance (18, 53, 54).

Children with PKU on diet have significantly lower IQ than unaffected peers, studies have shown that patients with PKU have substantially lower average IQ when compared to general population (55). A meta-analysis showed a 1.9-4.1 point reduction in IQ for every 100 umol/L increase in mean lifetime Phe concentrations in PKU patients (56).

The toxic effects of high blood Phe levels are also detrimental to adults, even when treated early. Adults with PKU that have been left untreated or poorly treated during childhood can have permanently lowered IQ, neurological complications such as tremor and fine motor control deficits, reduced EF, attention problems, decreased verbal memory, social and emotional difficulties, and significantly higher prevalence rates of psychiatric illness than the general population (8, 9, 17, 20, 52). Indeed, if left untreated, PKU can lead to irreversible intellectual disability with approximately 98% of individuals with untreated PKU falling in the range of global intellectual disability (8).

Neuropsychiatric symptoms such as depression, anxiety and attention deficit disorder are higher in PKU patients than the general population (17). The Bilder 2016 meta-analysis shows that high Phe levels adversely affect information processing in the brain (such as impaired EF) due to the reduced brain dopamine production, PKU patients with high Phe levels demonstrate significant reductions in attention, inhibitory control, and impulse control. Interventional and comparative studies show improved neurological performance in lower Phe cohorts. In contrast, higher Phe is associated with an increased prevalence of neuropsychiatric symptoms and executive functioning deficits. Findings further support lifelong low Phe maintenance (17) in individuals with PKU, and the recently published EU PKU guidelines recommend:

- regular clinical management for psychiatric function (at symptom onset),
- neurological function (when neurodegeneration occurs, otherwise annual examination in adults); and
- neurocognitive functioning (assessments at 12 and 18 years, otherwise when indicated) (9).

Lowering blood Phe reduces the prevalence of these neuropsychiatric and neurocognitive symptoms (17).

- **Quality of life outcomes**

The societal burden of PKU is driven by reduced quality of life for both patients and caregivers. Part of this reduced quality of life may be due, in part, to reduced EF. Many studies have reported EF deficits in children and adults (55, 57-59). Inattention and behavioural difficulties are detrimental to self-esteem and emotional development (20) and an indirect relationship has been demonstrated between quality of life and EF impairment (60).

The PKU diet is considered a heavy burden by patients, carers and healthcare professionals and the management of PKU is time-consuming for both adult patients and caregivers of PKU-affected children. The reasons for this are because patients and caregivers need to obtain the low-protein food products, plan the patient's daily Phe intake, prepare the daily menu (often involving extra cooking), and prepare and take (or supervise the intake of) supplements. Furthermore, blood Phe levels have to be closely monitored with regular blood tests. (61)

Assessing a patient's quality of life via self-reporting is extremely challenging. Patients with PKU are less able to report their own quality of life due to reduced executive function, which contributes significantly to hidden disabilities in these patient groups (20). As a result, patients are less able to undertake a subjective evaluation of his or her own functioning and emotional well-being. These challenges are also observed in other diseases areas such as psychiatry (62).

A number of health-related quality of life (HRQoL) studies have been undertaken in PKU across a range of countries and populations (63-71); the results, however, lack consistency due to:

- The use of a variety of generic and specific measurement techniques used to capture quality of life of patients and their carers;
- Blood Phe was not always collected in these studies;
- Sample sizes were invariably small; and

- Disease-specific tools have been found to be less sensitive and lacking discriminant qualities (such as Phe levels) although some neurocognitive tools have been effective in showing disease description.

Further research is ongoing regarding the development of new and relevant disease specific quality of life tools.

- **Growth and nutritional deficiencies**

The mainstay of controlling Phe prior to the introduction of pharmacological therapy has been optimal dietary management. This consists of following a Phe-restricted diet (avoidance of high-protein foods) along with Phe-free protein supplements.

PKU patients can experience nutritional problems, possibly as a result of PKU directly, but perhaps linked to the need to follow a Phe-restricted diet. A study by Enns 2010 (16) identified 34 studies (since 2000) relating to growth and nutrition in PKU patients of which 29 studies reported sub-optimal outcomes. These suboptimal outcomes included deficiencies in several essential nutrient and micronutrients, increased body mass index (BMI), altered folate metabolism, plasma lipid peroxidation and other oxidative stresses.

A large retrospective longitudinal study in Spain compared anthropometric characteristics in early-diagnosed HPA or PKU patients and healthy subjects (72). The results indicate that physical growth was impaired in patients with PKU, but not in those with mild-HPA. The two well-differentiated periods where height fell well below z-score = 0, were from birth to two years and on reaching adulthood. The findings were supported by another study that reported nutritional status and physical growth of 25 children with PKU in Jordan (73). All participants had been diagnosed by screening at birth; started dietary treatment early in life; were on a special PKU low protein diet as guided and were monitored by the health care centre. The results indicated that 48% had poor physical growth; 66% of 4-6-month olds, 40% of 8-12-month olds, 28% of 2 year olds and 57% of 4 year olds were underweight.

- **Bone pathology**

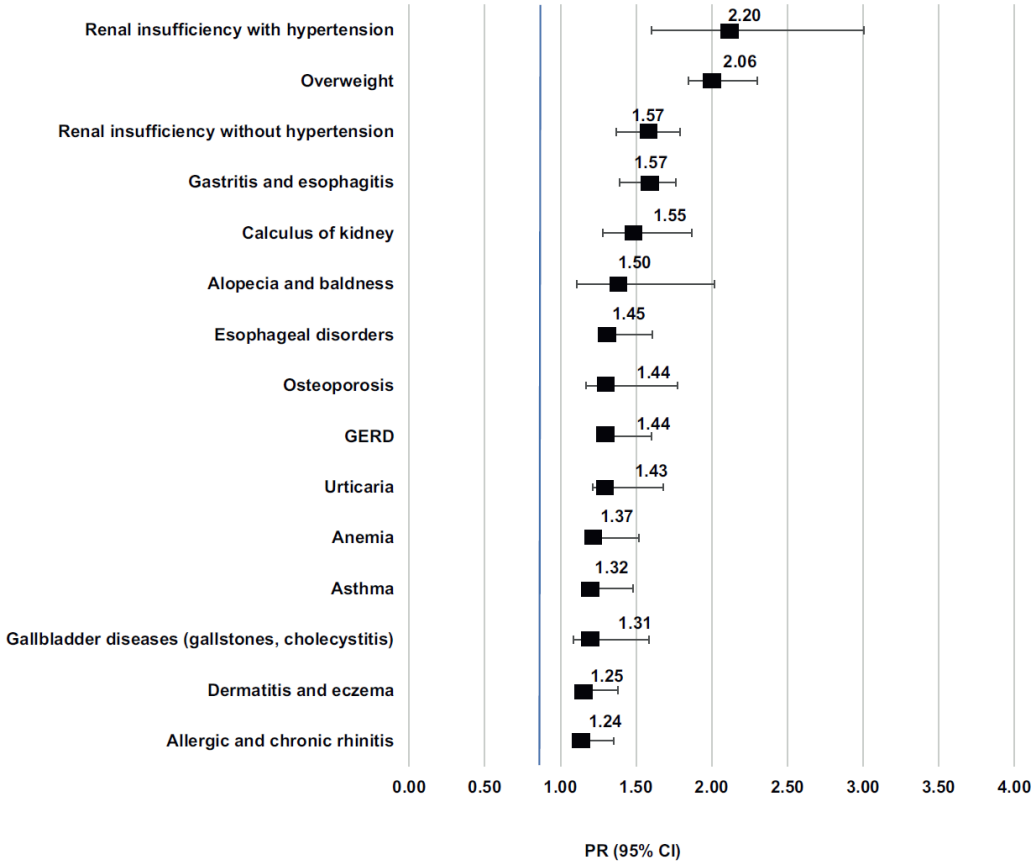
There is a higher prevalence of osteopenia and osteoporosis reported in individuals with PKU which may be related to diet, elevated blood Phe levels, and/or abnormal bone metabolism. Peak bone mass is reduced in individuals with PKU from childhood (74, 75) but it is unclear whether this is the consequence of the disease itself and/or the dietary management of PKU (40).

- **Associated comorbidities**

In addition to the effects of PKU on neurological function, quality of life and bone pathology and growth, recent evidence from real world databases have highlighted the impact PKU has on the development of co-morbidities. This is demonstrated in a publication by Burton, 2018 (22) and a recent publication by Trefz et al. (76) which demonstrated higher prevalence rates of a range of co-morbidities in PKU patients compared to non-PKU controls. These comorbid conditions include for example, renal insufficiency with and without hypertension (diets high in amino acids can lead to greater renal workload), obesity, osteoporosis, gastritis, urticarial and calculus of the kidney (see Figure 4 below). The clinical manifestations of PKU are considered to be related either to the elevated blood Phe levels or the Phe-restricted diet.

In addition, a few published reports of somatic comorbidities among PKU patients have shown higher prevalence of renal impairment, proteinuria, arterial hypertension, and obesity among PKU patients (77-79).

Figure 4. Adjusted prevalence ratio of comorbid conditions in PKU patients compared with non-PKU controls

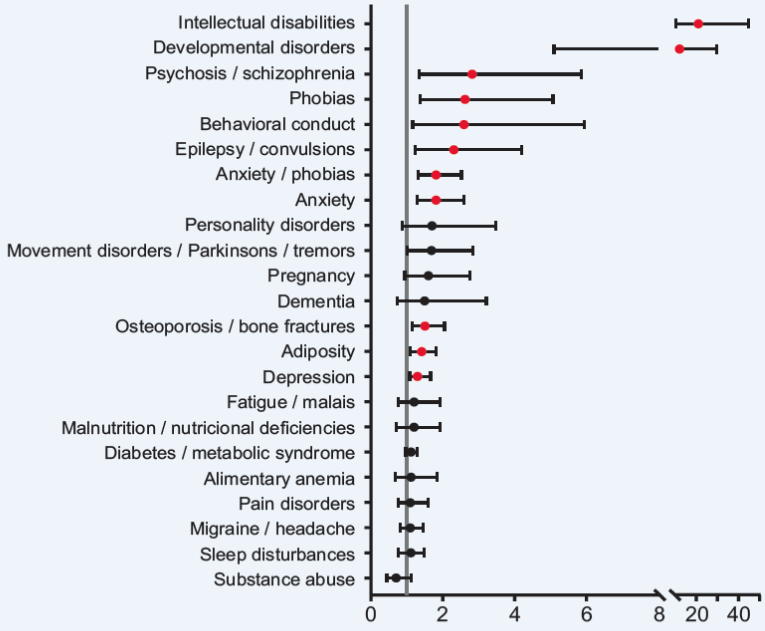


Source: Burton 2018 (22)

Another retrospective database study (23) in Germany showed similar results (Figure 5).

Figure 5. Prevalence ratios of selected comorbidities in PKU Patients compared with control subjects

Figure 1. Prevalence ratios of selected comorbidities* in PKU patients compared with control subjects



	PKU n=377	Control n=3,770
Prevalence ratio	Prevalence (%)	Prevalence (%)
21.02	5.6	0.3
12.21	2.9	0.2
2.81	2.4	0.8
2.62	2.9	1.1
2.59	1.9	0.7
2.26	3.2	1.4
1.82	10.6	5.8
1.81	9.3	5.1
1.73	2.4	1.4
1.68	4.2	2.5
1.60	4.0	2.5
1.54	2.1	1.4
1.53	13.0	8.5
1.41	16.2	11.5
1.33	19.6	14.8
1.21	5.3	4.4
1.17	4.5	3.8
1.11	42.7	38.4
1.10	4.2	3.9
1.09	7.7	7.1
1.08	11.7	10.8
1.05	8.8	8.3
0.69	6.9	6.9

*No PR generated for conditions in which <5 PKU patients had the condition - ADD/ADHD, alcohol dependency, bipolar disorder, cognitive and/or personality changes secondary to GMC, eating disorders, multiple sclerosis, OCD, PDD (autism spectrum disorders), and Tourettes/tic disorders. Red coloring highlights significant comorbidities based on PR and 95% CI values.

Source: Trefz (76)

Metabolic control becomes more difficult with age. Walter et al found 79% of subjects aged 15-19 years old had Phe levels greater than the clinically recommended range (30). A recent study by the National PKU Alliance showed that over 50% of subjects with PKU reported that their disease was difficult to manage; 61.5% of adults reported blood Phe greater than the recommended range, and the ability to control blood Phe worsens with age (80).

A study by Bilder et al (17) has shown that PKU is associated with significantly higher prevalence rates of neuropsychiatric comorbidities including inattention, hyperactivity, depression and anxiety when compared to the general population.

An interim analysis (22) of a further retrospective study examining the burden of illness in adults with PKU showed that as blood Phe concentrations increase capabilities for executive functioning and self-regulation diminish skills that are essential for jobs with

higher levels of independence. This study is ongoing and continuing to enrol subjects to further assess the relationship between blood Phe levels and executive functions in PKU adults as compared with healthy (non-PKU) matched control subjects (22).

Societal and Carer Burden associated with PKU

In 2018, the National Society for Phenylketonuria (NSPKU) (32) conducted one of the largest surveys that has been completed by both adults with PKU and parents/ caregivers of children in order to report the practical, social and psychological issues of living with PKU. Many PKU patients reported a struggle with long-term dietary management and they were only able to adhere to this with variable success. In addition, PKU affected physical, psychological and emotional health, social wellbeing, interpersonal relationships as well as education and work.

Reported problems experienced by children and adolescents with PKU included difficulty with maintaining focus, educational difficulties, anxiety or depression and gastrointestinal symptoms. A large percentage of children (51%) reported social exclusion and relationship issues with friends or family (32).

Problems identified in the survey that are experienced by adults include depression or anxiety, difficulty maintaining focus and low mood. Difficulties with relationships, social exclusion and gastrointestinal issues were experienced. Patients were also found to be taking antidepressants and anxiolytics, which is consistent with the consequences of elevated Phe and the impact on neurotransmitters (32).

The psychiatric burden on carers of PKU patients has also been found to be significantly higher compared to parents of healthy children. A study by Gunduz 2015 (81) investigated the existence and severity of depression and anxiety in parents of children with PKU. The authors found depression and anxiety scores were significantly higher in the PKU patient carer group than the parents with healthy children.

A cross-sectional study conducted in the UK to identify time and financial burden of caregivers of early and continuously treated children with PKU reported median time

burden associated with managing PKU for caregivers to be 19.3 hours per week (range 0-79). Organising, preparing and cooking low phenylalanine meals (in addition to regular meals for the rest of the family) were the most time-consuming tasks (82).

Caring for a child with PKU can have a negative impact on the carers professional life with over half of all caregivers in one study reporting an impact on their jobs from having a child with PKU (82). Caregivers have indicated that PKU treatment regimen was too time consuming to manage alongside their current working pattern (82). Changes to employment included: changed job (4.7%); reduced working hours (20.8%); stopped work (23.6%) and no change (50.9%).

The economic burden of PKU is driven by lifelong medical care, productivity losses due to ill health and neurocognitive deficits, and time spent managing the disease (20, 83, 84). The economic burden on patients and caregivers can include the direct costs of living with PKU, which relates to resource utilisation in managing the condition, such as low-protein foods, supplements, medications, laboratory monitoring, and healthcare visits. There may also be indirect costs such as those arising from the loss of productivity.

Ford's survey states that maintaining a lifelong low Phe diet is not a realistic option for many adults with PKU with some adults describing how they find dietary management complex, impractical and as a result have abandoned treatment or withdrawn from medical care entirely. Some of the adults who had stopped dietary treatment in childhood felt it was inconceivable to recommence diet (32).

In addition to the surveys published in the literature, BioMarin convened two advisory boards with PKU clinical experts to explore primarily the economic and societal impact of PKU on patients, caregivers and healthcare professionals. The first advisory board was held on 19th November 2018 with four PKU clinical experts. Dr Yusof Rahman, Prof. Anita Macdonald, Dr. Saikat Santra and Dr Germaine Pierre attended.
The clinical experts stated:

- There is a significant work burden being undertaken by the PKU clinicians that is often not recognised. For example, ongoing telephone advice to patients /

families / carers is carried out by the experts but it is generally not captured as it is not face-to-face appointment or a telephone appointment that is in place of a face to face appointment and therefore no local tariff is applied. The clinicians are providing this service through goodwill.

- Patients and carers have ad hoc communication with clinical experts for pre-school and school advice (occasionally experts might have to do a school visit) and children's trips / travels/ activities.
- PKU patients are often in need of professional psychological support, which is not only increasing the economic burden but also strains the capacity of the social services.
- The carer burden is strenuous and many people with PKU are eligible for the middle rate disability living allowance (DLA) which is £57.30 / week for children and adults (85).

A second advisory board was held with Dr Germaine Pierre, Diane Green, Dr Radha Ramachandran, Dr Tarekegn Hiwot, Dr Gisela Wilcox and Dr Saikat Santra. Dr Ramachandran, Dr Hiwot and Dr Wilcox are collectively experienced in the care of approximately 50% of the UK adult PKU population, whilst Dr Pierre and Dr Santra are collectively experienced in the care of approximately 20% of the UK paediatric PKU population. An advanced practitioner in metabolic disease and experienced dietitian also gave advice (86).

Feedback was provided via virtual meetings held over two separate days along with a series of questionnaires. The goal of these meetings was to gain an understanding of:

1. The clinical burden by age group who could have the greatest benefit (e.g. age specified by NICE)
2. The quality of life benefits by age group (and caregivers)
3. The strength of the evidence base to reflect clinical reality (long term registry data)
4. The cost and utility inputs necessary to validate the economic modelling
5. The approach necessary to secure reimbursement

The following key findings were the main outcomes of the tw meetings and related questionnaires:

- The experts identified paediatric patients, adolescents, women of child-bearing age and pregnant patients (maternal PKUs) as key patient sub-groups with elevated disease burden that could benefit most from sapropterin.
- The requirement to follow the Phe-restricted diet as part of standard therapy in PKU is a key determinant in reducing the quality of life of patients and parents / caregivers
- Compliance with the Phe-restricted diet (the current standard of care) was estimated as 87.5% of 0-4 years and 5-11 years, reducing to 79.5% in adolescents and 64.2% of adults
- The percentage of adolescents and adults who are symptom-free and optimally controlled is likely to be significantly lower than the compliance results suggest. While many patients can be minimally compliant with what is expected of them, this does not equate to them achieving optimal control at a desirable Phe level
- Adherence to the restricted diet reduces as children approach adolescence, as social interaction and peer pressure creates a significant barrier to adherence
- It was estimated that in the paediatric PKU population, 10% have difficulties with schooling, and 20% have poor social functioning caused by poor Phe control. When asked to score how the availability of sapropterin could influence this, all participants agreed that it would make either, somewhat, or a significant difference
- There was consensus that good early Phe control and optimal PKU management in childhood contributes to better academic achievement and social functioning, which is then carried forward into adult life
- Social wellbeing can be improved if the diet can be relaxed, as a highly restricted diet acts as a constant reminder of the disease. Some coping strategies are socially isolating
- Poor PKU management in childhood can contribute to serious issues in adulthood, including complex eating disorders, a lack of self-worth, anxiety, and depression. Therefore, it was widely agreed that it is important to achieve good control in early years to establish a ‘mindset’ that will continue throughout life

- It was estimated that in the adult PKU population, 38.3% struggle with executive functioning, over a fifth (22.1%) struggle with forming social relationships, and almost a third (31.7%) struggle with other symptoms (inattention, mood etc.). When asked to score how the availability of sapropterin could influence this amongst responsive patients, all participants agreed that it would make either somewhat, or a significant difference
- There was broad consensus that the report capturing the Swedish health utility data for adults is reflective of the UK PKU population (87)
- Consensus was reached around the greater impact of PKU on the health utilities of the paediatric population, subject to the same levels of dietary control and ongoing symptoms of uncontrolled PKU
- The decrease in health utility of parents or carers of PKU patients reflects the impact of this disease on the quality of life of parents, caregivers and the patient themselves
- There was an indication that overall, 14% of the paediatric PKU population and 26% of the adult PKU patient population would ultimately benefit from sapropterin therapy, were it made available (86).

In summary, both advisory boards concluded that PKU exerts a significant clinical, economic, social and financial burden on patients, caregivers and society, even when patients are trying to follow the Phe-restricted diet.

B.1.4 Equality considerations

BioMarin requested the evaluation of sapropterin under a Highly Specialised Technology (HST) evaluation as it believes sapropterin fulfils all the necessary criteria. The Single Technology Appraisal (STA) pathway does not accommodate the specific issues associated with a rare disease treatment (such as the nature of the evidence) which is targeting a very small patient population for lifetime therapy. An evaluation under the STA pathway will be disadvantageous potentially to the adult PKU population in whom it may be difficult to demonstrate cost-effectiveness. As such, the equality consideration relates to the adult population who will be disadvantaged by an STA.

Additional considerations then arise if adults cannot be shown to meet the stringent incremental cost-effectiveness thresholds that form part of the STA process. From the first advisory board convened by BioMarin in 2018, clinicians experienced in the management of PKU expressed their concern with limiting to certain populations based on their age. Patient advocacy groups such as the NSPKU had voiced the same concerns relating to equity of access, marginalisation of sub-groups and issues relating to implementation in specific groups of patients. Many of the early treated, but poorly controlled patients, affected by ongoing symptoms caused by high Phe levels, can suffer from mental health issues including anxiety, depression, phobias, withdrawal and cognitive impairment. They can be both unaware of, and unable to articulate, the disease burden that they suffer from on a day to day basis. The resulting disability paradox, where patients have a diminished ability to understand the full consequences of their clinical condition, also extends to their inability to understand how they effectively manage the disorder. There is risk that this group of patients are therefore being discriminated against with the current standard of care, as effectively these individuals on a practical level (in relation to their inability to manage their diet), have no therapy. As a direct result of this, and the stigma attached to therapy failure, they are disengaged from the specialised treatment centers and their only informed source of help and support. Access to second line therapies for these disadvantaged sub-groups of patients (unable to cope with the standard of care), would go some way to addressing this discrimination.

Given this is now being evaluated under an STA programme, these equality issues still exist.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review was undertaken (original search conducted 25th September 2018 and updated 13th July 2020) to identify all relevant studies on phenylketonuria and tetrahydrobiopterin deficiency in accordance with NICE methodology. The search strategies (keywords) were developed specifically for each database to identify all studies relating to:

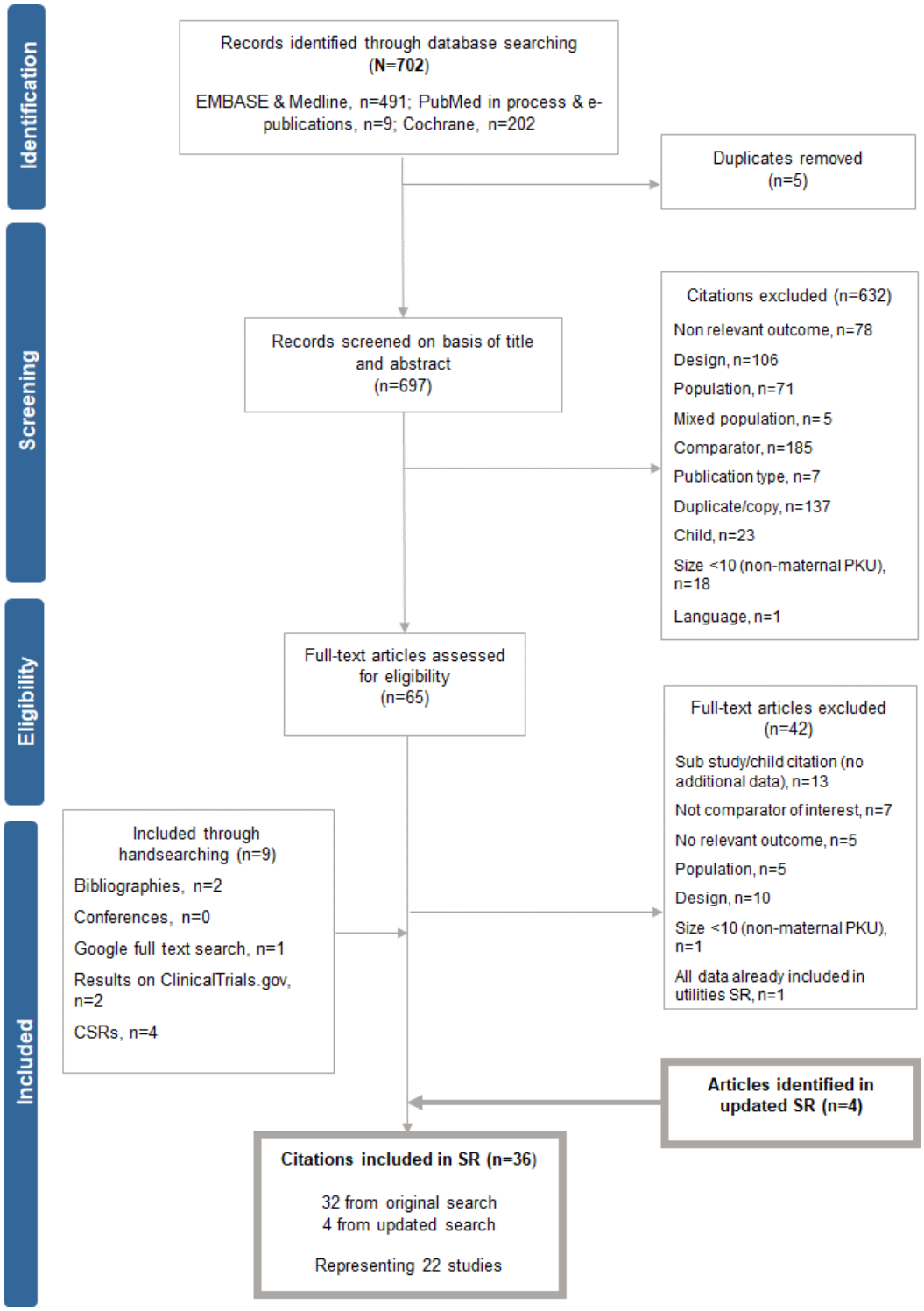
1. Clinical evidence;
2. Cost and resources;
3. Economic data; and
4. Health state utility values and mapping algorithms.

Please refer to Appendix D for a full list of keywords and search terms used for each database. Only studies conducted in humans were sought. Searches were not limited by language or publication status (unpublished or published).

Please see the PRISMA flow chart below for the systematic review undertaken of clinical evidence to support this submission.

The screening process is summarised in a PRISMA flow diagram for the original and update search in **Error! Reference source not found.**. Individual PRISMA diagrams for the original and update search are provided in Appendix D.

Figure 6. PRISMA Flow-chart for study identification and selection of clinical evidence (original search, conducted 25th September 2018; updated search, conducted 13th July 2020)



Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; CDSR, Cochrance Database of Systematic Reviews; CSR, Clinical Study Report; DARE, Database of Abstracts of Reviews of Effects; PKU, phenylketonuria; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SR, systematic review

B.2.2 List of relevant clinical effectiveness

Trials providing clinical effectiveness evidence are listed in Table 4 (RCT data),

Abbreviations: AEs, adverse events; HPA, hyperphenylalaninaemia; NR, not reported; Phe, phenylalanine; PKU,

phenylketonuria; PLA, placebo; PRD, Phe-restricted diet; pts, patients; RCT, randomised controlled trial; SAP, sapropterin; wk, week; yrs, years

Table 5 (single-arm follow-up/extension studies from RCTs) and

Table 6 (observational data).

Table 4: Clinical effectiveness evidence – RCTs

Study [Clinical trial name or primary author surname, year published]	**Levy et al. 2007** (5, 88) PKU003	**Trefz et al. 2009** (89) PKU006	**Burton et al. 2015** (90) [NCT01114737] ASCEND / PKU016	**Muntau et al. 2017** (91) SPARK
Study design	Phase III, multinational, multicentre, double-blind, randomized, PLA-controlled trial	Phase III multinational, multicentre, double blind, randomized, PLA-controlled trial	Multinational, multicentre double-blind, parallel-arm, randomised PLA-controlled study	Phase IIIb, multinational, multicentre, open-label, randomised controlled trial
Population	Paediatric PKU pts, >=8 yrs old, BH4-responsive	Paediatric PKU pts, mean age 7.3 yrs, BH-4-responsive with PAH deficiency	Paediatric and adult PKU pts, mean age 20 yrs, some with ADHD	Paediatric PKU pts, <4 yrs old, BH4-responsive
Intervention (s)	SAP + diet	SAP + PRD	SAP + PRD	SAP + PRD
Comparator(s)	PLA + diet	PLA + PRD	PLA + PRD	PRD
Does trial support application for marketing authorization?	Yes	Yes	No	Yes
Is trial used in economic model?	No	No	No	No
If no, rationale	See below	See below	See below	See below
Reported outcomes specified in the decision problem	Phe concentration in blood, AEs	Phe concentration in blood, protein intake, AEs	Phe concentration in blood, neuropsychological function, AEs	Phe concentration in blood, Phe tolerance, neuromotor development and physical growth parameters (height or length, weight and maximal occipital-frontal head circumference)
All other reported outcomes	NR	NR	BRIEF GEC and MI scale (includes initiation, working memory, planning/ organising, organising materials, and monitoring) and BRI (impulsivity and hyperactivity measure)	NR

Abbreviations: AEs, adverse events; HPA, hyperphenylalaninaemia; NR, not reported; Phe, phenylalanine; PKU, phenylketonuria; PLA, placebo; PRD, Phe-restricted diet; pts, patients; RCT, randomised controlled trial; SAP, sapropterin; wk, week; yrs, years

Table 5: Clinical effectiveness evidence – single-arm follow-up/extension studies from RCTs

Study [Clinical trial name or primary author surname, year published]	**Lee et al. 2008** (92) PKU004 (follow-up of PKU003)	**Burton et al. 2011b** (93) PKU008 (follow-up of PKU004 / PKU006)	**Rutsch et al. 2018** (94) SPARK extension study
Study design	Multinational, multicentre, open-label, 22-week extension study	Phase IIIb multinational, multicentre, open-label, 3-year extension study	Multinational, multicentre, open-label, 36-month extension of the SPARK study
Population	PKU and HPA pts >=8 yrs, who had participated in the 6-wk RCT PKU003	PKU pts >=8 yrs, BH-4-responsive, who had participated in PKU004 (PKU001/PKU003) or PKU006	Paediatric PKU pts, <4 yrs old (at start of SPARK RCT), BH4-responsive
Intervention (s)	SAP + PRD	SAP + local site recommendations for dietary control	SAP+PRD (previously on SAP+PRD in SPARK)
Comparator(s)	N/A (uncontrolled)	N/A	SAP+PRD (previously on PRD only in SPARK)
Does trial support application for marketing authorization?	Yes	No	No
Is trial used in economic model?	No	No	No
If no, rationale	See below	See below	See below
Reported outcomes specified in the decision problem	Phe concentration in blood, AEs	AEs	Phe concentration in blood (interpretation only), Phe tolerance, AEs
All other reported outcomes	NR	Bioavailability data for intact vs dissolved tablets	Withdrawal due to AEs

Abbreviations: AEs, adverse events; HPA, hyperphenylalaninaemia; NR, not reported; Phe, phenylalanine; PKU, phenylketonuria; PRD, Phe-restricted diet; pts, patients; RCT, randomised controlled trial; SAP, sapropterin; wk, week; yrs, years

Table 6: Clinical effectiveness evidence – observational data

Study [Clinical trial name or primary author surname, year published]	**Longo et al. 2015, Lilienstein et al. 2017** (5, 95) [NCT00778206] PKUDOS	**Burton et al. 2007** (96) PKU001	**Trefz et al. 2015, Muntau et al. 2018** (48, 97) [NCT01016392] KAMPER
Study design	Single country, multicentre, observational registry	Multinational, multicentre, open-label, prospective observational study	Multinational, multicentre, observational registry
Population	Paediatric, adolescent, and adult PKU pts, age range 0-63 yrs	PKU pts, mean age 21.8 yrs, not adhering to strict Phe-restricted diet	Paediatric and adult PKU pts, mean age 17.1 yrs, BH-4-responsive with PAH deficiency
Intervention (s)	SAP + Phe-restricted diet	SAP	SAP + Phe-restricted diet
Comparator(s)	N/A	N/A	N/A
Does trial support application for marketing authorization?	No	Yes	No
Is trial used in economic model?	Yes	Yes	Yes
If no, rationale		See below	
Reported outcomes specified in the decision problem	Phe concentration in blood, protein intake, AEs	Phe concentration in blood, AEs of tx	Phe concentration in blood, protein intake, AEs of tx
All other reported outcomes	NR	NR	NR

Abbreviations: AEs, adverse events; EAP, expanded access programme; FDA, Food and Drug Administration; KAMPER, Kuvan® Adult Maternal Paediatric European Registry; N/A, non-applicable; PAH, phenylalanine hydroxylase; PKUDOS, The Phenylketonuria Demographics, Outcomes and Safety registry; SAP, sapropterin; tx, treatment; yrs, years

Rationale for not using the following trials in the economic model

A detailed description of each of the following clinical trials is provided in sections 2.2-2.6 of this Document B. However, none of these trials were used in the economic model for the following reasons:

PKU-001 PKU-001 was the study from which the pivotal Phase III trial, PKU-003, and its extension PKU-004 draw their population. This study was not included in the economic model because it had short follow up period, it was not a controlled trial, and patients were not on a Phe-restricted diet.

PKU-003 The results of this study support lowering Phe levels and this is the pivotal phase III study and placebo-controlled. This study was not included in the economic model because of the short duration of the study.

PKU-004 The results of this study support safety and tolerability of long-term treatment. This study was not included in the economic model because of the duration of the study.

PKU-008 The results of this study support the safety and tolerability of sapropterin treatment. This study was not included in the economic model because Phe intake was not monitored.

PKU-016 The results of this study support data on neuropsychiatric symptoms in relation to Phe levels. This study was not included in the economic model because the study focusses on neuropsychiatric symptoms.

SPARK The results of this study support data focused on patients 0-4 years old. This study was not included in the economic model because the age limitation of the study.

In summary, the clinical trials are largely historical; the registry data are longer-term, in a real-life setting and, therefore, far more compelling as data sources for the economic model.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

The safety and efficacy of sapropterin in PKU patients has been studied over many years in a comprehensive clinical development programme that includes Phase II, III, IIIb and IV studies. These studies have been undertaken across a range of patient groups (such as patients below the age of 4 years, or those with maternal PKU) and patient relevant endpoints (such as reduction in Phe levels, Phe tolerance and neurological outcomes).

In addition, the manufacturer is sponsoring a range of registries as part of the EMA's post-approval commitments. The purpose of these registries is to collect long-term, real world data on the benefits and safety of therapy with sapropterin.

The clinical development programme to date comprises a Phase II screening study (PKU-001), seven Phase III/IIIb studies (PKU-003, PKU-004, PKU-006, PKU-016, PKU-008, SPARK, and PKU-015) and five Phase IV registry studies (PKUDOS, KAMPER, PKUMOMS, ENDURE and KOGNITO). A comparative summary of the methodology for each of the trial in the clinical development programme is presented in Table 7.

Table 7: Comparative summary of trial methodology

Trial number (acronym)	Location	Trial design	Eligibility criteria	Settings	Interventions	Primary outcomes	Other outcomes
PKU-001 (Phase 2) (96)	North America and Europe (30 sites)	A phase 2, multicentre, open-label, single group study	- Age >/= 8 years - Blood Phe level >/= 450 umol/L at screening - Clinical diagnosis of PKU with HPA documented by past medical history of at least one blood Phe measurement >/= 360 umol/L (6 mg/dL)	Interventional, non-randomised, open-label	489 patients were treated with 10mg/kg sapropterin administered orally once daily for 8 days. There was no comparator Disallowed concomitant medication: corticosteroids, methotrexate, levodopa, or vaccines	Degree and frequency of response as demonstrated by a reduction in blood Phe levels Phe levels recorded at Baseline (day 1) and on day 8	Safety
PKU-003 (Phase 3) (88)	North America and Europe (30 sites)	A phase 3, multicentre, randomised, double-blind, placebo-controlled, 6-week study	- 8 years of age and older - received at least 7 out of 8 scheduled doses in Study PKU 001 - responsive to sapropterin in Study PKU-001, - Blood Phenylalanine level >/=450 µmol/L at screening	Multicentre, interventional, randomised, double-blind, placebo-controlled study	After being randomised in 1:1 ratio, 42 patients received 10 mg/kg/day sapropterin, 47 patients received placebo Sapropterin (provided in tablets containing 100 mg of sapropterin each) or placebo (provided as tablets similar to sapropterin tablets) was administered orally once daily in the morning dissolved in 4–8 oz (120–240 mL) of water, apple juice, or orange juice Disallowed concomitant medication: corticosteroids, methotrexate, levodopa	Change in blood Phe levels from baseline to week 6 Phe levels recorded at Baseline (1 and 2 weeks before randomisation and week 0 of assessment) and on week 6.	- The mean change in weekly blood Phe levels during 6 weeks of treatment - The proportion of subjects that had blood Phe < 600 µmol/L at Week 6

PKU-004 (Phase 3) (92)	North America and Europe (30 sites)	A phase 3, multicentre, open-label, extension 22 week study	- 8 years of age and older - Received ≥ 80% of the scheduled doses in PKU-003, unless removed from the study after exceeding the Phe alert level value defined in PKU-003	Multi-centre, open-label extension study	Subjects received oral doses of sapropterin (intervention) taken once daily for 22 weeks. There was no comparator. Sapropterin was provided in tablets containing 100 mg of sapropterin and dissolved in 4-8oz (120-240 mL) of water, apple juice, or orange juice. The study was divided in 2 parts. In Part 1, all subjects received sapropterin at a dose of 5, 20, and 10 mg/kg/day, respectively, for 2 weeks each, followed by 4 weeks at a dose of 10 mg/kg/day. In Part 2, subjects received a fixed dose of 5, 10, or 20 mg/kg/day for 12 weeks. Disallowed concomitant medication: corticosteroids, methotrexate, levodopa	Safety and tolerability of long-term treatment. Phe levels recorded at Baseline (week 0) and weeks 2, 4, 6, 10, 12, 16, 20 and 22.	- Safety and tolerability of 3 difference doses; - Effect of various doses on blood Phe levels; - Population pharmacokinetics; - Reduction of Phe levels over a 24-hr period; - Persistence of benefit of treatment in the subject population as evidenced by long-term control of blood Phe levels.
PKU-006 (Phase 3) (98)	North America and Europe (15 sites)	A phase 3, multicentre, double-blind, placebo-controlled, 6-week study	- Clinical diagnosis of PKU with HPA documented by at least one blood Phe measurement >/=360 umol/L (6 mg/dL) - Under dietary control with a Phe-restricted diet as evidenced by:· Estimated daily Phe tolerance </=1000 mg/day - At least 6 months of blood Phe control (mean	Interventional, randomised, double-blind, placebo-controlled	A 3:1 ratio sapropterin: placebo randomisation was used for 90 children with PKU aged 4 to 12 years, who were on Phe-restricted diets and had blood Phe levels ≤480 µmol/L at Screening Sapropterin provided in tablets containing 100 mg of sapropterin each, was administered orally once daily in the morning as the number of tablets equivalent to a	Part 1: Response to sapropterin, defined as ≥ 30% decrease in blood Phe from baseline at Day 8. (90 patients) Part 2: Daily Phe supplement tolerated by the sapropterin group at the end of the treatment period (Week 10) while maintaining adequate blood Phe control (ie, blood	Change in Phe levels from baseline to week 3

			level of </=480 µmol/L) prior to enrolling in the study - Aged 4 to 12 years inclusive at screening - A blood Phe level </=480 µmol/L at screening		20mg/kg/day dose dissolved in 4-8 oz (120-240 mL) of water or apple juice for 6 weeks. A follow-up call or visit was made 4 weeks later. Placebo, provided as tablets similar to sapropterin tablets, was administered orally once daily in the morning as the number of tablets equivalent to a 20mg/kg/day dose dissolved in 4 8 oz (120-240 mL) of water or apple juice for 6 weeks. A follow-up call or visit was made 4 weeks later. Disallowed concomitant medication: corticosteroids, methotrexate, levodopa	Phe concentration <360 µmol/L). (46 patients) A longitudinal model with weekly blood Phe measurements as the response variable and treatment group, visit, and baseline blood Phe concentration (average of measurements at screening, day 1 of Part 1 and week 0 of Part 2) was set.	
PKU-008 (Phase 3b) (93)	United States, Canada (15 sites), Europe (13 sites)	A phase 3b, multicentre, open-label, single group, extension study	- Sapropterin responders who completed either PKU-004 or PKU-006; or - Subjects in PKU-006 who terminated early due to elevated Phe concentrations after experimental increases in Phe intake.	Phase 3b, interventional, multicentre, multinational, open-label extension study	111 subjects received sapropterin orally once daily at a dose between 5 and 20 mg/kg/day. There was no comparator. Patients were to follow local site recommendations for dietary control and management of high Phe concentrations. All subjects were evaluated for safety up to three years or until one of the following occurred: - Consent was withdrawn and study discontinued; - Subject discontinued at the discretion of the investigator;	Safety was monitored every 3 months for: - Adverse events (AEs) and serious AEs (SAEs) - Clinical laboratory evaluations - Physical examinations - Concomitant medication - Vital sign measurements	Blood Phe Levels

					- Drug became available via marketing approval; Study was terminated.		
SPARK (Phase 3b) (91)	This trial was conducted at 22 sites in 9 countries (2 in Austria, 2 in Belgium, 1 in the Czech Republic, 4 in Germany, 5 in Italy, 2 in The Netherlands, 3 in Slovakia, 1 in Turkey and 2 in the United Kingdom).	A phase 3b, multicentre, randomized, open-label, parallel group, 26-week, controlled study	- Subjects were male or female with PKU - Children aged <4 years at first day of enrolment - Had ≥2 independent blood Phe levels ≥400 µmol/L - Had a previous response to BH4 test. - Had good adherence to dietary treatment.	Phase IIIb, international, multicentre, randomised, controlled	Part 1: screen eligible patients (n=109) Part 2: 26-week (6 month) study period, randomised 1:1 to receive sapropterin (10 mg/kg per day) plus Phe-restricted diet (n-27) or just Phe-restricted diet (n=29) Part 3: 3-year extension period, all patients receive KUVAN up to 20 mg/kg per day Disallowed concomitant medication: corticosteroids, methotrexate, levodopa	Dietary Phe tolerance after 26 weeks of treatment with sapropterin + Phe-restricted diet vs. a Phe-restricted diet alone. Assessment schedule: screening (within 42 days prior Day 1), blood Phe levels every two weeks.	- Levels of blood Phe (measured bi-weekly for first 26 weeks and then every 3 months during 3 year extension period); - Change from baseline in dietary Phe tolerance after 26 weeks; - Number of subjects with adverse events; Neuromotor developmental milestones using Denver Developmental Scale; -Neurodevelopmental status using Bayley III Scales of Infant and Toddler Development and WPPSI-III; - Linear Growth; Body Weight; Maximal occipital-frontal head circumference; - Number of subjects with HPA; - Dietary Phe tolerance; Blood pressure; - Number of Subjects with PAH genotypes; - Pharmacokinetics – Apparent clearance (CL/f), Apparent

							volume of distribution (V/f), AUC0-infinity, Tmax, Cmax
PKU-015 (Phase 3b) (99)	United States, Canada (total of 14 study sites)	A phase 3b, multicentre, open-label, single group study	- Established diagnosis of PKU with hyperphenylalaninemia (HPA) >= 360 micromol/L - Age 0 to 6 years old, inclusive, at Screening.	An ongoing multicenter, international open-label study to evaluate the effect of sapropterin on neurocognitive function, maintenance of blood Phe concentrations, safety, and population pharmacokinetics in children.	Study design: In part 1: patients received a 4-week trial designed to identify BH4 responders. Part 2 is the 7-year trial component to evaluate long-term effects on neurocognitive function. Subjects who responded to sapropterin and attained a score of ≥80 on the infant developmental test or an IQ ≥80 were eligible to enter part 2, which included a 6-month safety and efficacy evaluation followed by a long-term neurocognitive evaluation for 7 years of follow-up. Disallowed concomitant medication: corticosteroids, methotrexate, levodopa	Long-term efficacy in preserving neurocognitive function when treatment is initiated at 0-6 years Phe concentration from baseline calculated from the average of phenyl-alanine levels at weeks 1, 2, 3, and 4. Sapropterin-responsive subjects received a baseline neurocognitive assessment within 6 weeks of confirmation of sapropterin responsiveness. Study visits occurred monthly up to 1 year and every 6 months thereafter through year 7. Interim assessments were conducted by telephone every 3 months to assess weight, adverse events (AEs), and concomitant medications.	Long-term safety; Growth; Neurocognitive function; pharmacokinetics
PKU-016 (also known as PKU-ASCEND) (Phase 3) (90)	United States, Canada (total of 36 study sites)	A phase 3, multicentre, double-blind, randomized, placebo-controlled, 26-week study	- ≥ 8 years of age - Confirmed diagnosis of PKU - Willing to continue current diet (typical diet for the 3 months prior to study entry) unchanged	Interventional, double-blind, placebo-controlled. Randomised for the first 13	A 1:1 ratio sapropterin: placebo randomisation was used. N = 98 sapropterin - A dose of 20 mg/kg/day was administered as oral tablets.	- Change in ADHD-RS/ Adult ASRS Total Score From Baseline to Week 13 [Time Frame: Baseline to Week 13]Effects of 6R-BH4 on symptoms of ADHD in PKU subjects who had symptoms of	- Effects on anxiety and depression; - Effects on neuropsychiatric symptoms and global function over 26 weeks in patients wo have a blood Phe

			while participating in the study	weeks of treatment	N = 108 A placebo tablet was administered orally for the first 13 weeks of treatment. Disallowed concomitant medication: corticosteroids, methotrexate, levodopa	ADHD at screening in the subjects that had a blood Phe level reduction after treatment with 6R-BH4. - Number of Participants With a Score of 1 or 2 in CGI-I From Baseline to Week 13. [Time Frame: 13 weeks]Effects of 6R-BH4 on global function in PKU subjects in subjects that had a blood Phe level reduction after treatment with 6R-BH4 at screening.	reduction after treatment and patients who do not; - Safety.
ENDURE (Phase 4) (100)	Norway and Denmark sites	A phase 4, non-randomized, multicentre, open-label, single group, uncontrolled, 28-day study	NA	Open-label, single-arm, cohort study	Sapropterin 20 mg/kg once daily for 28 ± 1 days. No comparator. Disallowed concomitant medication: corticosteroids, methotrexate, levodopa	Percentage of participants with ≥30% reduction from baseline in Blood Phe level	- Number of participants with AEs, TEAs, - TEAs leading to withdrawal; - Percentage of Early-, Late-, and Partial-Responders and Non-responders; - Percentage of participants with ≥30%, 20- 30%, 10-20%, and <10% reduction in blood Phe levels; - Percentage of Early-, Late-, and Partial-responders according to phenotype; - Mean change from baseline in Blood Phe-to-tyr Ratio
PKUDOS	United States (total of	A phase 4, voluntary, prospective,	Subjects must have a diagnosis of PKU and have: previously received	A phase 4, voluntary, prospective,	Subjects with continuous exposure to sapropterin.	To provide longitudinal observational data of	NA

(Phase 4 registry) (5, 95)	53 study sites)	observational, safety registry study	sapropterin, are currently receiving sapropterin, or intend to receive sapropterin therapy within 90 days of enrolment.	observational, safety registry study designed to provide longitudinal safety and efficacy data.	Subjects with intermittent exposure to sapropterin. Subjects who had prior short terms use of sapropterin	sapropterin safety and efficacy	
KAMPER (Phase 4 registry) (48, 97)	85 clinical sites in 9 countries (Austria, France, Germany, Italy, The Netherlands, Slovakia, Spain, Sweden, Portugal).	Observational Study on the Long Term Safety of sapropterin Treatment in Patients With Hyperphenylalaninemia (HPA) Due to Phenylketonuria (PKU) or BH4 Deficiency (KAMPER)	Adult or paediatric subject (4 years old or older) of either gender with HPA due to PKU.	A phase 4, voluntary, prospective, observational, safety registry study designed to provide longitudinal safety and efficacy data.	As this is an observational study, no diagnostic, therapeutic, or experimental intervention is involved	Incidence and description of Adverse Events and Serious Adverse Events (AEs/SAEs)	Incidence of AEs/SAEs in specific population (elderly, children, subjects with renal or hepatic insufficiency); Description on somatic growth (in BH4 deficient children < 3 years); Neurocognitive outcomes; Neurological and psychiatric assessment; Diet and sapropterin treatment adherence; Long-term sensitivity to sapropterin treatment; Blood Phe levels; Tyrosine (Tyr) levels; Pregnancy and delivery outcomes
KOGNITO (Phase 4) NCT01965912	Germany (3 sites), Italy (5 sites), Spain (4 sites),	A Phase 4 Open-Label, Single-Cohort Study of the Long-Term Neurocognitive Outcomes in 4	Patients 4-5 years old with PKU	Single-cohort, interventional, open-label trial to evaluate long-term	Sapropterin 5-20 mg/kg/day + Phe-restricted diet for 7 years	Mean Full Scale Intelligence Quotient Score (FSIQ) of the Wechsler Intelligence Scale for Children (WISC)-IV	Height; Weight; Blood levels of tyrosine, tryptophan, pre-albumin and methylmalonic acid; IQ score and subscores; Change in

	UK (5 sites)	to 5 Year-Old Children With Phenylketonuria Treated With sapropterin for 7 Years		neurocognitive outcomes			baseline in FSIQ score at 2, 4 and 7 years; Dietary Phe tolerance; Index of Dietary Control; Distribution of PAH genotype; Number of subjects with AEs and SAEs.

Abbreviations: ABPM = Ambulatory Blood Pressure Monitoring; ADHD = Attention-Deficit Hyperactivity Disorder; ADHD RS/ASRS = Attention-Deficit Hyperactivity Disorder Rating Scale and Adult ADHD Self-Report Scale; AE = Adverse event; AUC0-infinity = Area under the plasma concentration curve, time 0 to infinity; BH4 = tetrahydrobiopterin; CGI-I = Clinical Global Impression-Improvement; CGI-I = Clinical Global Impression-Severity; CL/f = Clearance; Cmax = Maximum observed plasma concentration; CSR = Clinical Study Report; CTD = Common Technical Document; FSIQ = Full Scale Intelligence Quotient ; GTPCH = Guanosine Triphosphate Cyclohydrolase; LNAA = Large Neutral Amino Acid; MRI = Magnetic resonance imaging; N = total number of patients; N/A = not applicable; PAD = Peripheral Arterial Disease; PAH = phenylalanine hydroxylase; PAT = Peripheral Arterial Tonometry; PAG = Parent Global Assessment Scale; Phe = Phenylalanine; PKU = phenylketonuria; PLS-4 = Preschool Language Scale-Fourth Edition; RCT = randomized controlled trial; SAE = Serious adverse event; SCD = Sickle Cell Disease; SRS = Social Responsiveness Scale; TEAE = Treatment emergent adverse event; Tmax = Time to maximum plasma concentration; V/f = Volume of distribution; WISC-IV = Wechsler Intelligence Scale for Children; WPPSI-III = Wechsler Preschool and Primary Scale of Intelligence

Settings: Settings and locations where the data were collected
Interventions: Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x]) Permitted and disallowed concomitant medication
Primary outcomes: Primary outcomes (including scoring methods and timings of assessments
Other Outcomes: Other outcomes used in the economic model/specified in the scope

Sapropterin (Kuvan®) has an EMA licence and an orphan designation since 2008 (2). Consequently, much of the early clinical trial data underpinning the marketing authorisation is now either historical or, given its primary regulatory purpose and the underlying design of the clinical trial, is of short duration. For example, in PKU-003, the pivotal registration trial, the primary endpoint was reduction in blood Phe concentrations from Baseline to Week 26. All of the Phase 3 studies are completed studies.

The more compelling, and longer-term, data evaluating the efficacy and safety of sapropterin treatment in a variety of PKU patient groups derives from a number of completed and ongoing Phase 3b studies, as well as Phase 4 patient registries designed to evaluate the long-term treatment experience of PKU patients in a real world setting. Taken together, these longer-term data represent the best available, real world evidence of the treatment benefits of sapropterin in a wide range of paediatric and adult PKU patients.

For simplicity, therefore, the methodology of the following studies is presented in this section:

- Pivotal registration studies:
    - PKU-001 – Phase 2, open label, uncontrolled
    - PKU-003 – Phase 3, randomised, placebo-controlled
    - PKU-004 – Phase 3, open-label extension of PKU-003
    - PKU-016 – Phase 3, randomised, placebo-controlled
- Phase 3b studies:
    - SPARK, with active comparator
    - PKU-008 – Phase 3b, open-label extension
- Ongoing Phase 4 registry studies providing long-term data:

- PKUDOS
- KAMPER

Details of the remaining studies (PKU-006, PKU-016, PKU-MOMS, ENDURE and KOGNITO), are presented in Appendix F. These studies are supportive in providing evidence of the benefit of sapropterin treatment; however, they have not been used in the cost-effectiveness model nor have been part of the marketing authorisation application. Therefore, they have been added in the appendices as further supporting evidence.

B.2.3.1 Pivotal trials design and methodology

PKU-001

PKU-001 is a completed Phase 2, multicenter, open-label, uncontrolled clinical trial to evaluate the response to and safety of an 8-day course of sapropterin treatment in subjects with PKU who have elevated Phe concentrations. The primary publication is Burton et al, 2007 (96).

A summary of the trial methodology is provided in Table 8.

Table 8. Summary of methodology for PKU-001 (uncontrolled study, completed, published)

Study name and NCT number	A Phase 2, Multicenter, Open-Label Study to Evaluate the Response to and Safety of an 8-Day Course of Phenoptin ™ Treatment in Subjects with Phenylketonuria Who Have Elevated Phenylalanine Levels (NCT00104260).
Objectives	Primary objective • To evaluate the degree and frequency of response to Phenoptin™ (sapropterin), as demonstrated by a reduction in blood phenylalanine (Phe) level among subjects with phenylketonuria (PKU) who have elevated Phe levels. Secondary objective • To evaluate the safety of Phenoptin™ treatment in this subject population and identify individuals in this subject population who respond to Phenoptin™ treatment with a reduction in blood Phe level.
Location	United States of America (12 sites)
Design	Interventional, non-randomised, open label

Duration of study	8 days
Sample size	N = 489
Inclusion criteria	• Age >/= 8 years • Blood Phe level >/= 450 umol/L at screening • Clinical diagnosis of PKU with hyperphenylalaninemia documented by past medical history of at least one blood Phe measurement >/= 360 umol/L (6 mg/dL) • Willing and able to provide written informed consent or, in the case of subjects under the age of 18, provide written assent (if required) and written informed consent by a parent or legal guardian, after the nature of the study has been explained • Negative urine pregnancy test at screening (non-sterile females of child-bearing potential only) • Male and Female subjects of childbearing potential childbearing potential (if sexually active and non-sterile) must be using acceptable birth control measures, as determined by the investigator, and willing to continue to use acceptable birth control measures while participating in the study • Willing and able to comply with study procedures • Willing to continue current diet unchanged while participating in the study.
Exclusion criteria	• Perceived to be unreliable or unavailable for study participation or, if under the age of 18, have parents or legal guardians who are perceived to be unreliable or unavailable • Use of any investigational agent within 30 days prior to screening, or requirement for any investigational agent or vaccine prior to completion of all scheduled study assessments • Pregnant or breastfeeding, or considering pregnancy • ALT > 5 times the upper limit of normal (i.e., Grade 3 or higher based on World Health Organization Toxicity Criteria) at screening • Concurrent disease or condition that would interfere with study participation or safety (e.g., seizure disorder, oral steroid–dependent asthma or other condition requiring oral or parenteral corticosteroid administration, or insulin-dependent diabetes, or organ transplantation) • Serious neuropsychiatric illness (e.g., major depression) not currently under medical control • Requirement for concomitant treatment with any drug known to inhibit folate synthesis (e.g., methotrexate)

	• Concurrent use of levodopa • Clinical diagnosis of primary BH4 deficiency.
Method of randomisation	Not applicable.
Method of blinding	Not applicable.
Intervention(s) (n =) and comparator(s) (n =)	489 patients were treated with 10mg/kg sapropterin administered orally once daily for 8 days. There was no comparator.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was blood Phe concentration. For purposes of this study, response to sapropterin treatment was defined as ≥ 30% decrease in blood Phe from baseline.

PKU-003

PKU-003 is a completed Phase III, randomised, placebo-controlled study exploring the efficacy of sapropterin on the reduction of Phe concentration in 89 patients with PKU. The primary publication is Levy et al, 2007 (88).

Subjects with PKU at least 8 years of age with elevated blood Phe levels at screening, who had responded to sapropterin in PKU-001 and who were not following a strict PKU diet, were potentially eligible for enrolment into PKU-003. The primary efficacy endpoint was change in blood Phe level from baseline at Week 6, a clinically relevant endpoint in this subject population.

A summary of the trial methodology for PKU-003 is presented in

Table 9.

Table 9. Summary of methodology for PKU-003 (randomised controlled, completed, published)

Study name and NCT number	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Phenoptin™ in Subjects With Phenylketonuria Who Have Elevated Phenylalanine Levels (NCT00104247)
Objectives	The primary objective of this study is to evaluate the efficacy of Phenoptin™ (sapropterin) in reducing blood Phe levels in subjects with PKU.
Location	United States of America (16 sites) and six countries in Europe: France, Ireland, Germany, Poland, the United Kingdom and Italy (14 centres).
Design	Multicentre, interventional, randomised, double-blind, placebo-controlled study
Duration of study	6 weeks
Sample size	Sample size was based on calculations for the primary efficacy endpoint, change in blood Phe from baseline to Week 6. The sample size calculation assumed a mean difference between placebo and sapropterin of 150 µmol/L, an SD of 85 µmol/L, and a 2-sided Type I error rate of 0.05. Under these conditions, a sample size of 80 randomized subjects (40 in each group) would provide over 95% power to detect a difference in mean blood Phe level between placebo and sapropterin groups.
Inclusion criteria	• 8 years of age and older • Received at least 7 out of 8 scheduled doses in Study PKU 001 • Responsive to Phenoptin™ in Study PKU-001, defined as a reduction in blood Phenylalanine level of >/=30% compared with baseline • Blood Phenylalanine level >/=450 µmol/L at screening • Willing and able to provide written informed consent or, in the case of subjects under the age of 18, provide written assent (if required) and written informed consent by a parent or legal guardian, after the nature of the study has been explained • Negative urine pregnancy test at screening (females of child-bearing potential)

	• Male and Female subjects of childbearing potential (if sexually active) must be using acceptable birth control measures, as determined by the investigator, and willing to continue to use acceptable birth control measures while participating in the study • Willing and able to comply with study procedures, including maintenance of existing diet throughout the study • Willing to continue current diet unchanged while participating in the study.
Exclusion criteria	• Perceived to be unreliable or unavailable for study participation or, if under the age of 18, have parents or legal guardians who are perceived to be unreliable or unavailable • Use of any investigational agent other than Phenoptin™ within 30 days prior to screening, or requirement for any investigational agent or investigational vaccine prior to completion of all scheduled study assessments • Pregnant or breastfeeding, or considering pregnancy • ALT >5 times the upper limit of normal (i.e., Grade 3 or higher based on World Health Organization Toxicity Criteria) at screening • Concurrent disease or condition that would interfere with study participation or safety (e.g., seizure disorder, oral steroid-dependent asthma or other condition requiring oral or parenteral corticosteroid administration, or insulin-dependent diabetes, or organ transplantation recipient) • Serious neuropsychiatric illness (e.g., major depression) not currently under medical management • Requirement for concomitant treatment with any drug known to inhibit folate synthesis (e.g., methotrexate) • Concurrent use of levodopa • Clinical diagnosis of primary BH4 deficiency.
Method of randomisation	1:1 ratio N = 42 patients received 10 mg/kg/day sapropterin N = 47 patients received placebo
Method of blinding	At randomisation (Week 0), an interactive voice-response telephone system was used to maintain blinding.
Study drugs	Sapropterin (provided in tablets containing 100 mg of sapropterin each) or placebo (provided as tablets similar to sapropterin tablets) was administered orally once daily in the morning dissolved in 4–8 oz (120–240 mL) of water, apple juice, or orange juice.

Permitted and disallowed concomitant medications	Subjects were not permitted to take drugs known to inhibit folate synthesis (e.g. methotrexate). Because co-administration of sapropterin and levodopa can cause excitability and irritability, the study also excluded subjects routinely taking levodopa. During the study, the investigator could prescribe additional medications as long as the protocol did not prohibit them. In an emergency, a treating physician could prescribe any needed medication without prior approval, but the PI was to notify the medical monitor of the use of any contraindicated medications immediately thereafter. Study staff recorded any concomitant prescription or over-the-counter medications added or discontinued during the study.
Baseline differences	See Table 10. Sex (gender) was the only difference at baseline between the treatment groups.
Duration of follow-up, lost to follow-up information	Subjects who took at least 80% of the scheduled doses of study drug in Study PKU-003 were eligible for enrollment in an open-label, long-term study (PKU-004) in which they would continue to receive sapropterin. After Week 6, subjects either enrolled in PKU-004 or were followed for safety until Week 10.
Primary outcomes (including scoring methods and timings of assessments)	Change in blood Phe level from baseline at Week 6.
Secondary outcomes (including scoring methods and timings of assessments)	• The mean change in weekly blood Phe levels during 6 weeks of treatment. • The proportion of subjects that had blood Phe < 600 µmol/L at Week 6.

All subjects were asked to undergo screening assessments to determine eligibility for PKU-003. Within 4 weeks of completing screening assessments, subjects underwent 2 baseline assessments, 1 week apart.

Following a protocol amendment, 80 to 100 subjects entered a double-blind treatment period in which they were randomised 1:1 to receive either 10 mg/kg sapropterin or placebo, administered orally once daily in the morning for 6 weeks.

Subjects were instructed to continue their usual diet without modification (i.e., no change in Phe consumption) throughout the study. Blood Phe concentrations were measured 2.5 to 5 hours after breakfast at Weeks 1, 2, 4, and 6, or upon early withdrawal from the study.

Safety was assessed by recording a medical history, monitoring adverse events and vital signs, performing physical examinations, and conducting clinical laboratory tests (chemistry, haematology, urinalysis, and thyroid function tests).

The patient demographics and baseline characteristics are presented by treatment group in Table 10.

Table 10. PKU-003 Patient demographics and baseline characteristics by treatment group

Category	Placebo group n=47	Sapropterin group n=41	Total n=88
Sex			
Male	24 (51%)	27 (66%)	51 (58%)
Female	23 (49%)	14 (34%)	37 (42%)
Mean Age in years (SD)	19.5 (9.8)	21.5 (9.5)	20.4 (9.7)
Age range IQR	8-49 (13-23)	8-42 (15-29)	8-49 (14-25)
≥8 years ≤12 years	11 (23)	6 (15)	17 (19)
>12 years	36 (77)	35 (85)	71 (81)
Race			
White	47 (100%)	39 (95%)	86 (98%)
Non-White	0 (0%)	2 (5%)	2 (2%)
Mean weight (kg)	68	64	
Blood Phe at screening			
Mean +/- SE Blood Phe at baseline (micromol/L)	888 +/- 47	843 +/- 47	
Phe <600 **µmol/L**	9 (19%)	7 (17%)	16 (18%)
Phe ≥600 **µmol/L**	38 (81%)	34 (83%)	72 (82%)

Source: Levy 2007 (88)

PKU-004

PKU-004 is an open-label extension study of PKU-003 designed to evaluate the long-term efficacy and safety of sapropterin in subjects with PKU who have elevated Phe

concentrations. The primary publication associated with this study is Lee et al, 2008 (101).

A summary of the study methodology is presented in Table 11.

Table 11. Summary of methodology for PKU-004 (open-label study, ongoing, published)

Study name and NCT number	A Phase 3, Multicenter, Open-Label Extension Study of Phenoptin™ in Subjects with Phenylketonuria Who Have Elevated Phenylalanine Levels (NCT00225615)
Objectives	The primary objective of this trial is to evaluate the safety and tolerability of long-term Phenoptin™ treatment in subjects with PKU.
Location	United States of America (16 sites) and six countries in Europe: Ireland, France, Poland, Germany, Italy, United Kingdom (14 centres).
Design	Multi-centre, open-label extension study.
Duration of study	22 weeks
Sample size	No formal calculation was conducted to determine the sample size for this study. Subjects who participated in PKU-003 were potentially eligible to enroll into PKU-004, providing a potential sample size of approximately 80 subjects, assuming that not all of the 88 subjects enrolled in PKU-003 would enroll in PKU-004. With 80 people, the probability of detecting at least one person with an AE is 90% for an AE with an event rate of 2.8% and 80% for an AE with an event rate of 2.0%.
Inclusion criteria	• 8 years of age and older • Received ≥ 80% of the scheduled doses in PKU-003, unless removed from the study after exceeding the Phe alert level value defined in PKU-003 • Willing and able to provide written informed consent or, in the case of subjects under the age of 18, provide written assent (if required) and written informed consent by a parent or legal guardian • Negative urine pregnancy test within 24 hours prior to enrollment (females of child-bearing potential only) • Currently using acceptable birth control measures, as determined by the investigator, and willing to continue to use acceptable birth control measures while participating in the study • Willing and able to comply with study procedures • Willing to continue current diet unchanged while participating in the study.
Exclusion criteria	• Perceived to be unreliable or unavailable for study participation or, if under the age of 18, had parents or legal guardians who were

	perceived to be unreliable or unavailable • Withdrew from, or otherwise did not successfully complete, PKU-003 except for subjects who were removed from the study because their blood Phe exceeded the alert level • Expected to require any investigational agent or vaccine prior to completion of all scheduled study assessments • Pregnant or breastfeeding, or planning pregnancy • Concurrent disease or condition that would interfere with study participation or safety (eg, seizure disorder, oral steroid-dependent asthma or other condition requiring oral or parenteral corticosteroid administration, or insulin-dependent diabetes) • Requirement for concomitant treatment with any drug known to inhibit folate synthesis (e.g. methotrexate) • Concurrent use of levodopa.
Method of randomisation	N/A
Method of blinding	N/A
Intervention(s) (n =) and comparator(s) (n =)	Subjects received oral doses of sapropterin (intervention) taken once daily for 22 weeks. There was no comparator. Sapropterin was provided in tablets containing 100 mg of sapropterin and dissolved in 4-8oz (120-240 mL) of water, apple juice, or orange juice. The study was divided in 2 parts. In Part 1, all subjects received sapropterin at a dose of 5, 20, and 10 mg/kg/day, respectively, for 2 weeks each, followed by 4 weeks at a dose of 10 mg/kg/day. In Part 2, subjects received a fixed dose of 5, 10, or 20 mg/kg/day for 12 weeks.
Permitted and disallowed concomitant medications	Subjects were prohibited from taking drugs known to inhibit folate synthesis (eg, methotrexate) during study participation because of interference between the activities of pterin and folate reductases. Because co-administration of sapropterin and levodopa can cause excitability and irritability, subjects routinely taking levodopa were excluded from this study. The investigator could prescribe additional medications during the study, as long as the prescribed medication was not prohibited by the protocol.
Primary outcomes (including scoring methods and	The primary efficacy variable was mean blood Phe level (µmol/L). Blood Phe measurements for each patient at Week 2, 4, and 6 visits, which corresponded to measurements taken after each 2-week dosing period (5, 20, and 10 mg/kg/day), were used to estimate the effect of dose titration on mean changes in blood Phe concentrations.

timings of assessments)	
Secondary outcomes (including scoring methods and timings of assessments)	Long-term persistence of sapropterin as evidenced by long-term control of blood Phe level was assessed using blood Phe levels measured at Week 10, 12, 16, 20, and 22 visits.

Study design

PKU-004 included 80 patients who completed PKU-003 and received >80% of doses or who were removed from the trial because of high levels of blood Phe. This study occurred in two parts:

Part 1: Patients underwent forced dose-titration with 3 different doses of sapropterin. Treatments consisted of 3 consecutive 2-week courses of daily single oral doses of 5 mg/kg/day, followed by 20 mg/kg/day and, finally, 10 mg/kg/day. Following this 6-week forced dose-titration period, patients continued to receive 10 mg/kg/day for 4 more weeks.

During this 4-week dose-analysis period, blood Phe concentrations from the Week 2 and 6 visits were evaluated in order to establish the sapropterin dose for each patient during Part 2 (beginning of study Week 11 through end of Week 22).

Patients who responded to sapropterin treatment in Part 1 of the study, and who completed Part 2 of the study, underwent 6 weeks of forced dose-titration with 3 different doses of sapropterin.

Part 2: During this 12-week fixed-dose period, which initiated at Week 11, each patient's daily dose of sapropterin was established within the range of 5 to 20 mg/kg/day on the basis of the patient's blood Phe concentrations according to the following guidelines:

- Patients with a blood Phe concentration of <240 µmol/L at the Week 6 visit and a blood Phe concentration <600 µmol/L at the Week 2 visit a fixed dose of 5 mg/kg/day

- Patients with a blood Phe concentration <240 µmol/L at the Week 6 visit and a blood Phe concentration ≥ 600 µmol/L at the Week 2 visit received a fixed dose of 10 mg/kg/day

- Patients with a blood Phe concentration at the Week 6 visit of ≥ 240 µmol/L and <600 µmol/L received a fixed dose of 10 mg/kg/day

- Patients with a blood Phe concentration at the Week 6 visit of ≥ 600 µmol/L received a fixed dose of 20 mg/kg/day.

Patients receiving sapropterin at a fixed dose of 5 mg/kg per day whose blood Phe concentration at the Week 12 visit was ≥ 600 µmol/L were instructed to increase their dose to 10 mg/kg/day for the remainder of the study.

Patients were followed at the clinic at Weeks 0, 2, 4, 6, 10, 12, 16, 20, and 22 and were instructed to continue their usual diet without modification throughout the study (i.e, no change in Phe intake per day).

The demographic and characteristics of the study subjects at PKU-004 baseline are presented in Table 12 by PKU-003 treatment group and for all subjects.

Table 12. PKU-004 demographic and baseline characteristics of study subjects

Characteristic	PKU-003 treatment group		Total (N=80)
	Placebo (N=41)	Sapropterin (N=39)	
Gender, n (%)			
Male	21 (51)	26 (67)	47 (59)
Female	20 (49)	13 (33)	33 (41)
Age (years)			
N	41	39	80
Mean ±SD	19.5 ± 9.9	21.3 ± 9.3	20.4 ± 9.6
Percentiles (25^{th}, med, 75^{th})	13,17,22	14,18,29	14,18,25
Range (min, max)	8, 49	8, 43	8, 49
Age category (years), n (%)			
8≤ Age ≤ 12	10 (24)	5 (13)	15 (19)

12 < Age	31 (76)	34 (87)	65 (81)
Race, n (%)			
Caucasian	41 (100)	37 (95)	78 (98)
Asian/ Pacific Islander	0	1 (3)	1 (1)
Other: Caucasian/ Black/ Arab	0	1 (3)	1 (1)
Standing height (cm)			
N	41	39	80
Mean ± SD	164 ± 15	166 ± 11	165 ± 13
Percentiles (25^{th}, med, 75^{th})	157, 166, 174	157,167,175	157,166,175
Range (min, max)	126,191	137,186	126, 191
Weight (kg)			
N	41	39	80
Mean ± SD	69.8 ± 26	64.8 ± 16	67.3 ± 22
Percentiles (25^{th}, med, 75^{th})	51,68,78	55,60,76	54,67,76
Range (min, max)	28,144	36,101	28,144
N is the number of subjects who received at least one dose of study drug. For categorical variables, n is the number of subjects with that characteristic, and percentages (%) were calculated using subjects with non-missing data. For continuous variables, only subjects with non-missing data (n) were included in the summary of those variables.			

Source: PKU-004 Clinical Study Report.(92, 102)

All 80 patients were included in the intention-to-treat (ITT) analysis. A total of 79 patients completed week 22 of the study: 1 patient withdrew at week 16 due to non-compliance with study procedures.

PKU-016

PKU-016 is a double blind, placebo-controlled, parallel-arm study enrolled individuals with PKU ≥ 8 years old who were willing to continue with their current Phe-restricted diet and comply with study procedures.

The aim of study PKU-016 was to evaluate the therapeutic effects of sapropterin on PKU-associated symptoms of ADHD, executive functioning, and global functioning in sapropterin-responsive individuals with PKU. It is the largest study of ADHD symptoms and executive functioning in subjects with PKU to date (90).

Subjects with known sensitivity to sapropterin, who had taken sapropterin within 16 weeks, or adjusted or initiated treatment for ADHD, depression, or anxiety ≤ 8 weeks before study randomisation were excluded. Patients were randomised 1:1 to receive either treatment or placebo for 13 weeks. At Week 13, those receiving placebo were crossed over to receive sapropterin for a 13-week open-label treatment period.

Patients were stratified by age (<18 or ≥18 years of age), presence/absence of ADHD symptoms, and ADHD medication use.

Therapeutic response to sapropterin was defined as a ≥20% reduction in blood Phe levels following sapropterin treatment.

A summary of the study methodology of PKU-016 is presented in Table 13.

Table 13. Summary of methodology for PKU-016 (randomised controlled, completed, published)

Study name and NCT number	A Double-blind, Placebo-controlled, Randomized Study to Evaluate the Safety and Therapeutic Effects of sapropterin on Neuropsychiatric Symptoms in Subjects with Phenylketonuria (NCT01114737)
Objectives	To evaluate the safety and therapeutic effects of sapropterin on neuropsychiatric symptoms in subjects with PKU.
Location	United States of America, Canada (total of 36 study sits)
Design	Interventional, double-blind, placebo controlled. Randomised for the first 13 weeks of treatment.
Duration of study	26 weeks in total: a 13-week randomised treatment period, followed by a 13 week open-label extension phase
Sample size	206 subjects were enrolled into the study.
Inclusion criteria	• ≥ 8 years of age • Confirmed diagnosis of PKU • Willing to continue current diet (typical diet for the 3 months prior to study entry) unchanged while participating in the study • Willing and able to provide written, signed informed consent or in the case of subjects under the age of 18, provide written assent (if required) and written informed consent by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures • Sexually active subjects must be willing to use an acceptable method of contraception while participating in the study and for at least 30 days following the last dose of sapropterin • Females of childbearing potential must have a negative pregnancy test at screening and be willing to have additional pregnancy tests during the study. Females considered not of childbearing potential include those who have been in menopause at least 2 years, or had tubal ligation at least 1 year prior to screening, or have had total hysterectomy. • Willing and able to comply with all study procedure.

Exclusion criteria	• Has known hypersensitivity to sapropterin or its excipients • Subject breastfeeding at screening or planning to become pregnant (subject or partner) at any time during the study • Use of any investigational product or investigational medical device within 30 days prior to screening, or requirement for any investigational agent prior to the completion of all scheduled study assessments • Received sapropterin within 16 weeks of randomisation • Have initiated or adjusted medication for treatment of ADHD, depression, or anxiety ≤ 8 weeks prior to randomization • Taking medication known to inhibit folate synthesis (eg, methotrexate) • Any condition requiring treatment with levodopa or any PDE-5 inhibitor • Concurrent disease or condition that would interfere with study participation, compliance or safety as determined by the Investigator • Any condition that, in the view of the Investigator, places the subject at high risk of poor treatment compliance or of not completing the study.
Method of randomisation	1:1 sapropterin: placebo
Intervention(s) (n =) and comparator(s) (n =)	N = 98 sapropterin - A dose of 20 mg/kg/day was administered as oral tablets. N = 108 A placebo tablet was administered orally for the first 13 weeks of treatment.
Primary outcomes	• Change in Attention-Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS) / Adult ADHD Self-Report Scale (ASRS) • Number of Participants with a Score of 1 or 2 in Global Function Evaluation (CGI-I).
Secondary outcomes	• Change in Hamilton Anxiety Rating Scale (HAM-A) Score • Change in Hamilton Depression Rating Scale (HAM-D) • Change in CGI-S from Baseline to Week 13 • Change in Behavior Rating Inventory of Executive Function (BRIEF) Adult-Global Executive Composite (GEC) T core • Change in ADHD-RS / Adult ASRS • Change in HAM-A Score • Change in HAM-D Score • Change in CGI-S • Change in BRIEF Adult-GEC T Score with 6R-BH4. • Change in ADHD-RS / ASRS Total Score • Change in HAM-A Score • Change in HAM-D Score • Change in CGI-S • Change in BRIEF Adult-GEC T Score

Demographic information and subject characteristics at baseline are presented in Table 14.

Table 14. PKU-016 Demographics and baseline characteristics for study subjects

	Placebo (n=108)	**Sapropterin (20mg/kg/day) (n = 98)**	**Overall (n=206)**
Age at enrolment (y)	22.0 (10.44)	23.1 (12.70)	22.5 (11.55)
< 18 yrs	43 (39.8%)	43 (43.9%)	86 (41.7%)
≥ 18 yrs	65 (60.2%)	55 (56.1%)	120 (58.3%)
Sex			
Female	54 (50.0%)	41 (41.8%)	95 (46.1%)
Male	54 (50.0%)	57 (58.2%)	111 (53.9%)
Race, White	102 (94.4%)	96 (98.0%)	198 (96.1%)
Blood Phe (µmol/L)	888.9 (472.94)	790.0 (470.28)	841.4 (473.09)
Tyrosine (µmol/L)	56.4 (29.88)	55.7 (31.39)	56.1 (30.53)

Source: Burton 2015 (90)

B.2.3.2 Phase 3b studies design and methodology

SPARK

SPARK is a Phase IIIb, open label, randomised, controlled study designed to evaluate the safety and efficacy of saproterin administered in conjunction with a restricted Phe diet in increasing Phe tolerance (that is, the ability to digest Phe-containing proteins) versus diet alone in PKU patients aged under 4 years. SPARK is the first controlled study on sapropterin therapy in PKU patients <4 years in Europe and, as noted in section 2, a restricted Phe diet is the most clinically-relevant comparator to sapropterin (91).

After completing the Study Period, subjects were eligible for enrolment in the Extension Period, in which all subjects who continued in the trial were to receive sapropterin treatment plus a Phe-restricted diet. For those subjects randomised to the Phe-restricted diet alone during the 26-week Study Period, their starting sapropterin 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. 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 (94).

Table 15. SPARK study – Summary of design, methodology

Name and Study Number	A Phase IIIb, Multicentre, Open-Label, Randomized, Controlled Study of the Efficacy, Safety, and Population Pharmacokinetics of Sapropterin Dihydrochloride (Kuvan®) in Phenylketonuria (PKU) Patients < 4 Years Old. (NCT01376908)
Objectives	Primary: 1. To evaluate the efficacy after 26 weeks of sapropterin treatment plus phenylalanine (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 µmol/L (defined as ≥ 120 to < 360 µmol/L). 2. To evaluate the safety after 26 weeks of sapropterin treatment in < 4-year-old infants and children with PKU. 3. To evaluate tetrahydrobiopterin (BH4; sapropterin) blood levels via scheduled population pharmacokinetics (PopPK) samplings. Secondary: 1. To evaluate blood Phe levels for all subjects during the 26-week Study Period. 2. To evaluate the effectiveness of sapropterin treatment in increasing dietary Phe tolerance, as compared with pre-sapropterin treatment during the 26-week Study Period in < 4-year-old infants and children with PKU. 3. To assess neurodevelopmental function during sapropterin treatment, as compared with dietary treatment alone, during the 26-week Study Period in < 4-year-old infants and children with PKU. 4. To assess potential effects on blood pressure during the 26-week Study Period and the 3-year Extension Period. 5. To assess potential effects on growth during the 26-week Study Period and the 3-year Extension Period. 6. To evaluate long-term safety, neurodevelopmental outcomes, dietary Phe tolerance, and blood Phe levels in the 3-year Extension Period. 7. To investigate the predictive value of the phenylalanine hydroxylase (PAH) genotype in BH4 responsive individuals.
Location	This trial was conducted at 22 sites in 9 countries (2 in Austria, 2 in Belgium, 1 in the Czech Republic, 4 in Germany, 5 in Italy, 2 in The Netherlands, 3 in Slovakia, 1 in Turkey and 2 in the United Kingdom).
Study design	Phase IIIb, international, multicentre, randomised, controlled
Duration	26 weeks treatment in the study period (followed by a 3-year extension that is ongoing).

Method of Randomisation	After the screening period of 42 days, all eligible subjects were randomised 1:1 to receive a Phe-restricted diet with or without 10mg/kg sapropterin per day over a 26-week study period. Randomisation was stratified by age group as follows: □ < 12 months: 15 subjects randomised □ 12 to < 24 months: 18 subjects randomised □ 24 to < 48 months: 23 subjects randomised
Sample size	Approximately 50 paediatric PKU subjects <4 years of age at the time of the Day 1 visit in the 26-week Study Period were to be enrolled in this trial. Enrolment could be re-opened (i.e., subjects could be replaced following discontinuation) if the enrolment target of 50 subjects at the start and 46 completers by the end of the 26-week Study Period was not achieved. A minimum of 23 subjects per each of the two treatment groups was needed to complete the Study Period for efficacy analysis purposes. 56 subjects were enrolled in the study and randomised to treatment.
Population	PKU patients aged <4 years at enrolment
Inclusion criteria	• Subjects were male or female with PKU • Children aged <4 years at first day of enrolment • Had ≥2 independent blood Phe levels ≥400 µmol/L • Had a previous response to BH4 test. • Had good adherence to dietary treatment. • The parent(s) and/or guardian(s) were willing to comply with all trial procedures.
Exclusion criteria	If the subject: • Had taken any preparation of BH4 within the previous 30 days; • Had a known hypersensitivity to sapropterin or its excipients or to other approved or non-approved formulations of BH4. – A previous diagnosis of BH4; • Were currently using methotrexate, trimethoprim, dihydrofolate reductase inhibitors, levodopa, or any experimental drug; • Had a concurrent disease affecting trial participation or increasing risk of AE; or • Had a history of organ transplant.
Study drugs	From a total of 109 patients screened, 56 patients were randomised with 27 subjects in the sapropterin plus Phe-restricted diet group and 29 patients in the Phe-restricted diet only group.
Duration of follow-up and lost to follow-up information	All subjects underwent a clinic visit 4 weeks post-treatment as a standard safety assessment.

Primary outcomes	The primary endpoint was the dietary Phe tolerance at 26 weeks, defined as the prescribed amount of dietary Phe (mg/kg per day) while maintaining the mean filter-paper blood Phe levels within the target ranges of 120–360 µmol/L.
Secondary outcomes	• Safety of sapropterin treatment in infants<4 years ago and children with PKU at 26 weeks. • Evaluation of tetrahydrobiopterin (BH4; sapropterin) blood levels via scheduled population pharmacokinetics (PopPK) samplings.

Source:Muntau 2017(91), CRS SPARK (103)

SPARK design

Following Screening, eligible subjects were randomized 1:1 to receive either (a) 10 mg/kg per day sapropterin 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 sapropterin dose could have been increased in a single step to 20 mg/kg per day (91, 103).

A population pharmacokinetic (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 (91, 103).

Extension Period

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 that 26-week phase, unless prematurely discontinued from the study.

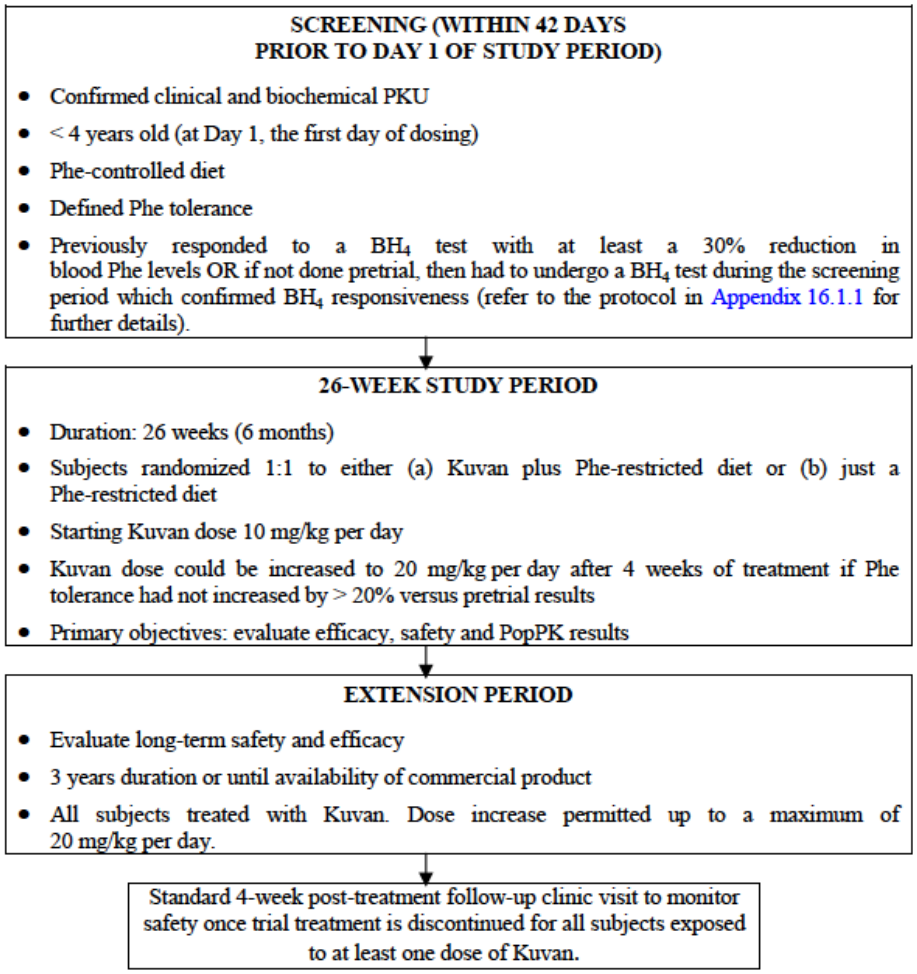
At the end of the 26-week study period, 51 eligible subjects entered the extension period. The Intention to Treat Extension (ITTE) population for "sapropterin continuous" and "sapropterin extension" groups consisted of 25 and 26 subjects, respectively;

corresponding Per Protocol Extension (PPE) populations consisted of 21 and 24 subjects (94).

Baseline was defined as the start date of sapropterin treatment in the study period (Week 0) for the “continuous sapropterin” group and at the start date of sapropterin treatment within the extension period for the “sapropterin extension” group (94).

The SPARK extension study was designed to evaluate the long-term safety, neurodevelopmental outcomes, dietary Phe tolerance, and blood Phe levels over an additional 36 months of treatment with sapropterin (94).

Figure 7. SPARK. Schematic of study design



Source: SPARK CSR(103)

Both treatment groups were balanced in all demographic characteristics. The overall mean ± SD age was 21.2 ± 12.1 months (range 2 to 47 months) and the overall mean BMI was 16.5 ± 1.2 kg/m2 (range 14 to 20 kg/mg2). The majority of subjects were white (96.4%). There were slightly more males (59.3%) than females (40.7%) in the sapropterin + Phe-restricted diet group and 1 more female than males in the Phe-restricted diet alone group. Height (cm) and weight (kg) were also balanced across both groups.

The patient demographics and baseline characteristics are presented by treatment group in Table 16.

Table 16. SPARK. Patient demographics and baseline characteristics by treatment group

Characteristics	Statistics	Sapropterin + Phe=restricted diet (N = 27)	Phe-restricted diet alone (N = 29)	Total (N = 56)
Age (Months)	**N (missing)**	27 (0)	29 (0)	56 (0)
	Mean ± SD	21.1 ± 12.3	21.2± 12.0	21.2± 12.1
	Median	21.0	21.0	21.0
	Q1; Q3	11.0; 29.0	9.0; 27.0	10.0; 28.0
	Min; Max	2; 47	2; 44	2; 47
Age Group N (%)	**N (missing)**	27 (0)	29 (0)	56 (0)
	<12M	7 (25.9)	8 (27.6)	15 (26.8)
	12 - <24M	9 (33.3)	9 (31.0)	18 (32.1)
	24-<48M	11 (40.7)	12 (41.4)	23 (41.1)
Sex, N (%)	**N (missing)**	27 (0)	29 (0)	56 (0)
	Male	16 (59.3)	14 (48.3)	30 (53.6)
	Female	11 (40.7)	15 (51.7)	26 (46.4)
Race, N (%)	**N (missing)**	27 (0)	29 (0)	56 (0)
	White	26 (96.3)	28 (96.6)	54 (96.4)
	Asian	0 (0.0)	1 (3.4)	1 (1.8)
	Other	1 (3.7)	0 (0.0)	1 (1.8)
Height (cm)	**N (missing)**	27 (0)	29 (0)	56 (0)
	Mean ± SD	82.0 ± 11.3	82.3 ± 11.6	82.2 ± 11.4
	Median	85.5	85.0	85.3
	Q1; Q3	73.0; 88.0	75.8; 90.0	74.0; 89.5
	Min; Max	59; 108	57; 105	57; 108
Weight (kg)	**N (missing)**	27 (0)	29 (0)	56 (0)
	Mean ± SD	11.3 ± 3.1	11.3 ± 2.8	11.3 ± 2.9
	Median	11.7	11.8	11.8
	Q1; Q3	9.1; 13.2	9.0; 13.6	9.0; 13.3
	Min; Max	5; 20	6; 16	5; 20
BMI (kg/m2)	**N (missing)**	27 (0)	29 (0)	56 (0)
	Mean ± SD	16.5 ± 1.0	16.5 ± 1.4	16.5 ± 1.2
	Median	16.6	16.6	16.6
	Q1; Q3	16.0; 17.3	15.6; 17.3	15.7; 17.3
	Min; Max	14; 18	14; 20	14; 20

Source: SPARK CSR .(103)

PKU-008

PKU-008 is a completed Phase IIIb study designed to examine the safety of extended treatment with sapropterin in patients with PKU. It is a three-year, open-label extension study in patients who participated in either PKU-004 (after having previously

completed PKU-001 and PKU-003) or PKU-006. The primary publication associated with this study is Burton et al (93).

A summary of the design and methodology of study PKU-008 is presented in Table 17.

Table 17. Summary of methodology of study PKU-008 (completed, open-label, published)

Study name and NCT number	A Phase 3b, Multicenter, Open-Label Extension Study of Phenoptin™ in Subjects with Phenylketonuria Who Participated in Protocols PKU-004 or PKU-006
Objectives	To evaluate the long- term safety of sapropterin in patients with PKU who participated in studies PKU-004 (after previously completing PKU-001 and PKU-003) or PKU-006
Location	15 sites in the United States and Canada and 13 European sites.
Design	Phase 3b, interventional, multicentre, multinational, open-label extension study.
Duration of study	3 years
Sample size	128 subjects were eligible for enrolment. 111 subjects of 4 years of age or older did enrol.
Inclusion criteria	• Sapropterin responders who completed either PKU-004 or PKU-006; or • Subjects in PKU-006 who terminated early due to elevated Phe concentrations after experimental increases in Phe intake.
Exclusion criteria	• Screening alanine aminotransferase value N2× upper limit of normal (ULN; Grade 1 or higher per WHO Toxicity Criteria); • Concurrent use of levodopa or folate inhibitors; • Females who are pregnant or with childbearing potential unwilling to continue with birth control.
Method of randomisation	Not applicable.
Method of blinding	Not applicable.
Intervention(s) (n =) and comparator(s) (n =)	111 subjects received sapropterin orally once daily at a dose between 5 and 20 mg/kg/day. There was no comparator. Patients were to follow local site recommendations for dietary control and management of high Phe concentrations.
Duration of follow-up, lost to	All subjects were evaluated for safety up to three years or until one of the following occurred: • Consent was withdrawn and study discontinued;

follow-up information	• Subject discontinued at the discretion of the investigator; • Drug became available via marketing approval; • Study was terminated.
Primary outcomes (including scoring methods and timings of assessments)	Safety was monitored every 3 months for: • Adverse events (AEs) and serious AEs (SAEs) • Clinical laboratory evaluations • Physical examinations • Concomitant medication • Vital sign measurements Blood Phe concentrations were assessed 2.5-5 hours after eating. Abnormal results were repeated until: the cause of the abnormality was determined; the value returned to baseline or within normal limits; or the abnormal value was considered no longer clinically significant by the investigator.

B.2.3.3 Phase IV registry studies providing long-term data

Compelling long-term, real world data in more than 2,700 PKU patients is now available from the ongoing registry studies (PKUDOS and KAMPER). These data highlight the long-term (up to 6-7 years of treatment) benefits of sapropterin treatment when used as an adjunct to a low Phe diet including sustained and clinically meaningful Phe reduction and the ability to eat more natural protein, as well as a tolerable safety profile.

Interim efficacy outcomes from PKUDOS and KAMPER are presented in this section B2.3.3. Safety outcomes are summarised in section B.2.10.

PKUDOS

PKUDOS (Phenylketonuria (PKU) Demographics Outcomes and Safety) is an ongoing phase 4, voluntary, prospective, observational, safety registry study. As of February 2018, 1922 PKU patients who have previously received or are currently receiving sapropterin had enrolled in the registry. The study is estimated to complete in late 2025.(104)

In order to evaluate the safety and efficacy data of pregnancy and lactation for sapropterin-treated women with PKU in the Maternal Phenylketonuria Observational Program (PKU-MOMS), a sub-registry of the Phenylketonuria Demographics Outcomes and Safety (PKUDOS) registry was created, and the interim results are presented in Appendix F.

A summary of the study methodology is presented in Table 18.

Table 18. PKUDOS. Summary of design, methodology and interim findings

Title	Phenylketonuria (PKU) Demographics Outcomes and Safety Registry (PKUDOS) is a phase 4, voluntary, prospective, observational, safety registry study
Study design	A phase 4, voluntary, prospective, observational, safety registry study designed to provide longitudinal safety and efficacy data on subjects with PKU who are (or have been) treated with sapropterin.
Objectives	• Long-term safety and efficacy of sapropterin in subjects with HPA, PKU up to 15 years • Increase knowledge about the course of disease in sapropterin - treated patients (both responders and non-responders) • Evaluate impact of sapropterin on blood Phe levels, dietary Phe prescription and actual intake, concomitant medications, neurocognitive evaluations and behavioural status over time.
Enrolled to date	1639 subjects enrolled as at February 2017
Population	Subjects must have a diagnosis of PKU and have previously received sapropterin, are currently receiving sapropterin, or intend to receive sapropterin therapy within 90 days of enrolment. The PKUDOS population consists of 1639 subjects of whom 908 were continuously exposed to sapropterin from date of registry enrolment. Age distribution, ranged from 0 to 71 years.
Intervention	Sapropterin
Study arms	Subjects with continuous exposure to sapropterin Subjects with intermittent exposure to sapropterin Subjects who had prior short terms use of sapropterin
Outcomes	**Primary:** To provide longitudinal observational data of saproterin safety and efficacy.
Abstracts / publications	Longo N, Arnold GL, Pridjian G, Enns GM, Ficicioglu C, Parker S, Cohen-Pfeffer JL. Long-term safety and efficacy of sapropterin. The PKUDOS registry experience. Molecular Genetics and Metabolism 2015;114(4):557- 63 (104)

KAMPER

The Kuvan Adult Maternal Paediatric European Registry (KAMPER) is an ongoing observational, multicentre European registry study designed to provide long-term safety and efficacy of sapropterin treatment in PKU patients. It is due to complete in 2024, with a maximum observation period of 15 years per registry subject (97).

A summary of the key study features is presented in Table 19.

Table 19. KAMPER (The Kuvan Adult Maternal Pediatric European Registry) – Summary of design, methodology and interim findings

Title	Observational Study on the Long-Term Safety of sapropterin Treatment in Patients With Hyperphenylalaninemia (HPA) due to Phenylketonuria (PKU) or BH4 deficiency (KAMPER)
Randomised	627 (estimated)
Population	Adult or paediatric subjects (4 years old or older) of either gender with HPA due to PKU.
Locations	85 clinical sites in 9 countries (Austria, France, Germany, Italy, The Netherlands, Slovakia, Spain, Sweden, Portugal).
Intervention	As this is an observational study, no diagnostic, therapeutic, or experimental intervention is involved
Comparator	None
Outcomes	**Primary:** Incidence and description of Adverse Events and Serious Adverse Events (AEs/SAEs). **Secondary:** Incidence of AEs/SAEs in specific population (elderly, children, subjects with renal or hepatic insufficiency); Description on somatic growth (in BH4 deficient children < 3 years); Neurocognitive outcomes; Neurological and psychiatric assessment; Diet and sapropterin treatment adherence; Long-term sensitivity to sapropterin treatment; Blood Phe levels; Tyrosine (Tyr) levels; Pregnancy and delivery outcomes.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Table 20 Summary of statistical analyses

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
PKU-001(96)	30% reduction in baseline Phe level on day 8.	95% CIs, descriptive statistics	Sample size, 400 patients, initially, raised to 700 patients after response rate lower than 30%. Power calculation, 26%-35%, about 80-100 patients	Phe levels recorded at baseline (day 1) and on day 8. 1patient was excluded due to poor compliance, 3 patients were lost to follow up and 1 discontinued treatment for other reasons
PKU-003(88)	Based on the results of PKU-001, a difference was assumed between treatment groups in mean change at week 6 of 150 (SD 85) µmol/L, and a two-sided type I error rate of 0·05.	Primary Outcome Analysis, covariance model, LOCF imputation Secondary Outcome Analysis, longitudinal model, Fisher's Exact Test	Sample size, 80 patients (40 in each group) 95% calculation power to detect a significant difference between treatment groups at week 6	LOCF for missing data. Phe levels recorded at Baseline (1 and 2 weeks before randomisation and week 0 of assessment) and on week 6 (if week 6 missing, last observation carried forward method to impute the data. 1 patient discontinued (non-compliant with specified dosing)
PKU-004 (92)	To assess reduction in blood [Phe] and long-term persistence of this response to SAP (wk 12, 16, 20, 22)	Efficacy analysis: longitudinal model	No formal sample-size calculation was not performed	Blood Phe levels were measured at the Week 12, 16, 20, and 22 visits. Adverse events and serious adverse events were collected between ICF completed and the final study visit
PKU-008 (93)	Study was designed to monitor safety, not randomised/	Descriptive statistics	No formal sample-size calculation was not performed	21 out of 111 patients discontinued the study (3 for AE reasons, 3 were removed for non-compliant/

				uncooperative behaviour, 9 withdrew consent, 4 were not responsive to treatment and 2 moved away).
PKU-016 (90)	Change in ADHD RS/ASRS total score from baseline to week 13 compared the treatment effect between sapropterin-treated and placebo-treated subjects	Primary and secondary efficacy endpoints were generated by analysis of covariance (ANCOVA) using least squares (LS) mean with standard error (SE), 95% confidence intervals (CI), and P value determined by t-test	Sample size, 200 patients, 100 per group 80% power calculation to detect projected differences between the sapropterin and placebo arms, assuming mean improvements in ADHD RS/ASRS score of 13 in sapropterin-treated subjects and 5 in placebo-treated subjects, a common SD of 9, and 2-sided Type I error rate of 0.05	LS mean used to impute for missing data (for MMRM analysis) and stratified Wilcoxon rank-sum test. ADHD RS/ASRS and CGI-S were done at screening and Weeks 4, 8, 13, and 26; CGI-I assessments were done at Weeks 4, 8, 13, and 26. BRIEF completed by adult participants at baseline and Weeks 13 and 26. No study discontinuations
SPARK (91, 103)	Improvement in dietary Phe tolerance, defined as the daily amount of Phe (mg/ kg/day while sustaining mean blood Phe levels (120–360 µmol/L)	Dietary Phe tolerance: repeated measures analysis of covariance (ANCOVA). Pharmacokinetic parameters: Non-linear mixed-effect modelling (NONMEM)	Sample size, 23 patients per group Power of 80% to demonstrate treatment group difference, (Phe tolerance of 20 mg/kg/day, dietary therapy alone) and difference of 75% (sapropterin plus diet group)	Blood Phe concentrations were measured twice weekly, diet evaluation every 2 weeks. 5 patients discontinued (2 from the sapropterin plus Phe –restricted diet group and 3 from the Phe restricted only group)

PKUDOS	No formal hypotheses on the primary endpoint.	Phe levels: analysis of variance (ANOVA) at 95% confidence A Fisher's	No formal sample-size calculation was not performed	Assessments performed according to current medical practice at each participating medical center. Patient withdrawal: NA

KAMPER	No formal hypotheses on the primary endpoint.	95%	No formal sample-size calculation was not performed (however, after assuming a dropout rate of 20% over the full course of the study, an initial population of 625 patients was required).	An initial baseline visit is followed-up with visits that occur quarterly to annually according to the routine care practice at participating sites and the needs of the individual patient

PKU- 001

Primary Outcome Analysis

Response to sapropterin was defined as a ≥30% reduction in baseline Phe level on day 8. The choice of the 30% threshold was chosen arbitrarily. Descriptive statistics for the change from baseline in blood Phe levels were determined for patients who experienced a response on day 8. The sample size was based on the desired precision of the estimated response rates. Before any patients were enrolled in the study, the estimated response rate was 30% and the proposed sample size was 400 patients. Based on these assumptions, the 95% CI was 26–35% and this response rate would yield 80–100 patients suitable for enrolment into the subsequent long-term phase III trial. Subsequent calculations showed the observed response rate to be lower than 30%; therefore, the sample size was increased to approximately 700 to maintain the

required number of patients. A total of 485 (99%) patients completed the 8-day course of sapropterin and had Phe levels recorded at baseline and on day 8. The baseline level was the day-1 Phe level, with the exception of one patient for whom the day-1 Phe level was not available; a Phe value obtained within 4 weeks prior to enrolment as part of the study eligibility evaluation was used instead (96).

PKU- 003

Primary Outcome Analysis

Baseline was calculated as the average of the blood Phe measurements taken at the 2 baseline visits and the Week 0 visit. If a subject had no post-screening blood Phe result, then the Screening blood Phe result was used as the baseline measurement.

A single blood Phe measurement was taken at Week 6. For subjects who were missing their Week 6 blood Phe measurement, the last post-baseline observation carried forward (LOCF) was used to impute complete data for the analysis.

The effect of sapropterin was evaluated using an analysis of covariance model. This model had the change from baseline in blood Phe at Week 6 measurement as the response variable with baseline blood Phe level and treatment as the only covariates.

As a supportive analysis to assess the impact of the LOCF imputation, change in blood Phe was assessed by an analysis of covariance model with only those subjects who had both baseline and Week 6 blood Phe measurements (a “completer” analysis) (88).

Missing Data

For subjects without a Week 6 blood Phe measurement, the last available measurement of blood Phe after baseline was carried forward to Week 6. No other imputation was performed (88).

Secondary Outcome Analysis

Mean Change in Weekly Blood Phe Levels

A longitudinal model was used to compare the sapropterin and placebo groups with regard to the mean change in weekly blood Phe levels during the 6 weeks of treatment. Longitudinal modeling reduces unexplained variability in the response by using

repeated measurements on each subject, thereby increasing power to detect differences in the effect of treatment. Important properties of the model are:

- The model is a repeated measures linear model.
- The model uses baseline blood Phe as a continuous covariate.
- The time of measurement and treatment group enter the model as categorical variables.
- The model uses a compound symmetry covariance structure.
- The model includes a treatment-by-visit covariate; should this covariate be shown to be statistically insignificant; it was to be removed, and a “reduced” model would be presented as well as the “full” model.

Week 6 Blood Phe<600 µmol/L

Fisher’s Exact Test was used to compare the sapropterin and placebo groups with respect to the proportion of subjects whose blood Phe measurement was <600 µmol/L at Week 6. Note that the protocol specified ≤ 600 µmol/L, but to conform to the defined baseline strata, the analysis used a <600 µmol/L cut-off.

The analysis was performed for all subjects as well as for the subgroup of subjects whose Screening blood Phe measurement was ≥ 600 µmol/L (88).

Safety Analysis

All AEs were coded and listed by System Organ Class and preferred term based on the Medical Dictionary for Regulatory Activities (MedDRA version 8.1) coding dictionary. A listing summarises by treatment group the frequencies, investigator-reported relationship to study drug, and severity for all AEs and SAEs that occurred during the study. Tables summarize laboratory data at Week 0 and Week 6 as well as changes from Week 0 to Week 6. Clinically significant laboratory results are listed (88).

PKU-004

Efficacy Analysis

The efficacy analyses included data for all subjects enrolled in this study. The data from each subject had three two-week periods at each of the 3 pre-established doses, followed by a 10 mg/kg/day dose for 4 weeks, followed by a subject-specific dose for

12 weeks. The protocol indicated that an analysis of variance for crossover designs would be used to estimate average within-person changes in Phe level for the three dose levels. Given the study design, this approach was not appropriate, so a repeated measures model was used instead. Long-term persistence of sapropterin (as evidenced by long-term control of blood Phe levels) was assessed using the blood Phe levels measured at Weeks 10, 12, 16, 20, and 22 (101).

Blood Phe was measured at Week 0 (enrollment visit) of Study PKU-004 if the subject did not enroll immediately into PKU-004 from PKU-003 (ie, had a treatment gap of > 1 day). If the subject enrolled immediately (ie, no interruption in treatment) into PKU-004 from PKU-003 and had a Week 6 blood Phe measurement from PKU-003, the Week 6 blood Phe measurement was considered the Week 0 visit measurement for PKU-004. (At the Week 6 visit, when subjects received their last study drug dose in PKU-003, subjects were either receiving 10 mg/kg/day of sapropterin or Placebo) (101).

The Week 0 visit blood Phe level was defined as the baseline blood Phe measurement for all efficacy analyses in PKU-004.

Interim analysis

At the completion of Part 1 of the study, an analysis was performed to compare the safety and tolerability of the 3 different doses of sapropterin and to determine the effect of the 3 doses of sapropterin on blood Phe levels.

The primary purpose of the study was to evaluate the safety and duration of benefit of long-term sapropterin treatment in the subject population. Therefore, the study continued through the end of Part 2 regardless of the efficacy seen in Part 1) (101).

Safety Analysis

The analyses of safety included data for all subjects who received at least 1 dose of sapropterin. Adverse events and serious adverse events were collected between the

time the subject completed the ICF and the final study visit. For all AEs and SAEs that occurred during the study, tables summarize their frequencies and percentages and relationship of the AEs and SAEs to study drug. All AEs were coded and summarized by System Organ Class (SOC) and preferred term based on the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, Version 8.1 (101).

Missing Data

There was no imputation for missing data. The analyses used all available data.

PKU 008

The objective of this study was to monitor the safety of longer-term exposure to sapropterin, therefore, the study was neither randomized nor powered for efficacy (93).

SPARK

Primary endpoint:

The following null hypothesis regarding the primary endpoint for the Study Period was specified in the statistical analysis plan (SAP) and tested:

- H0: The mean dietary Phe tolerance (mg/kg/day) with sapropterin along with dietary therapy at Week 26 does not differ from the mean dietary Phe tolerance (mg/kg/day) with dietary therapy alone, against

- H1: The mean dietary Phe tolerance (mg/kg/day) with sapropterin along with dietary therapy at Week 26 differs from the mean dietary Phe tolerance (mg/kg/day) with dietary therapy alone.

The dietary Phe tolerance (mg/kg/day) was described using summary statistics at each visit of the Study Period, according to treatment group (sapropterin 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 (103).

Secondary endpoints:

The secondary endpoints were analyzed using descriptive and inferential statistics to compare the two treatment groups during the Study Period (103).

PKU- 016

Primary and Secondary Endpoints

Total Score from baseline to Week 13 compared the treatment effect between sapropterin-treated and placebo-treated subjects, with randomization stratification factors entered as covariates in the sapropterin-Phe responder population and in the subset of sapropterin-Phe responders with ADHD symptoms at baseline. Treatment effect estimates in primary and secondary efficacy endpoints from baseline to Week 13 were generated by analysis of covariance (ANCOVA) using least squares (LS) mean with standard error (SE), 95% confidence intervals (CI), and P value determined by t-test. Change from baseline was also analysed with mixed-effect model repeated measure (MMRM) analysis using LS mean to impute for missing data and stratified Wilcoxon rank-sum test (90).

PKUDOS

Primary endpoint:

Blood and dietary Phe values were assessed with analysis of variance (ANOVA) at 95% confidence. A Fisher's exact test was used to compare peak blood Phe by cohort. All interim analyses are focused on two populations based on the use of sapropterin:

- Uninterrupted use population: subjects who have continuously been on sapropterin.
- Short-term use population: subjects who were on sapropterin ≤3 months. Dose gaps were allowed within 3 months of exposure (104).

KAMPER

All endpoints are analysed using descriptive statistics only. For the primary endpoint and selected secondary endpoints, 95% CIs were displayed, including overall AE rates, as well as the rates for AEs of particular interest. Unless otherwise specified, the 95% CIs around the proportions were calculated using exact methods described by Clopper and Pearson (48).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The Quality Assessment of each RCT is provided in Appendix D.

B.2.6 Clinical effectiveness results of the relevant trials

The efficacy and safety of sapropterin has been studied in a comprehensive clinical development programme of completed and ongoing Phase II, III, IIIb and Phase IV studies, across a range of patient groups (including children under 4 years of age, patients with maternal PKU and adults) and clinically- and patient-relevant endpoints.

Sapropterin treatment is associated with significant and sustained reductions in blood Phe levels in responsive patients of all ages, leading to improvements in neurocognitive and neuropsychological performance. In addition, sapropterin treatment is associated with, improvement in measures of white matter integrity and an increase in dietary phenylalanine tolerance allowing for increased consumption of more natural protein (105, 106).

Table 21 below presents the results of the clinical development programme of the key studies as presented in section B2.

Table 21. Results of sapropterin key studies

Endpoints	Results						
	PKU-001 (96)	**PKU-003 (88)**	**PKU-004 (101)**]	**PKU-016 (90)**	**SPARK (91, 103)**	**PKUDOS (95)**	**KAMPER (48, 97)**
Patients with Phe reduction >30%.	96 patients (20%, 95% CI of [16%, 23%])	Sapropterin group:18 patients (44%, 95% CI of 28–60) placebo group: 4 patients (95% of CI 2%–20%)	NA	NA	NA	NA	NA
Change in blood Phe levels	391.8 (T 185.3) mmol/L	Sapropterin group: −235·9 (257·0) µmol/L placebo group: 2·9 (239·5) µmol/L	NA	NA	Sapropterin plus Phe-restricted diet group: 110.7 (±20.1) µmol/L	392 ± 239 µmol/L (p = 0.0009) after 5 years	NA
Safety and tolerability of long-term treatment	NA	NA	Sapropterin is efficacious at a range of doses. Each patient showed an individualised optimal dose	NA	NA	NA	NA

Effects of treatment on symptoms of ADHD (ADHD RS/ASRS measurement) and global function (CGI-I scale)	NA	NA	NA	Sapropterin group: ADHD RS/ ASRS change: -3.7 (1.1 9-5.9, -1.6) Placebo group: -1.9 (1.1) 9-4.0, 0.2) CGI-I scale: 1 (very much improved) or 2 (much improved) sapropterin (21.7%) placebo (26.3%) (95% CI: 0.46 to 1.64)	NA	NA	NA
Dietary Phe tolerance	NA	NA	NA	NA	Sapropterin plus Phe-restricted diet group (80.6 mg/kg/day) Phe-restricted diet alone group (50.1 mg/kg/day).	1.7 increase in dietary Phe tolerance. 1539 ± 840 mg/day after 6 years	1.5 to 2 times increase for all ages

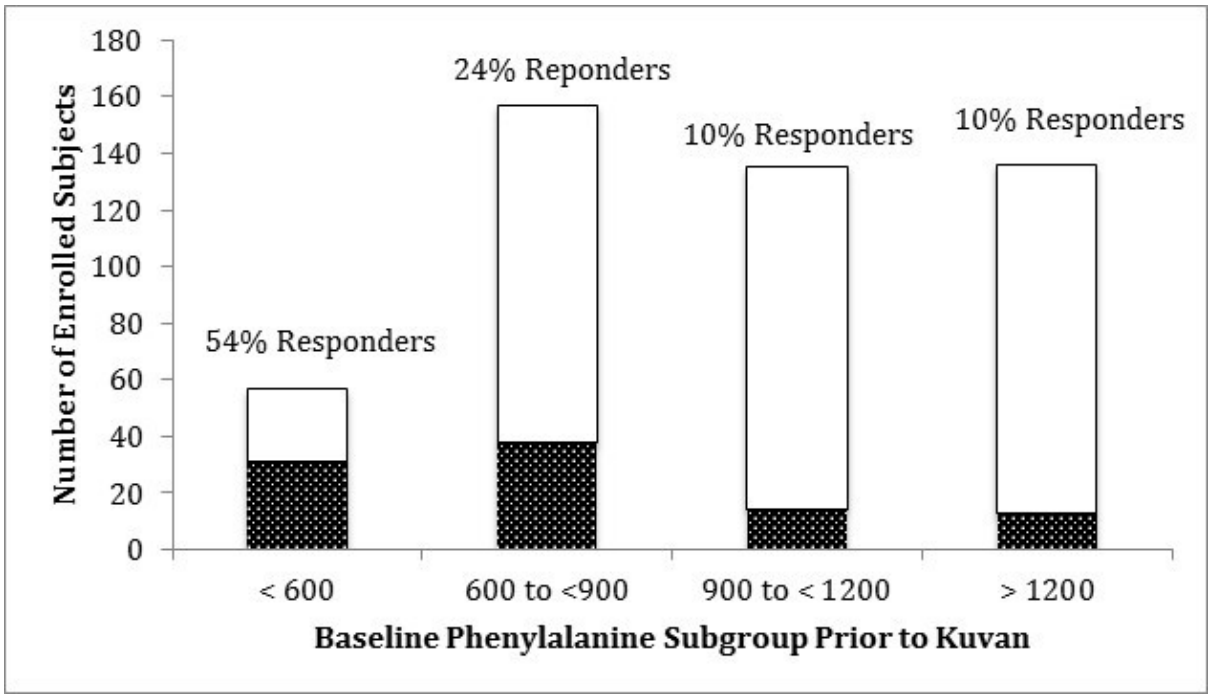
B.2.6.1 Pivotal Trials results

PKU-001 results (96)

489 patients were treated with 10mg/kg sapropterin administered orally once daily for 8 days. Patients were instructed to continue their usual diet without modification. Blood Phe concentrations were measured on Screening, Day 1 (just prior to first dose) and Day 8.

Of the 485 PKU patients with blood Phe measurements at Day 1 and Day 8, 96 (20%; 95% CI 16%, 23%]) responded to sapropterin treatment with a reduction of >30% in blood Phe concentration at Day 8, compared to Day 1. A >=30% reduction in Phe level was observed in all baseline subgroups, although response was greater in patients with lower baseline phenylalanine levels Figure 8. The safety data indicated an acceptable risk-benefit profile, with adverse events (AEs) that were generally mild and minimal treatment-emergent laboratory abnormalities (96).

Figure 8. PKU-001. Sapropterin responders across a range of baseline Phe levels



Source: Burton 2007 (96)

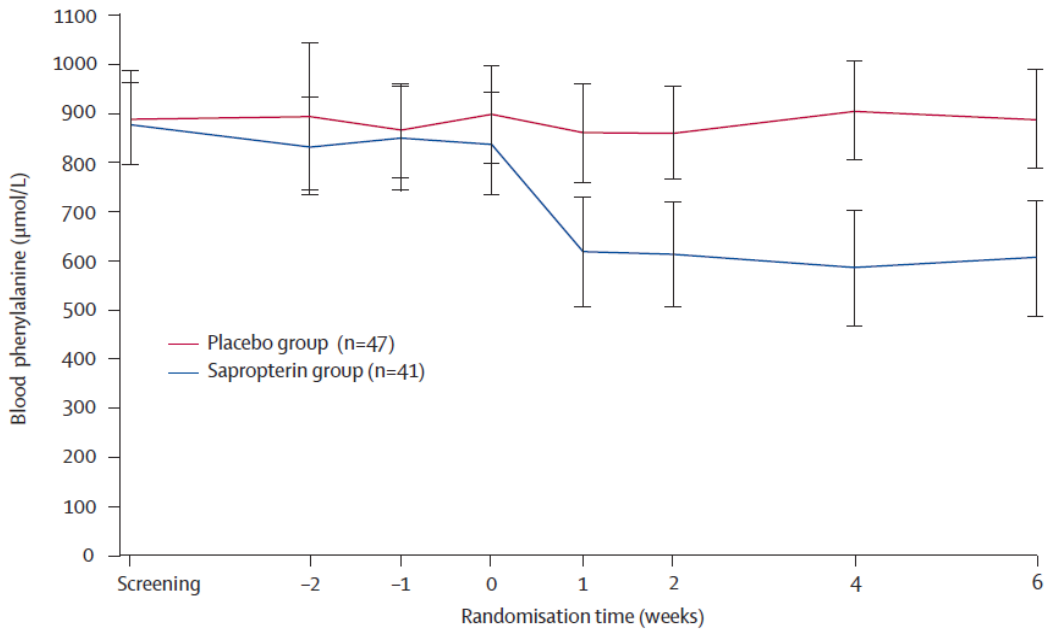
PKU-003 results (88)

Primary Endpoint

Of the 87 patients who completed study PKU-003, 18/41 (44%) of patients treated with sapropterin had a reduction in blood Phe concentration of 30% or more after 6 weeks (95% CI 28-60), compared to 4/47 (9%) of patients in the placebo arm (95% CI, 2-20) (p=0.0002).28 Blood Phe concentration was reduced by 50% or more in 13/41 (32%) of sapropterin-treated patients (95% CI 18-48), compared to 1/47 (2%) of placebo-treated patients (95% CI 0-11). (88) After 6 weeks, sapropterin patients experienced a decrease in mean blood Phe of 236 (SD 257) µmmol/L, compared to an increase in mean blood Phe levels of 3 (SD 240) µmmol/L in placebo-treated patients (p<0.0001) (88).

The primary analysis showed a significant mean decrease in blood Phe concentrations for the sapropterin group compared to the placebo group with a difference of 245 ± 52.5 µmol/L between treatment groups (p=0.0002). Change in blood Phe was noted in the sapropterin-treated group at Week 1 and was sustained through Week 6 (see Figure 9).

Figure 9. PKU-003 Mean blood phenylalanine concentration over time.

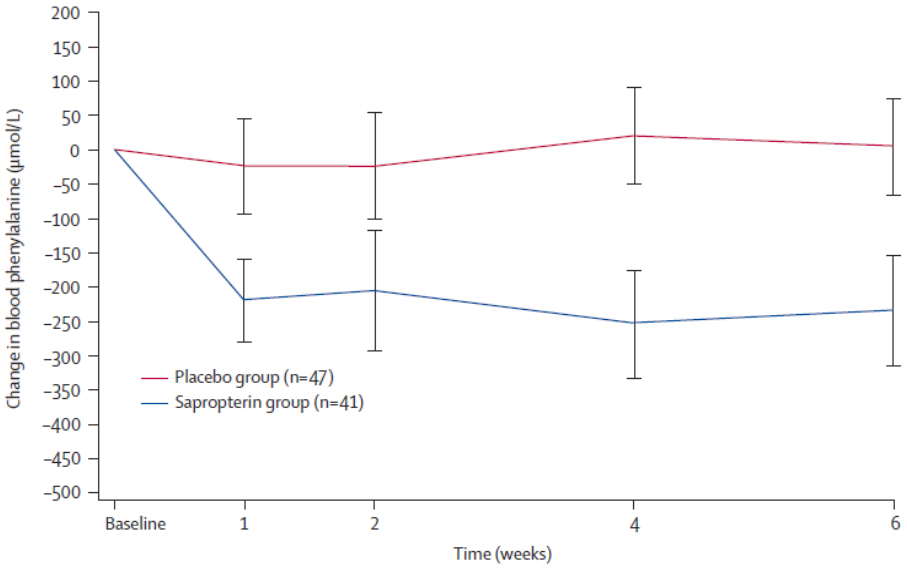


Notes. Bars indicate 95% CI. Last observation carried forward method used to impute missing data. At week 2, n=40 for the sapropterin group.
Source: Levy(88)

Secondary Endpoints

The difference in mean blood Phe between treatment groups at week 6 was 230 ± 43.4 µmol/L (see Figure 10).

Figure 10. PKU-003 Mean change in blood phenylalanine concentration over time.

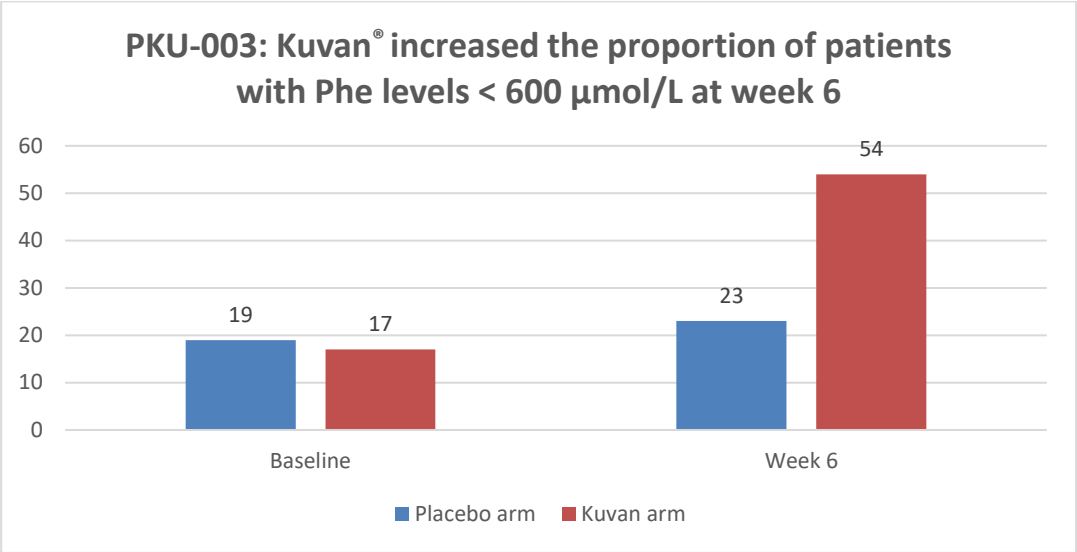


Notes Bars indicate 95% CI. Baseline data is average of duplicate measurements. At week 2, n=40 for the sapropterin group.

Source: Levy (88)

Fifty-four percent of the sapropterin-treated patients and 23% of the placebo-treated patients had Week 6 blood Phe concentrations <600 µmol/L (p=0.004), versus 17% and 19%, respectively, at baseline (see Figure 8). In the subgroup whose screening Phe had been ≥ 600 µmol/L, 15 of 34 (44%) of sapropterin patients and 4 of 38 (11%) of placebo patients had Week 6 blood levels <600 µmol/L (p=0.003). Thirteen of 41 (32%) of sapropterin patients and 1 of 47 (2%) Week 6 blood levels <360 µmol/L (p<0.001) (88).

Figure 11. PKU-003 Proportion of patients with Phe levels lower than 600 micromol/L



Adapted from Levy (88)

Overall study conclusions (88)

There was a consistent reduction over time in the average mean change in weekly blood Phe concentrations in the sapropterin group ($p<0.001$). Mean blood phenylalanine fell in the sapropterin group at week 1 and remained lower than in patients in the placebo group for the duration of the study.

The PKU-003 results suggest that sapropterin treatment might be used as an adjunct to the restrictive low-Phe diet that PKU patients are prescribed (88).

PKU-004 Results (92)

Primary Endpoint: Forced dose-titration phase (weeks 1-6)

On the primary endpoint in the ITT analysis (n=80), reductions in plasma Phe concentration were observed in the forced dose-titration phase for all 3 doses of sapropterin studied(91) These reductions were dose-dependent; mean blood Phe concentration observed at the end of each 2-week dosing period decreased as the dose of sapropterin increased, demonstrating an inverse relationship between the highest dose of sapropterin and mean blood Phe concentrations (92).

After 2 weeks of treatment the mean blood Phe concentration was reduced for each of the sapropterin doses overall indicating that, on average, patients experienced a decrease from Week 0 in blood Phe concentrations with each of the 3 doses (see Table 22 below). The percentages of patients with ≥ 30% reduction in blood Phe concentrations increased in line with a dose increase suggesting a dose dependent change in blood Phe level exists. 46% of patients achieved this 30% reduction after an additional 4 weeks of dosing at 10 mg/kg/day (92).

Table 22. PKU-004 Primary Endpoint. Mean blood Phe reductions with sapropterin after 2 weeks

Dose/Week	Proportion of patients achieving a 30% reduction in blood Phe after 2 weeks of treatment
5mg/kg/day	25%
10mg/kg/day	46%
20mg/kg/day	55%
10mg/kg/day after further 4 weeks	46%

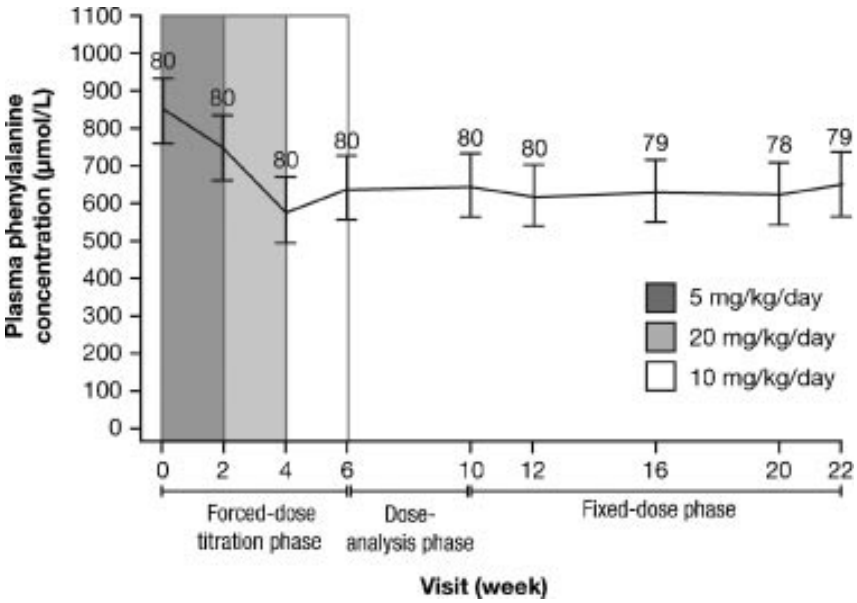
Source: Lee 2008 (92)

Primary Endpoint. Dose-Analysis Period (Weeks 7–10)

At both the Week 6 and Week 10 visits (during which all patients were on a 10 mg/kg/day dose), 46% of patients experienced a ≥ 30% reduction in blood Phe from Week 0. In addition, the mean blood Phe concentrations remained essentially unchanged from Week 6 to Week 10(92).

During the forced dose-titration and dose-analysis phases of the study, the mean (SD) plasma Phe concentration decreased from 844.0 (398.0) mmol/L (14.1 [6.6] mg/dl) at baseline (week 0) to 743.9 (384.4) mmol/L (12.4 [6.4] mg/dl) at week 2, 580.8 (398.8) mmol/L (9.7 [6.7] mg/dl) at week 4, 639.9 (381.8) mmol/L (10.7 [6.4] mg/dl) at week 6, and 645.2 (393.4) mmol/L (10.8 [6.6] mg/dl) at week 10 (see Figure 12) (92).

Figure 12. PKU-004 Primary endpoint. Mean plasma phenylalanine concentrations over time.



Source: Lee 2008 (92)

Secondary Endpoint. Fixed-Dose Period (Weeks 11–22)

During the fixed-dose period, each patient's fixed sapropterin dose was based on his/her Week 2 and Week 6 blood Phe concentrations. Overall, 8%, 46%, and 46% of patients received 5, 10, and 20 mg/kg per day sapropterin, respectively. On average, patients maintained low blood Phe concentrations (ranging from 619.8 to 652.2 µmol/L). These results suggest the persistence of effects for sapropterin for at least 10 weeks. Moreover, almost half of the patients (44% to 49%) had a ≥ 30% reduction in blood Phe concentrations from Week 0 consistently throughout this period.

Patients receiving a fixed-dose of 10 or 20 mg/kg/day achieved comparable mean blood Phe concentrations at Weeks 12, 16, 20, and 22 as they had previously achieved on the same dose in the dose-titration period (92).

Overall study conclusions

Sapropterin decreased mean blood Phe concentrations after 2 weeks by: 100.1 µmol/L at 5 mg/kg/day, 204.1 µmol/L at 10 mg/kg/day, 263.3 µmol/L at 20 mg/kg/day. Change in blood Phe correlates with the dose of sapropterin. Study PKU-004 demonstrates that treatment with sapropterin can reduce and sustain reduced blood Phe concentrations over a period of 22 weeks (101).

PKU- 016 Results (90)

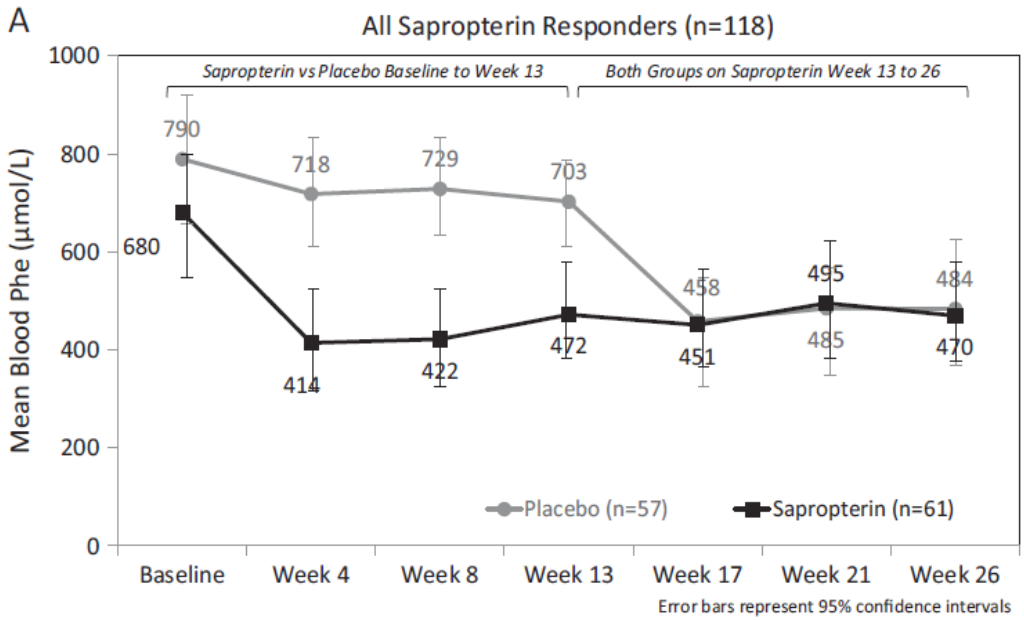
Primary efficacy endpoints were change in symptoms of ADHD based on Total Score on the ADHD Rating Scale (RS) completed by parents/guardians of children/adolescents and the adult ADHD Self-Report Scale (ASRS) and measurement of executive function based on the results of the Clinical Global Impression of Improvement (CGI-I) after 13 weeks of treatment. ADHD RS/ASRS and Clinical Global Impression of Severity (CGI-S) were done at screening and Weeks 4, 8, 13, and 26; CGI-I assessments were done at Weeks 4, 8, 13, and 26 (90).

Secondary endpoints included the Global Executive Composite (GEC) and Index scores from the Behavior Rating Inventory of Executive Function (BRIEF), completed by parents of child participants, and the adult self-reported BRIEF, completed by adult participants at baseline and Weeks 13 and 26. Results of the CGI-I scale between baseline and Week 13 in sapropterin responders with ADHD symptoms at baseline, as well as the change in ADHD symptoms in all sapropterin-responsive participants following the open-label treatment phase from weeks 13 to 26, were reported (90).

118 (57%) of the 206 subjects that enrolled at 36 sites in Canada and the United States were responsive to sapropterin treatment. 38 of these patients (32%) had symptoms of ADHD at baseline, with 84% of these not being medicated for ADHD symptoms. Subjects treated with sapropterin revealed improvements in ADHD inattentive symptoms and executive functioning, indicating that these symptoms are potentially reversible when blood Phe levels are reduced (90).

The mean blood Phe level in the sapropterin group declined within the first 4 weeks of treatment and remained lower throughout the study period than at baseline. After placebo-treated subjects switched to sapropterin at Week 13, mean blood Phe levels in that arm declined by Week 26 (see Figure 13 below) (90).

Figure 13. PKU-016 Primary Endpoint. Mean blood Phe levels for all sapropterin responders (N=118)



Source: Burton 2011 (84)

On the primary endpoint of change in ADHD RS/ASRS Total Score, there was a clinically relevant difference between the sapropterin-treated group and the placebo group of sapropterin responders with ADHD symptoms (a decline of 4.2 points (p = 0.085), but this did not reach statistical significance (see Table 23 below).

Table 23.PKU-016 Primary Endpoint. ADHD RS/ ASTS Changes in Scores

	ADHD RS/ASRS Scores Change from Baseline at Week 13 in sapropterin Responders with ADHD Symptoms (n=38) Total Score	
	Placebo (n=19)	Sapropterin (n=19)
Baseline ADHD/ASRS Score (SE)	31.2 (2.2)	28.9 (2.4)

LS Mean Change from Baseline (SE) (95% CI)	-4.9 (2.0) (-8.9, -0.9)	-9.1 (2.2) (-13.5, -4.7)
LS Mean Change Difference from Placebo (SE) (95% CI)	—	-4.2 (2.3) (-8.9, 0.6) *P*=0.085

Source: Burton 2011 (90)

The Inattention Subscale Score was statistically different between the groups at Week 13, with a significant reduction of -3.4 points (p = 0.036) for sapropterin treatment compared with placebo. Importantly, the mean improvement of −3.4 in Inattention Subscale Score with sapropterin compared with placebo in our study is close to the range of −4 to −6 associated with the ADHD medications in ADHD patients (see Table 24) (90).

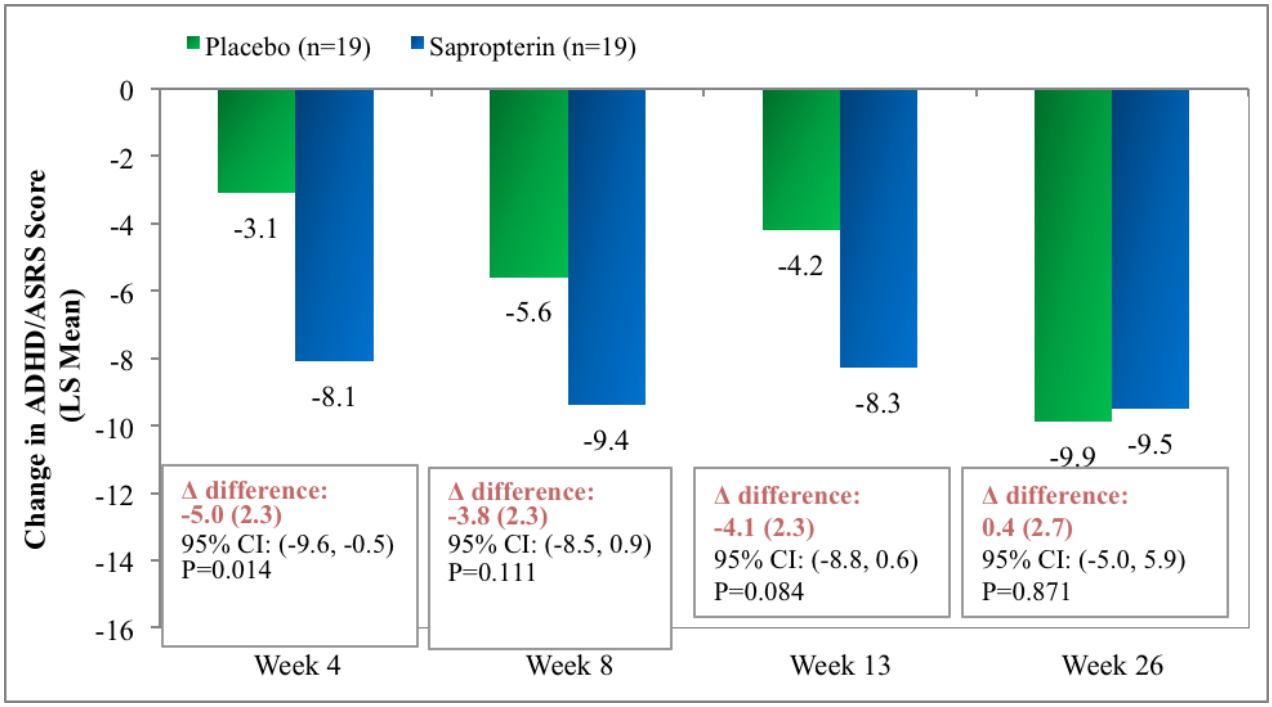
Table 24. PKU-016 ADHD RS/ ASRS for Inattention subscales

	ADHD RS/ASRS Scores Change from Baseline at Week 13 in sapropterin Responders with ADHD Symptoms (n=38) – Inattention subscale	
	Placebo (n=19)	**Sapropterin (n=19)**
Baseline ADHD/ASRS Score	19.2 (1.2)	18.0 (1.3)
LS Mean Change from Baseline (SE) (95% CI)	-2.5 (1.3) (-5.2, 0.1)	-5.9 (1.4) (-8.9, -3.0)
LS Mean Change Difference from Placebo (SE) (95% CI)	—	-3.4 (1.6) (-6.6, -0.2) *P*=0.036

Source: Burton 2011(84)

The change in ADHD/ASRS Total Score over time can be viewed below in Figure 14 (change from baseline to week 26). The Phe Responders with ADHD Symptoms (n=38) across the two arms to week 13 show differences in ADHD / ASRS scores but once the placebo group moves onto sapropterin the ADHD / ASRS scores become similar further supporting the beneficial effects on sapropterin on the ADHD / ASRS scores (90).

Figure 14. PKU-016 Change in ADHD/ ASRS Total Score over time



Source: Burton 2011(84)

Overall study conclusions

Although PKU-016 did not meet either of its primary endpoints, sapropterin treatment was associated with a significant improvement in ADHD inattentive symptoms that were maintained throughout the study for individuals with PKU and ADHD symptoms. The study reinforced the finding of an increased incidence of ADHD with inattentive symptoms, and that symptoms declined with decline in Phe levels associated with sapropterin treatment. The mean improvement of -3.4 in Inattention Subscale Score associated with sapropterin is close to the range of -4 to -6 improvement associated with the ADHD medications in ADHD patients (90).

B.2.6.2 Phase 3b studies results

SPARK Results

Overall adherence to sapropterin over the study period was very good, ranging from 82% to 107%, with an average of 100%. The patient with 82% adherence was an early termination due to a protocol violation and the patient with 107% received a sapropterin

overdose. Almost all patients remained on 10 mg/kg/day throughout the study. Only 2 patients received an increased dose of 20 mg/kg/day. Overall adherence to prescribed Phe was good but less than 100% in both groups (range 65% to 183%) (91).

The primary endpoint was the dietary Phe tolerance at 26 weeks, defined as the prescribed amount of dietary Phe (mg/kg per day) while maintaining the mean filter-paper blood Phe levels within the target ranges of 120–360 µmol/L.66,30 (91).

In the intent-to-treat population, mean±SD baseline Phe tolerance was 37.1±17.3 mg/kg/day in the sapropterin+diet group (n=27, 21.1±12.3 months, 16 males) and 35.8±20.9 mg/kg/day in diet only group (n=29, 21.2±12.0 months, 14 males) (91).

At 26 weeks, adjusted Phe tolerance was 80.6±4.2 in the sapropterin+diet group versus 50.1±4.3 mg/kg/day in the diet only group. The adjusted difference between the two treatment groups was 30.5 mg/kg/day (95% CI: 18.7; 42.3) and was statistically significant ($p < 0.001$)(Table 11) (91).

Table 25. SPARK. Adjusted Mean Treatment Difference at Week 26 in Dietary Phe Tolerance Based on Prescribed Phe (mg/kg/day) – ITT Population

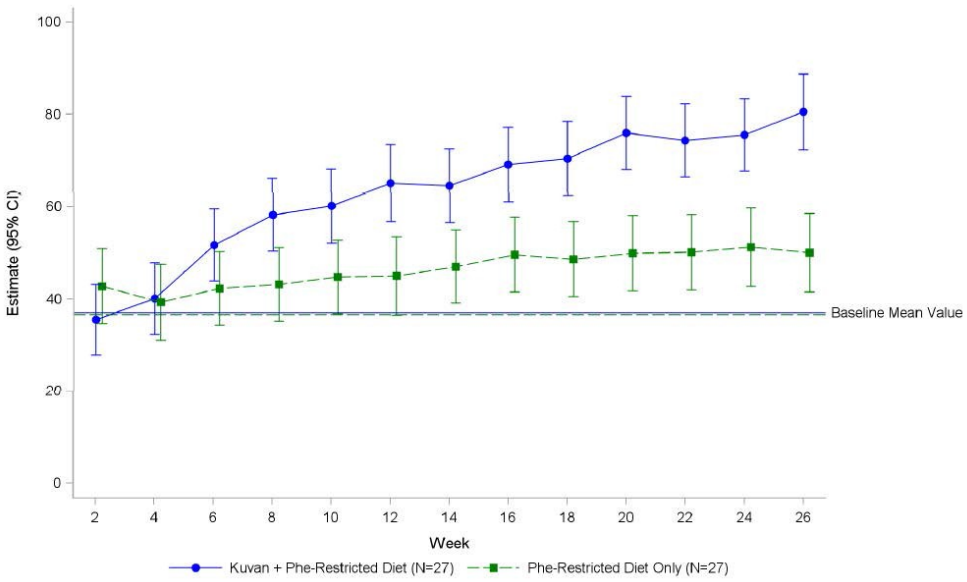
Timepoint	Statistics	sapropterin + Phe-restricted diet (n=27)	Phe-restricted diet alone (n=29)
	Number of subjects included in the model	27	27
Week 2	Adjusted mean (SE) 95% CI	35.5 (3.8) [27.9; 43.1]	42.8 (4.1) [34.6; 51.0]
Week 4	Adjusted mean (SE) 95% CI	40.2 (3.9) [32.4; 47.9]	39.4 (4.2) [31.1; 47.6]
Week 6	Adjusted mean (SE) 95% CI	51.7 (3.9) [44.0; 59.5]	42.3 (4.0) [34.3; 50.2]
Week 8	Adjusted mean (SE) 95% CI	58.3 (4.0) [50.4; 66.2]	43.2 (4.0) [35.2; 51.2]
Week 10	Adjusted mean (SE) 95% CI	60.2 (4.1) [52.1; 68.2]	44.9 (4.0) [36.9; 52.8]
Week 12	Adjusted mean (SE) 95% CI	65.1 (4.2) [56.8; 73.5]	45.0 (4.3) [36.5; 53.5]
Week 14	Adjusted mean (SE) 95% CI	64.6 (4.0) [56.6; 72.5]	47.0 (4.0) [39.1; 54.9]
Week 16	Adjusted mean (SE) 95% CI	69.2 (4.1) [61.1; 77.2]	49.7 (4.1) [41.5; 57.8]
Week 18	Adjusted mean (SE) 95% CI	70.5 (4.1) {62.4; 78.5]	48.7 (4.1) [40.5; 56.8]
Week 20	Adjusted mean (SE) 95% CI	76.0 (4.0) [68.0; 84.0]	50.0 (4.1) [41.8; 58.1]
Week 22	Adjusted mean (SE)	74.4 (4.0)	50.2 (4.1)

	95% CI	[66.5; 82.3]	[42.0; 58.3]
Week 24	Adjusted mean (SE) 95% CI	75.6 (3.9) [67.8; 83.4]	51.2 (4.3) [42.7; 59.7]
Week 26	Adjusted mean (SE) 95% CI	80.6 (4.2) [72.3; 88.8]	50.1 (4.3) [41.6; 58.6]
	Adjusted Difference Between groups (SE) 95% CI p-value	 30.5 (6.0) [18.7; 42.3] <0.001	

Source: SPARK CSR (103)
SE = standard error of the estimate; CI = confidence interval
Adjusted means, estimates, SEs and 95% CIs were based on the repeated measures ANCOVA.
The repeated measure ANCOVA included the fixed categorical effects of treatment, age group, visit, treatment x visit as well as the continuous fixed covariates of baseline dietary Phe tolerance and baseline mean filter-paper blood Phe level, with a compound symmetry matrix for the within-subject error variance-covariance.

The adjusted mean Phe tolerance over time is presented in Figure 15. A difference between the treatment groups is evident from 8 weeks onwards.

Figure 15. SPARK Adjusted Means and 95% CI in Dietary Phe Tolerance based on Prescribed Phe (mg/kg/day) – ITT Population



Note: Baseline mean value is presented for both treatment groups.
Source: SPARK CSR.(103)

A supportive analysis was performed in which dietary Phe tolerance was based on the Phe intake reported in the 3-day Phe diet diary. At Week 26, the adjusted mean Phe tolerance was higher in the sapropterin plus Phe-restricted diet group (75.7 mg/kg/day) compared with the Phe-restricted diet alone group (42.0 mg/kg/day). The adjusted difference between the two treatment groups was 33.7 mg/kg/day (95% CI: 21.4; 45.9)

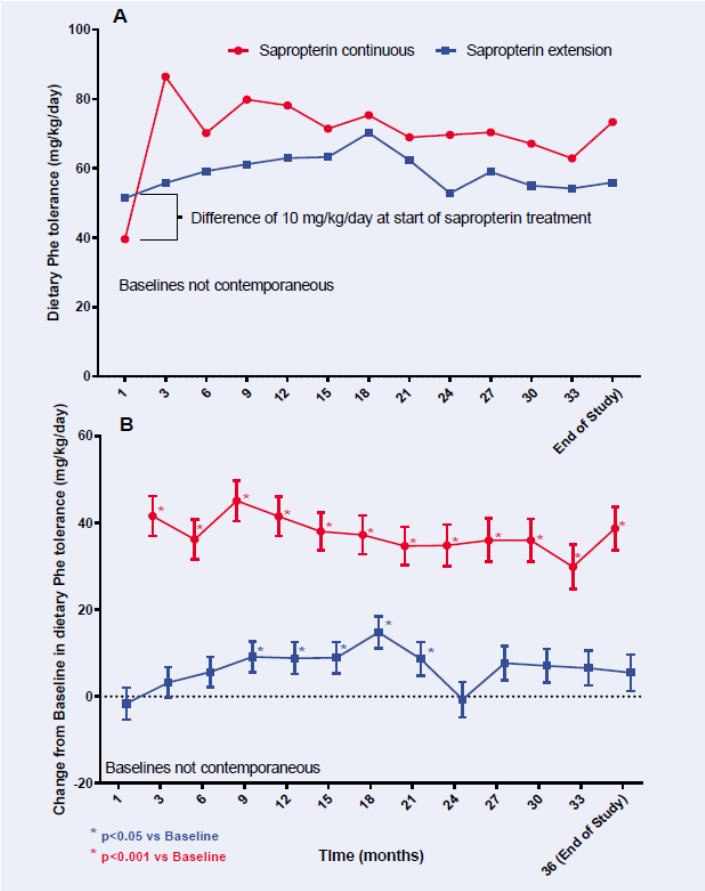
and was statistically significant ($p < 0.001$) (103).

Overall, consistent results were achieved in the sensitivity analysis, in the supportive analysis of Phe intake based on the 3-day Phe diet diary and in the PP population, thus confirming the robustness of the primary analysis. After 26 weeks of treatment, there was an adjusted mean reduction in blood Phe levels of 10.1 µmol/L in the sapropterin plus Phe-restricted group compared with an adjusted mean increase of 23.1 µmol/L in the Phe-restricted diet alone group. The difference of 33.2 µmol/L was not statistically significant. Blood Phe levels over time in the sapropterin plus Phe-restricted diet group were in line with the significant increase in dietary Phe tolerance at Week 26 in this group (91, 103).

Extension Study results

Phe-tolerance increased significantly and maintained throughout the 36 month duration of the study (Figure 16) and dietary Phe tolerance at the end of study increased by 38.74 mg/kg/day vs. Baseline (95% CI: 28.9, 48.6; $p<0.0001$) (94)

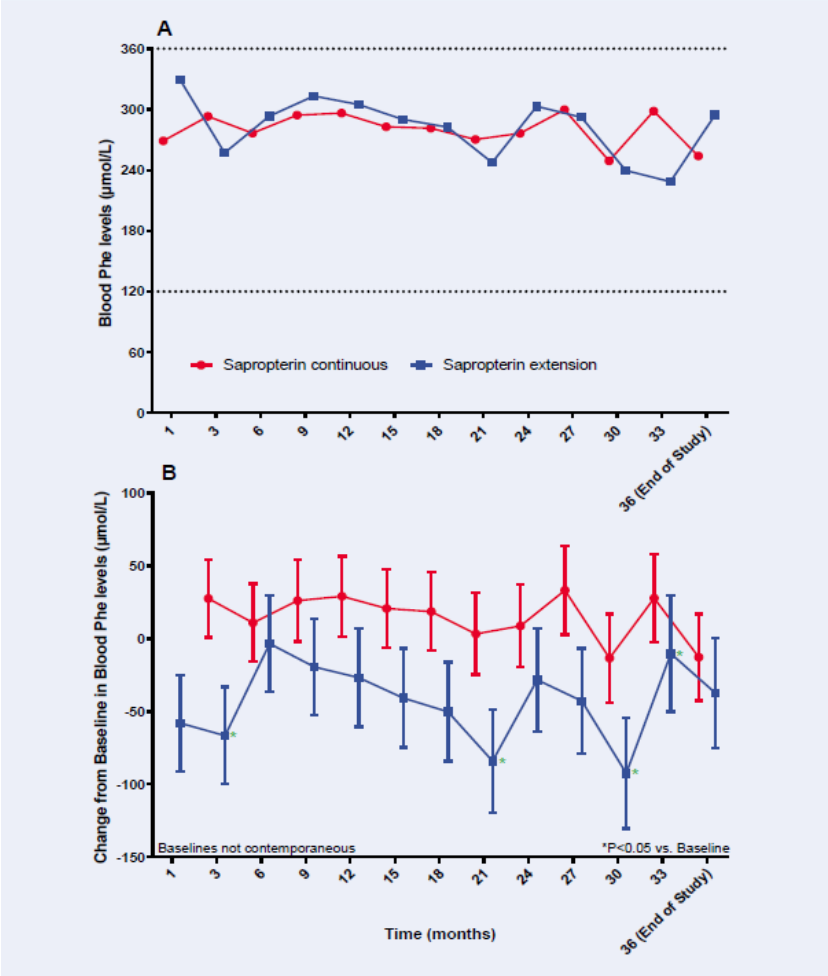
Figure 16. Dietary Phe tolerance (A) and change from baseline (B) during the extension period



Source: Rutsch et al. 2018 (94)

All the patients maintained blood Phe levels within the desired range during the extension period of the study (Figure 17).

Figure 17. Blood Phe levels (A) and change from baseline (B) during the extension period



Source: Rutsch et al. 2018 (94)

Study conclusions

In SPARK, dietary Phe tolerance was significantly increased with sapropterin plus Phe-restricted diet compared with dietary therapy alone. At Week 26, the adjusted mean Phe tolerance was higher in the sapropterin 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 ($p<0.001$) (103) .

Details of PKU-008 study, where safety was the primary endpoint, are presented in Section B.2.10.

B.2.6.3 Phase IV registry studies providing long-term data

Interim efficacy outcomes from PKUDOS and KAMPER are presented in this section. Safety outcomes are summarised in section B.2.10.

PKUDOS results

The interim published results available are taken from the paper by Longo 2015 (95), a 2017 presentation by Lilienstein et al. and the most recent data cut from the registry in 2018 (5, 107).

The Longo paper reports on patient numbers of 1189 subjects of which 42% (504/1189) were on continuous sapropterin use (uninterrupted use population) and 18% (211/1189) discontinued the drug within 3 months (95).

Table 26 below shows the changes in mean blood Phe from pre-sapropterin (baseline) to 6 years for both uninterrupted use and short-term use populations.

Table 26: PKUDOS. Mean ± SD for blood phenylalanine (Phe, µmol/L), from pre-sapropterin up to 6 years of exposure, for uninterrupted use and short-term use populations.

Time period	Uninterrupted use population			Short-term use population		Uninterrupted use vs. short-term use cohorts		
	Mean ±SD (N) µmol/L	Δ blood Phe µmol/L (%)	p	Mean ±SD (N)[c] µmol/L	Δ blood Phe µmol/L (%)	p	Mean difference µmol/L[f]	p
Pre-sapropterin baseline	591±382 (128)	-		830±476 (66)	-		239	0.0002
0 to ≤ 1year	418±333 (318)	-173 (29)	0.0001	792±461 (129)	-38 (5)	NS[e]	374	0.0001
> 1 year to ≤ 2 years	415±299 (333)	-176 (30)	0.0001	752±413 (143)	-78 (9)	NS	338	0.0001
> 2 years to ≤ 3 years	432±298 (312)	-160 (27)	0.0001	800±412 (135)	-30 (4)	NS	369	0.0001
> 3 years to ≤ 4 years	441±288 (237)	-150 (25)	0.0001	817±380 (106)	-13 (2)	NS	376	0.0001
> 4 years to ≤ 5 years	421±265 (161)	-170 (29)	0.0001	823±380 (64)	-7 (1)	NS	402	0.0001
> 5 years to ≤ 6 years	392±239 (48)	-199 (34)	0.0009	759±366 (30)	-71 (9)	NS	366	0.0001

Source: Longo et al. 2015 (95)

For the uninterrupted use population, the data show significant (p = 0.0009 to 0.0001) and sustained (−25% to −34%) decreases in blood Phe from 1 to 6 years after starting sapropterin compared to baseline. For the short-term use population, blood Phe data over this same time interval show smaller (−1% to −9%) decreases, and none are significantly different from baseline. These results are presented in Table 27 below (95).

Table 27: PKUDOS. Decreases in blood Phe, uninterrupted use population

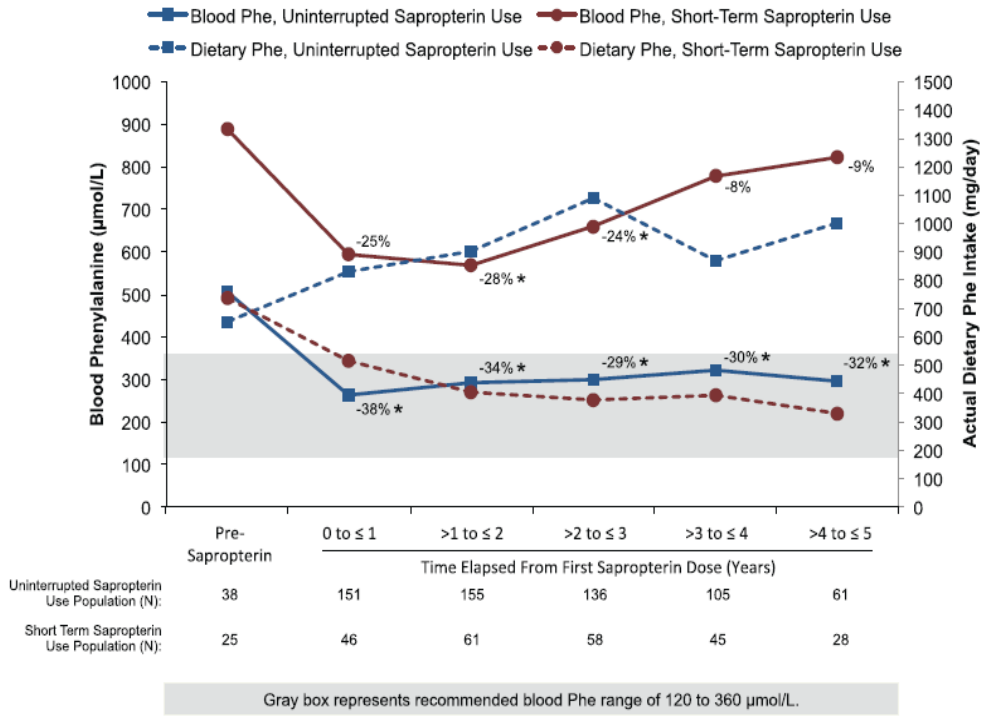
Population	Results (blood Phe)	P-value
Uninterrupted use	-25% to -34% decrease in Phe from 1-6 years after starting sapropterin	p = 0.0009 to 0.0001
Short-term use population	−1% to −9% reduction in blood Phe	Not significant compared to baseline

Source: Longo et al. (95)

The subjects continuously exposed to sapropterin had an average 34% decrease in blood Phe from 591 ± 382 µmol/L at baseline to 392 ± 239 µmol/L (p = 0.0009) after 5 years. This drop, in blood Phe occurred in conjunction with a 54% increase in dietary Phe tolerance from 1000 ± 959 mg/day (pre-sapropterin baseline) to 1539 ± 840 mg/day after 6 years. (see Figure 18 below) (95).

Patients with short-term sapropterin use (i.e., discontinued treatment within 3 months) experienced a smaller decline in blood Phe and average dietary Phe decreases from 815 mg/day to 725 mg/day over the same time interval (see Figure 18 below) (95).

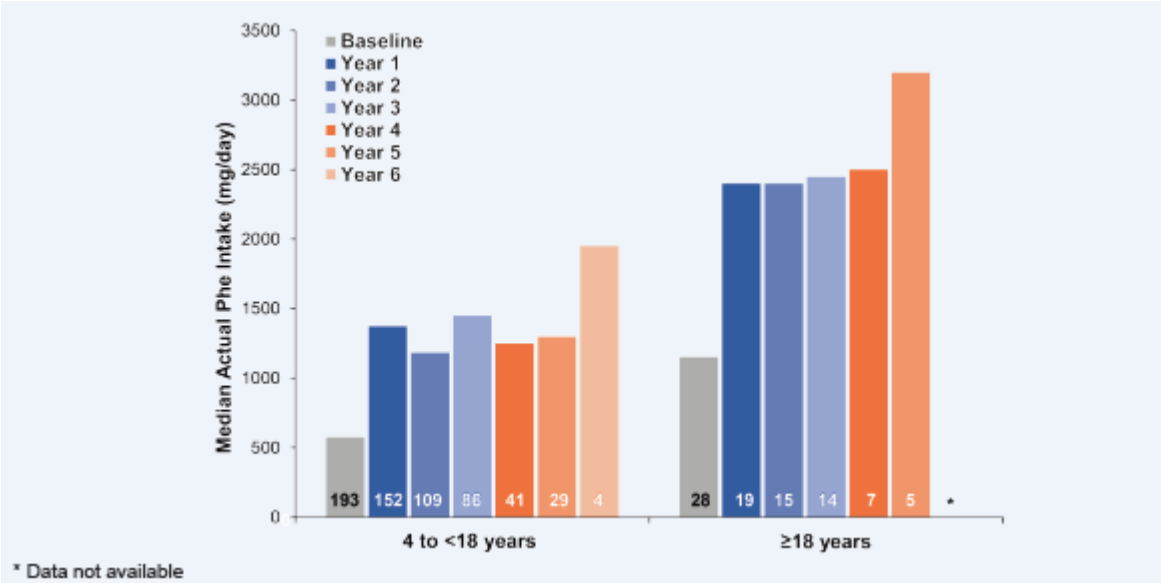
Figure 18. PKUDOS. Median blood Phe concentrations and median dietary Phe intake from pre-sapropterin up to 5 years of exposure for a subgroup of uninterrupted use and short-term use populations who had diet Phe intake and blood Phe measured at the same time points



Source: Longo et al. (95)

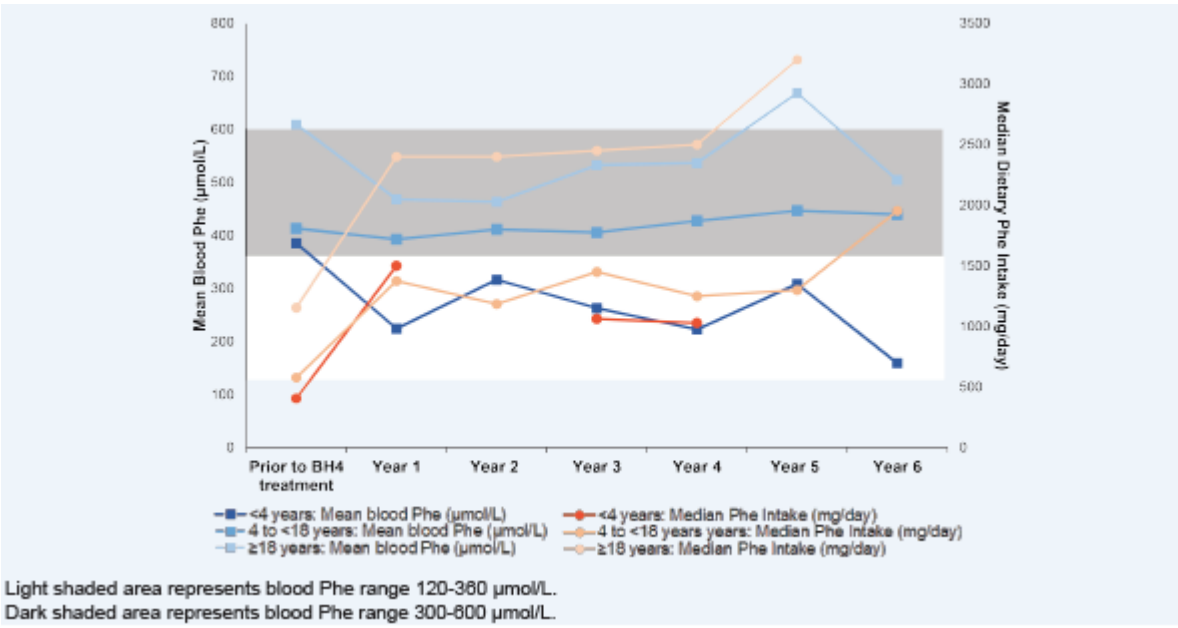
On the 7th interim analysis that was presented in 2017 (5) the dietary Phe and natural protein intakes increased in all age groups by 1.5 to 2 times compared to baseline (prior to sapropterin treatment), while maintaining their dietary Phe tolerance in line with EU guidelines as shown in Figure 19 and Figure 20.

Figure 19. Median dietary Phe intake prior to BH4 treatment and at follow-up (mg/day)



Source: Lilienstein 2017 (5)

Figure 20. Mean blood Phe and median dietary Phe intake at baseline and follow-up for <4 years, 4 to <18 years, and ≥18 years age groups



Source: Lilienstein 2017 (5)

At the most recent interim analysis (December 2018), 1922 patients out of a total population of 1993 that had enrolled to the registry since 2008, had received sapropterin treatment continuously since enrolment. The authors concluded that patients taking sapropterin had higher prescribed and actual dietary Phe intake while maintaining lower blood Phe levels, compared to those who had taken sapropterin previously or who had yet to start treatment (108).

Furthermore, a recent sub-analysis on adult PKU patients in the registry with Phe levels ≤600 µmol/L, showed that in 2 years, [redacted]

In year 2, [redacted]. [unpublished data]

Regarding the interim results of the PKU-MOMS registry (21), sapropterin was shown to be an effective treatment option in pregnant women with PKU who cannot maintain their blood Phe levels within the recommended range with a Phe-restricted diet alone. This interim analysis of the PKU MOMS sub-registry revealed that sapropterin was generally well tolerated and does not appear to increase the risk of spontaneous abortions, which is associated with high concentrations of blood Phe. Blood Phe levels for women exposed to sapropterin during pregnancy were 23% lower and had a 58% smaller standard deviation compared to women who were exposed to sapropterin prior to pregnancy. When median blood Phe concentrations were maintained at <360 µmol/L, 75% of pregnancy outcomes were normal as compared to 40% when median blood Phe levels were >360 µmol/L (21).

In conclusion, long-term data from the PKUDOS registry suggest that sapropterin has a tolerable safety profile and that continuous use is associated with a significant and persistent decrease in blood Phe and improvements in dietary Phe tolerance (48, 97, 108).

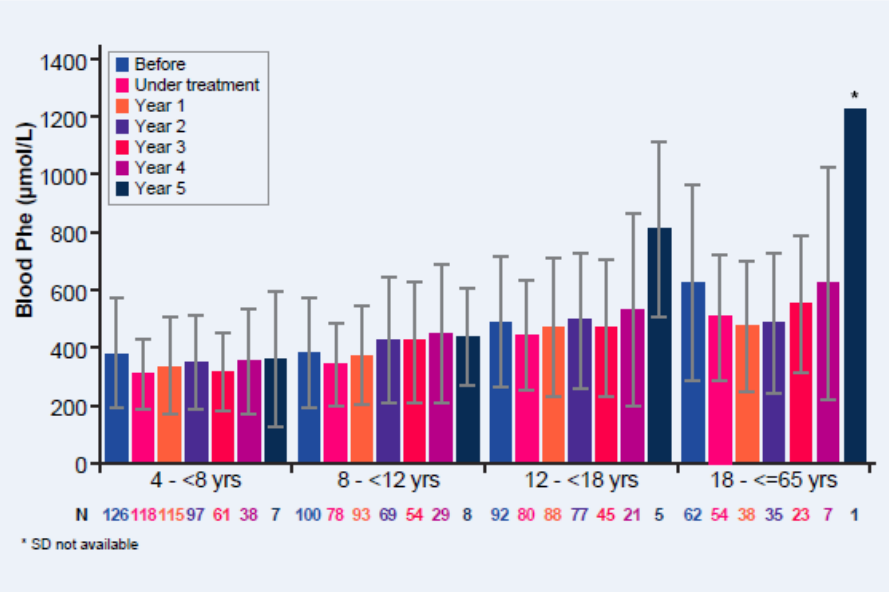
Safety data from the PKUDOS registry study is presented in section B.2.10.

KAMPER results

An interim data analysis (the seventh interim analysis) on 627 PKU patients aged between 0.2 years and 46.5 years (median 10.0 years) from 69 study sites was carried out on the first 6 years of data and the results are summarised below (48).

Mean Phe concentration was measured at baseline and during follow-up. Mean blood Phe levels for patients 4≤8 years were maintained near the recommended range of 120-360 µmol/L; older age groups had levels above this range, increasing with age, although generally still <600 µmol/L. Blood Phe concentrations remained constant and within recommended ranges in the younger PKU patients. Mean blood Phe levels were somewhat more variable in adolescent and adult patients, but most remained at approximately 600 µmol/L. The authors concluded that the increased blood Phe values at year 5 reflect a limited dataset with small n values for each age group rather than worsening blood Phe control (see Figure 21) (48).

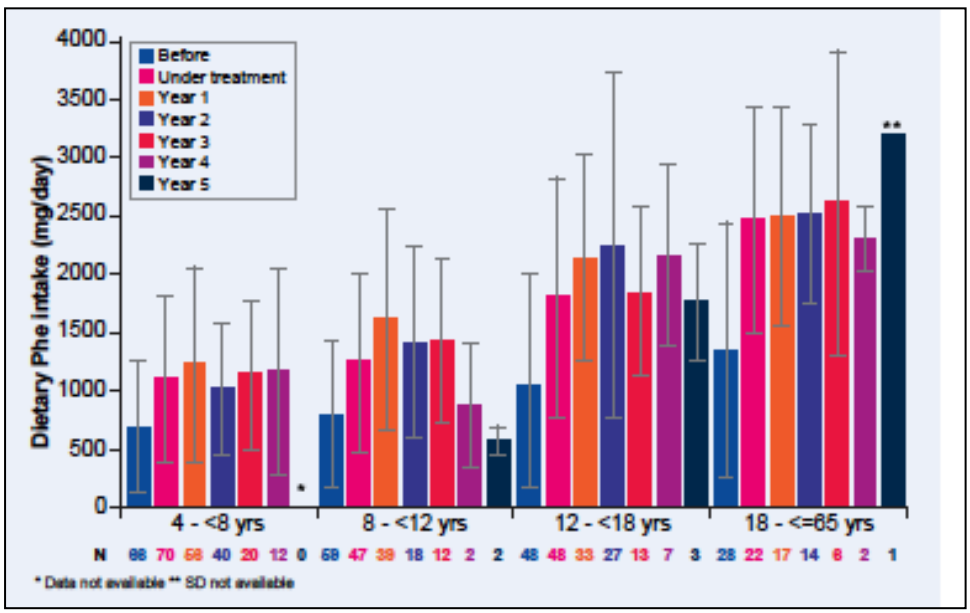
Figure 21. KAMPER. Mean (SD) blood Phe concentration by age group at baseline and follow up in PKU patients



Source: Muntau et al. (48)

At the six-year follow-up, dietary Phe consumption had increased in all age groups by 1.5 to 2 times the subject's intake prior to sapropterin treatment. Levels of natural protein followed similar patterns (see Figure 22).

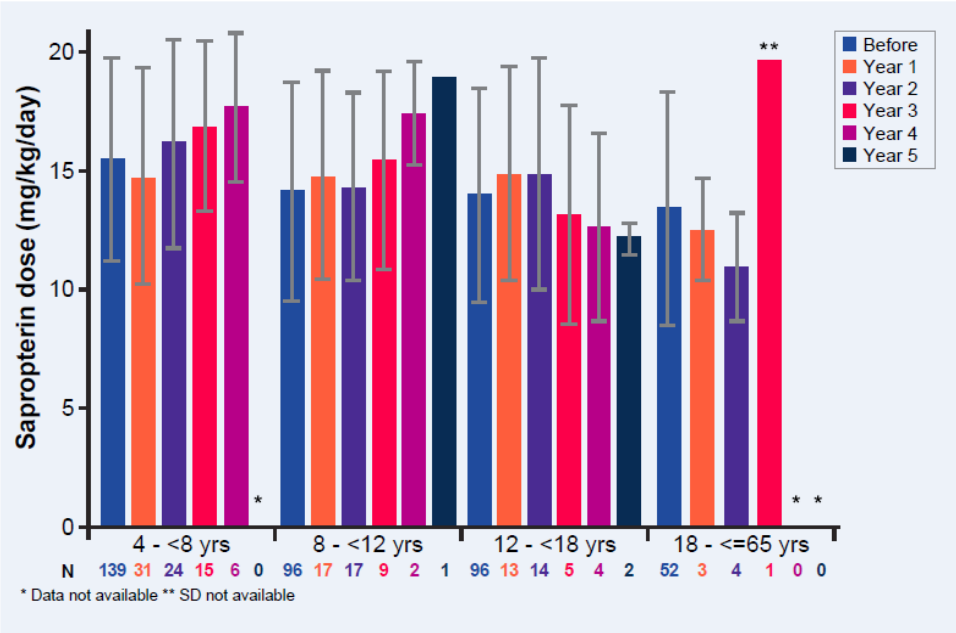
Figure 22. KAMPER. Mean (SD) dietary Phe intake (mg/day) by age group at baseline and follow up in PKU patients



Source: Muntau et al. (48)

Whilst dietary Phe has increased over this period, the dosage of sapropterin remained relatively constant in the 4 to<8 year group, the 8 to <12 year group and 12 to <18 year old group, as can be seen in Figure 23 below. The average dose of sapropterin was 16.0mg/kg/day.

Figure 23. KAMPER. Mean (SD) sapropterin dose (mg/kg/day) in PKU patients



Source: Muntau et al.(48)

In conclusion, the 7th interim analysis of the KAMPER study shows that following treatment with sapropterin, patients in the 4-8, 8-12 and 12-18-year-old groups have been able to increase their dietary Phe intake. Patients in the ≤ 8 year age group, maintained their blood Phe near the recommended range whilst the older age groups had levels above this range, increasing with age, though generally <600 µmol/L (48, 97).

The most recent interim data analysis (10th interim analysis) on 627 patients from the KAMPER study revealed that blood Phe levels for sapropterin patients

[redacted]

[redacted]. During follow-up period of the eleven years, [redacted], however, it is very difficult to draw conclusions given the very limited number of patients at increasing periods of follow-up. [redacted](109)[redacted](110).

Safety data from the KAMPER registry study is presented in section B.2.10.

B.2.7 Subgroup analysis

BioMarin has not conducted any subgroup analysis across the clinical trials However, subgroup analysis studies were identified in the SLR. Appendix E details the systematic search strategies and searches performed to identify the subgroup analyses.

B.2.8 Meta-analysis

BioMarin has not conducted any meta-analysis of clinical trials. However, three meta-analysis studies were identified in the SLR:

- Sapropterin dihydrochloride for phenylketonuria (111)
- A Meta-analysis of Growth Outcomes in Phenylketonuria Patients Treated with Phenylalanine-restricted Diet + Sapropterin (112)
- Efficacy and safety of sapropterin dihydrochloride in patients with phenylketonuria: A meta-analysis of randomized controlled trials (113).

A summary of the methodologies and key findings follows:

<u>Sapropterin dihydrochloride for phenylketonuria (111)</u>

The aim of this study was to assess the safety and efficacy of sapropterin in lowering blood phenylalanine concentration in people with phenylketonuria (111).

Two clinical trials were included in this meta-analysis, PKU-003 (88) and PKU-006 (89).

The following outcomes were assessed:

Primary Outcome:

- Change in blood phenylalanine concentration

Secondary Outcomes:

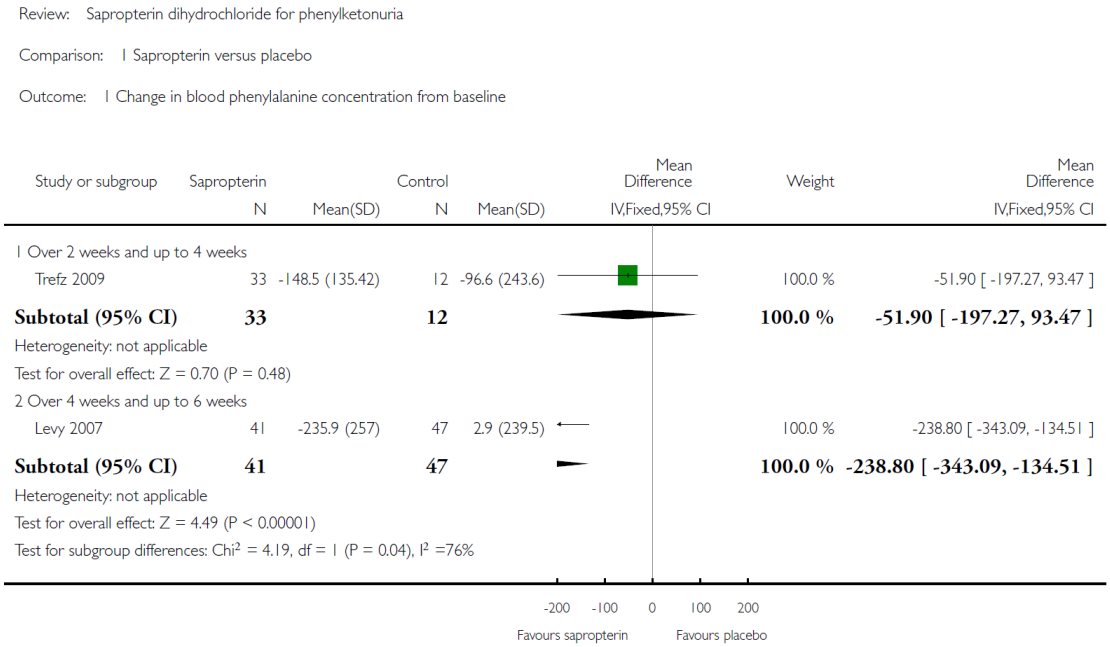
- Adverse events which may be associated with sapropterin
- Validated quality of life measures (not measured in either trial)
- Validated measures of Intelligence and neuropsychometric performance (not measured in either trial)
- Measures of nutritional status and growth (not measured in either trial)
- Change in protein (phenylalanine) tolerance.

Key findings

Change in blood phenylalanine concentration

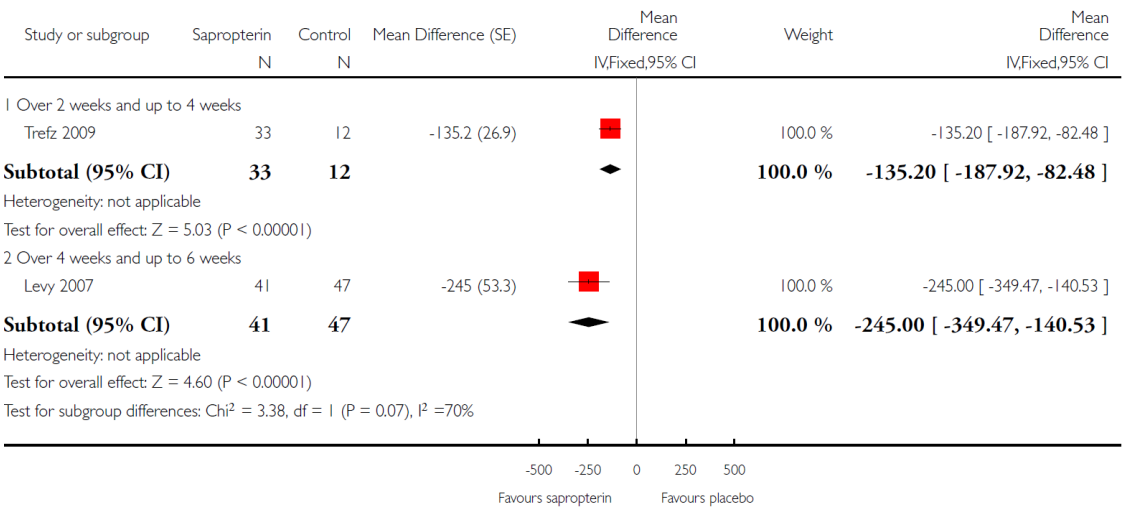
The results from the comparison of sapropterin to placebo in change in blood Phe concentration from baseline can be found in Figure 24 and Figure 25.

Figure 24. Comparison 1 sapropterin versus placebo, Outcome 1 Change in blood phenylalanine concentration from baseline.



Source: Somaraju 2015 (111)

Figure 25. Comparison 1 sapropterin versus placebo, Outcome 2 Mean difference in blood phenylalanine concentration between treatment groups

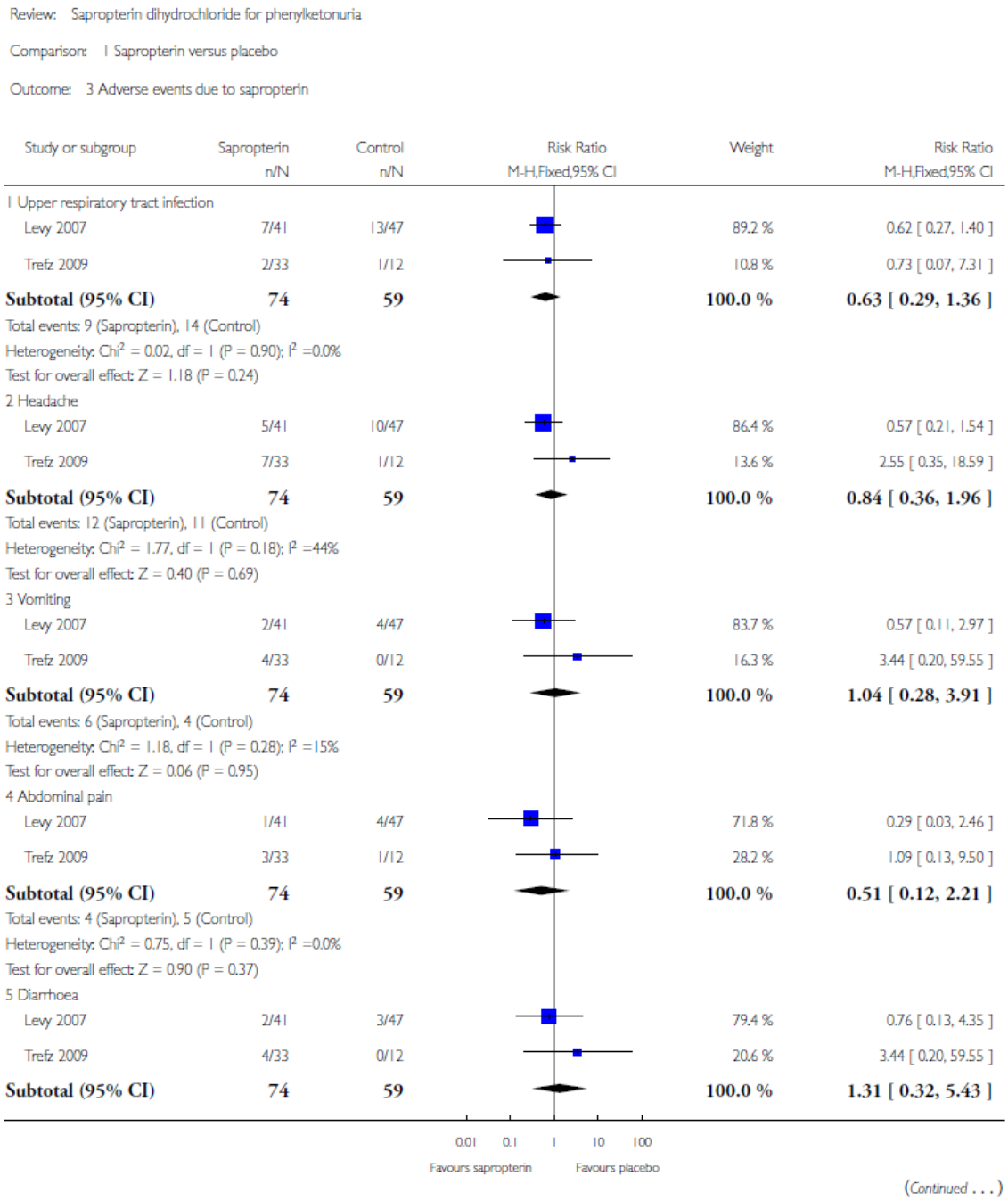


Source: Somaraju 2015 (111)

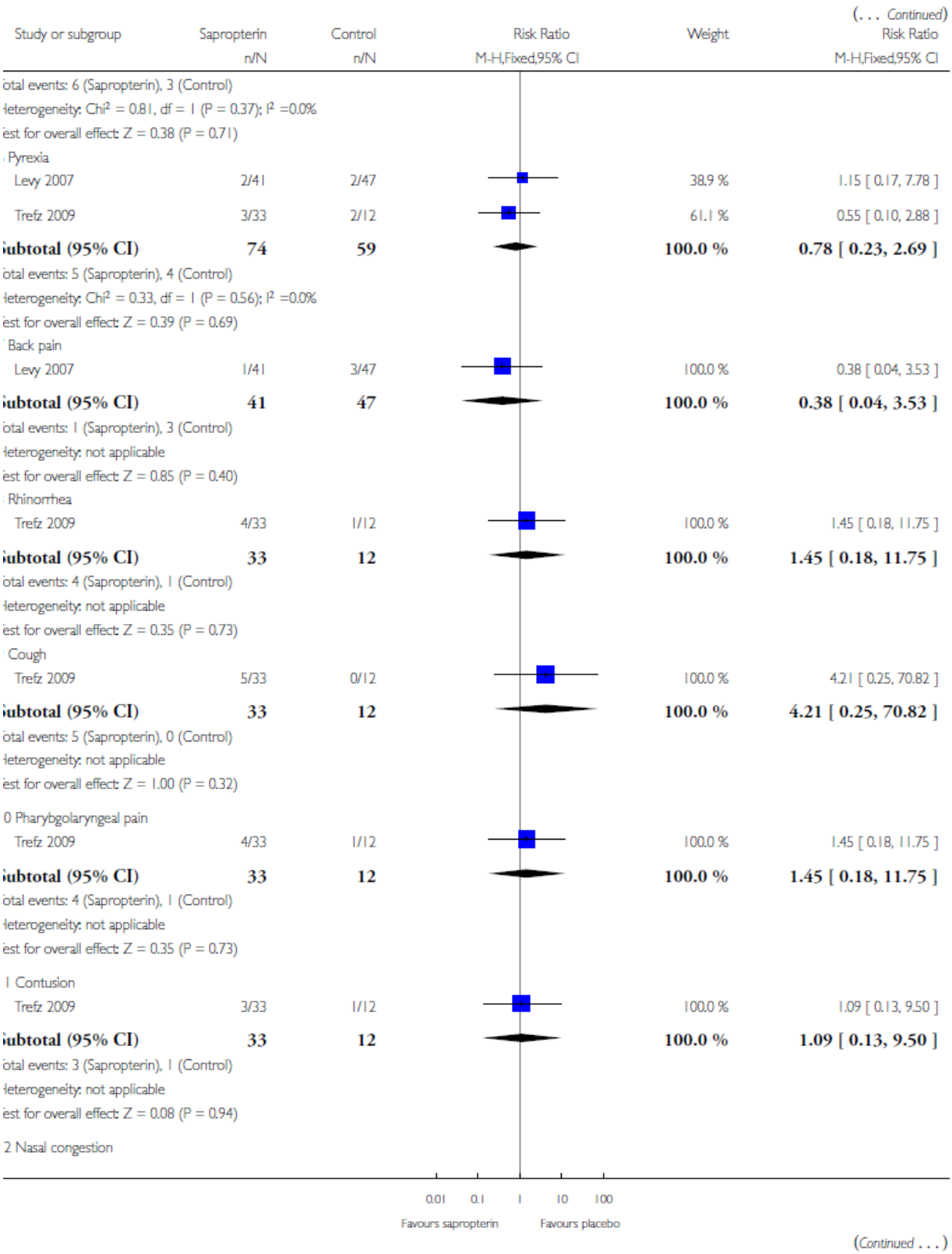
Adverse events which may be associated with sapropterin

The results from the comparison of sapropterin to placebo in adverse events due to sapropterin are shown in Figure 26.

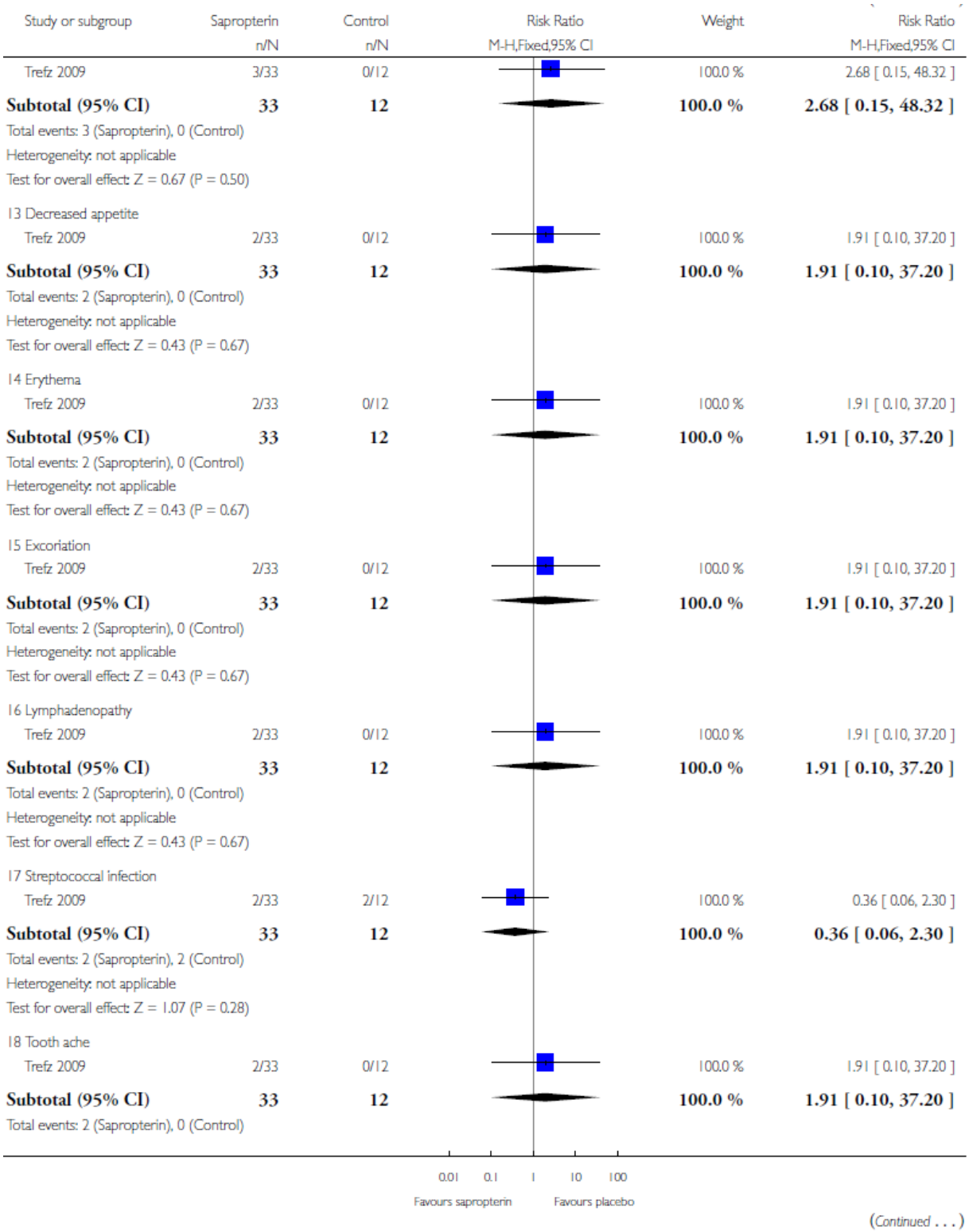
Figure 26. Sapropterin versus placebo, Outcome 3 Adverse events due to sapropterin



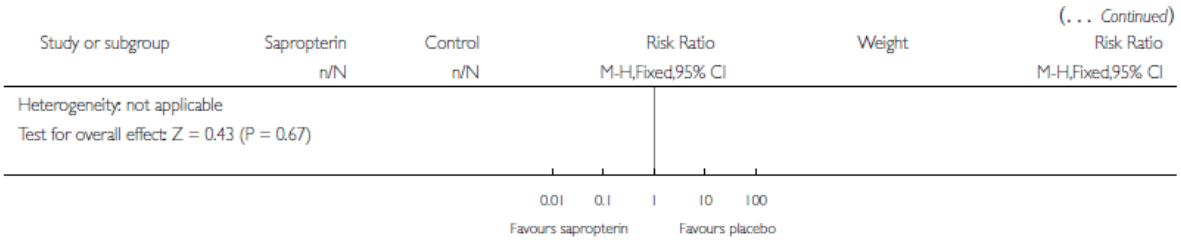
Source: Somaraju 2015 (111)



Source: Somaraju 2015 (111)



Source: Somaraju 2015 (111)



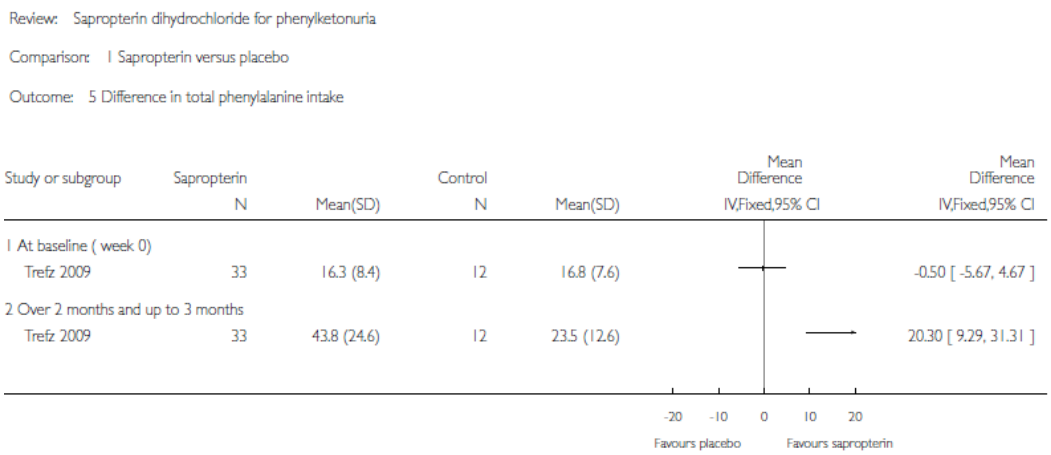
Source: Somaraju 2015 (111)

Change in protein (phenylalanine) tolerance

The results from the comparison of sapropterin to placebo in change in Phe tolerance are shown in Figure 27 and

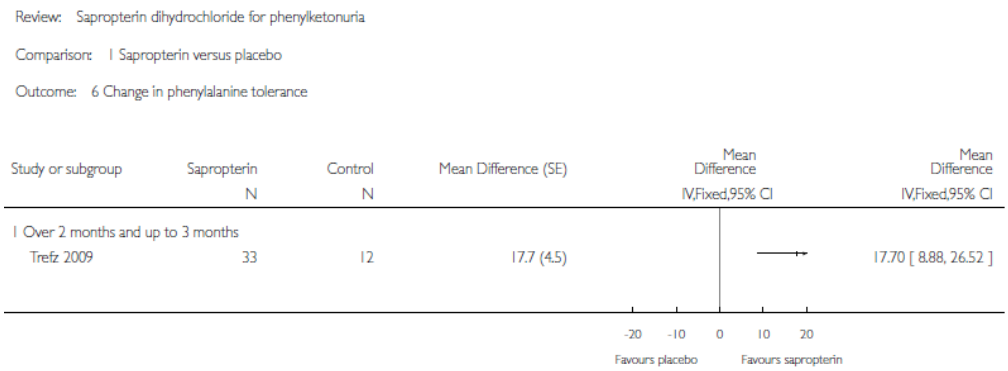
Figure 28.

Figure 27. Comparison 1 sapropterin versus placebo, Outcome 5 Difference in total phenylalanine intake



Source: Somaraju 2015 (111)

Figure 28. Comparison 1 sapropterin versus placebo, Outcome 6 Change in phenylalanine tolerance.



Source: Somaraju 2015 (111)

Conclusions

In this study, there was evidence of short-term benefit from using sapropterin in some people with sapropterin-responsive forms of PKU; blood Phe concentration was lowered and protein tolerance increased. There were no serious adverse events associated with using sapropterin in the short term. As the meta-analysis included the two RCTs with the specific timeframes and population, there was no way to comment on the evidence of the long-term effects of sapropterin and no clear evidence of effectiveness in severe PKU (111).

A Meta-analysis of Growth Outcomes in Phenylketonuria Patients Treated with Phenylalanine-restricted Diet + Sapropterin (112)

The objective of this meta-analysis was to assess growth outcomes in children (aged 0–4 years) with PKU treated with sapropterin (112).

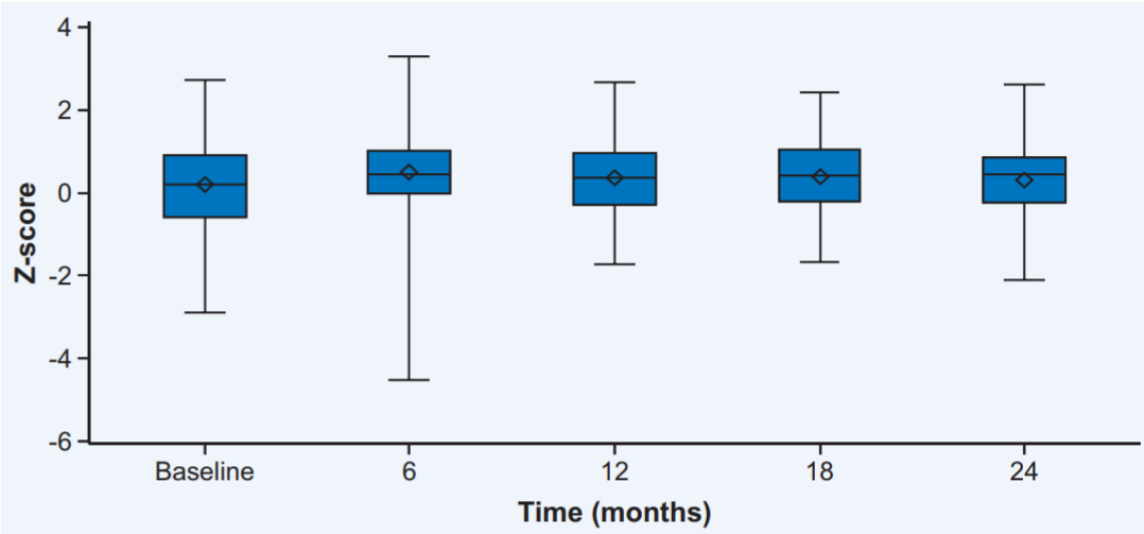
Growth data on children (aged 0–4 years) treated with sapropterin were derived from one registry in which patients were followed in a real-world setting, PKUDOS (5, 95), an open-label Phase 3b trial (PKU-015) (99), and one randomized controlled trial, SPARK (91, 103).

The following growth outcomes were assessed:

- Height
- Weight
- Head circumference

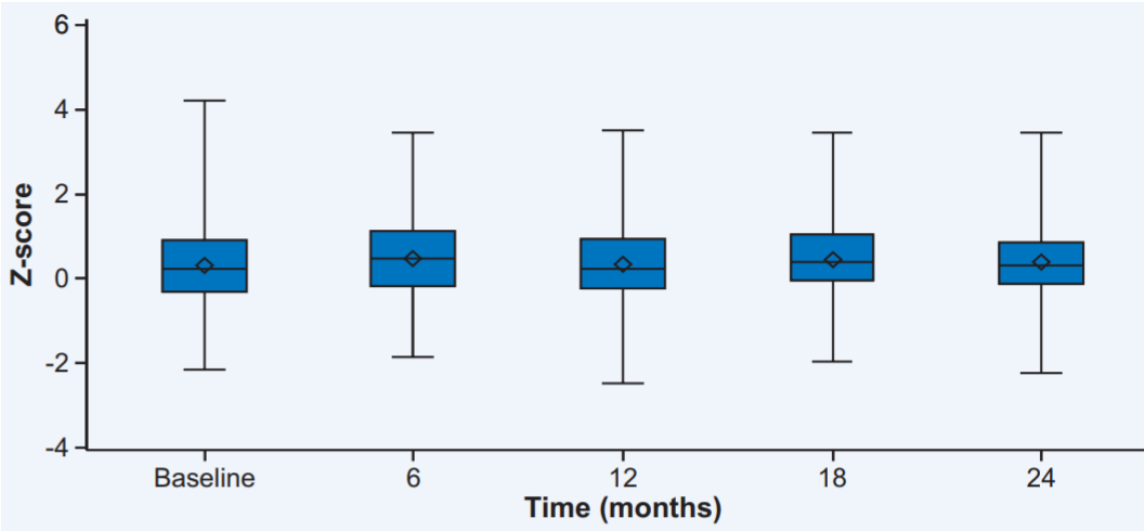
The results from the meta-analysis for each outcome can be found in Figure 29, Figure 30 and Figure 31.

Figure 29. Height for age Z-scores



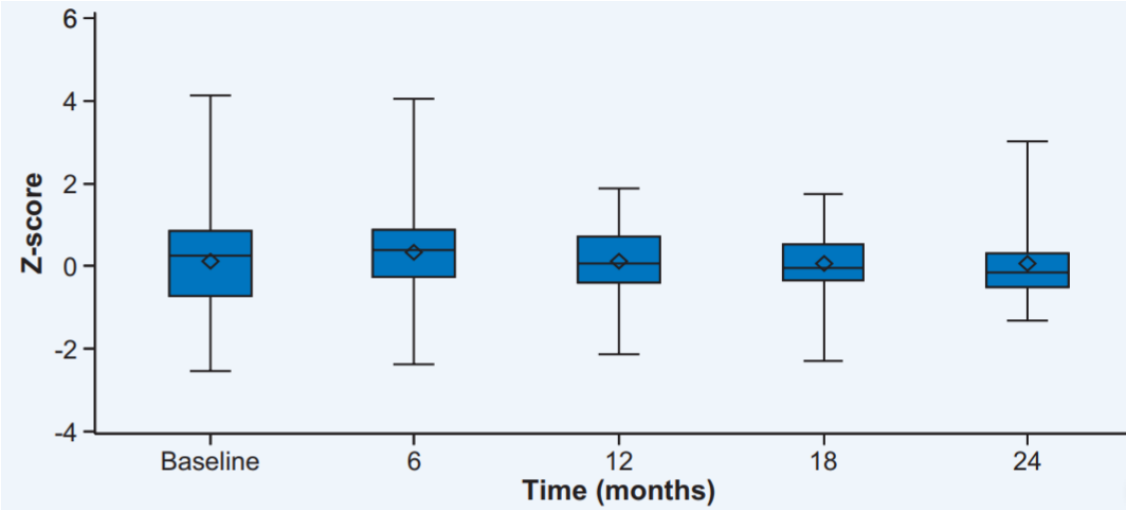
Source: Muntau 2018 (112)

Figure 30. Weight for age Z-scores



Source: Muntau 2018 (112)

Figure 31. Head circumference for age Z-scores



Source: Muntau 2018 (112)

Conclusions

In this meta-analysis of approximately 250 children (aged 0-4 years) with PKU, PKU patients treated with sapropterin and diet exhibited normal growth parameters (height, weight, and head circumference) in contrast to the suboptimal growth observed in children with PKU treated with diet only, over 2 years of follow-up (112).

Efficacy and safety of sapropterin dihydrochloride in patients with phenylketonuria: A meta-analysis of randomized controlled trials (113).

The aim of this meta-analysis was to evaluate the efficacy and safety of sapropterin in PKU patients.

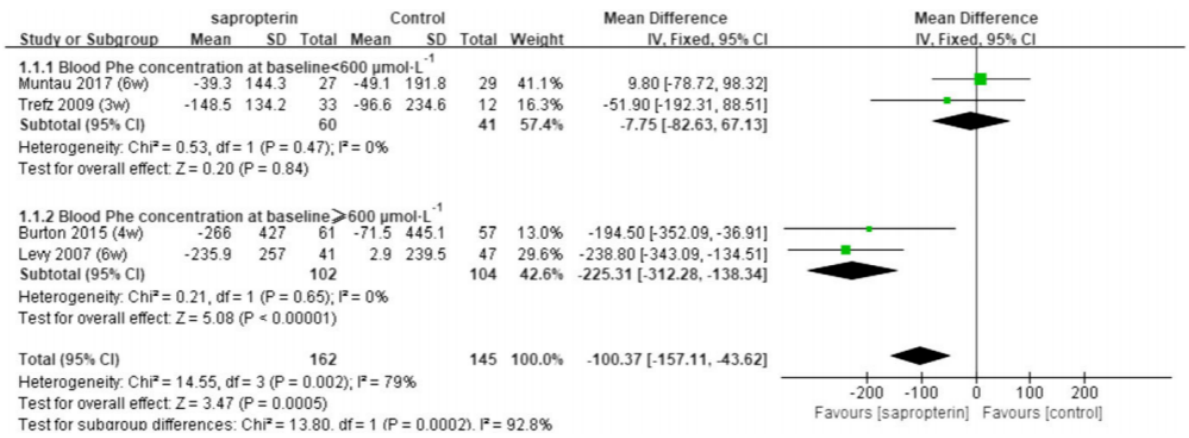
Studies were systematically searched in the PubMed, Embase, Cochrane Library and ClinicalTrials up to 5 September 2018. The following search strategy was used: (kuvan OR phenoptin OR sapropterin OR tetrahydrobiopterin) AND (phenylketonuria OR PKU OR hyperphenylalaninemia OR HPA). Four studies met the inclusion criteria, Levy 2007 [PKU-003] (88), Trefz 2009 [PKU-006] (89), Burton 2015 [PKU-016] (90), Muntau 2017 [SPARK] (91).

Results

Change in blood Phe concentration

Participants were stratified according to the severity of PKU at baseline. Subgroup analysis of patients with low baseline blood Phe level (< 600 μmol L−1) revealed no substantial difference in the change in blood Phe concentration (WMD = −7.75 μmol L−1 ; 95% CI: −82.63 to 67.13, P = 0.84, I 2 = 0%; Figure 32). While subgroup analysis of subjects with high blood Phe concentration (≥ 600 μmol L−1) at baseline showed significant decrease in blood Phe concentration in sapropterin groups (WMD = −225.31 μmol L−1 ; 95% CI: −312.28 to −138.34, P < 0.00001, I 2 = 0%; Figure 32).

Figure 32. Forest plot for the weighted mean difference of change in blood Phe concentration with 95% confidence interval in the fixed effects model

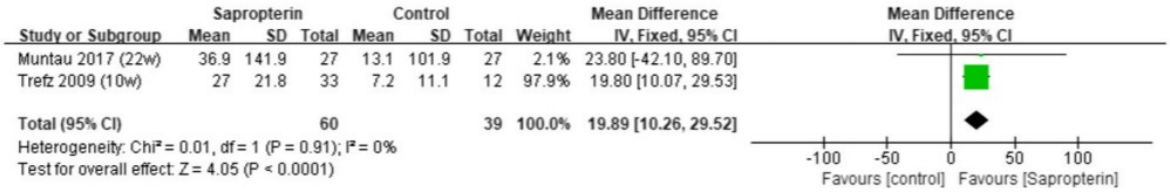


Qu et al. 2019 (113)

Change in dietary Phe tolerance

Two studies (89, 91) measured the dietary Phe tolerance. The meta-analysis demonstrated that sapropterin significantly improved dietary Phe tolerance (WMD = 19.89 mg kg−1 d−1 ; 95% CI: 10.26 to 29.52, P < 0.0001, I 2 = 0%;).

Figure 33. Forest plot for the weighted mean difference of change in dietary Phe tolerance with 95% confidence interval in the fixed effects model



Qu et al. 2019 (113)

Conclusions

Sapropterin could bring benefit for PKU patients with high or low Phe level, due to Phe reduction in a short time or dietary Phe tolerance improvement respectively. Sapropterin has an acceptable safety profile (113).

B.2.9 Indirect and mixed treatment comparisons

No indirect or mixed treatment comparisons have been carried out for sapropterin treatment.

B.2.10 Adverse reactions

The safety of sapropterin treatment has been evaluated across the full clinical development programme for a total period of period of more than 10 years; safety data continue to be collected in the ongoing studies. Only PKU-008 was designed to investigate differences between sapropterin and a comparator treatment (active or placebo) as a primary endpoint; in all other studies (PKU-001, PKU-003, PKU-004, PKU-006, PKU-016, SPARK, PKUDOS, KAMPER) safety was a secondary endpoint.

These studies have consistently demonstrated that sapropterin treatment is generally well-tolerated and demonstrates a favourable risk-benefit profile for treatment in children and adults with PKU of all ages. In all cases, the vast majority of AEs observed were mild or moderate in nature and did not result in withdrawal from treatment or the study.

PKU-008 is an open-label, non-comparative study designed to evaluate the long-term safety of sapropterin as the primary outcome and the results of the study have been presented in section B.2.6.2.

Phase IV patient registry studies KAMPER and PKUDOS both provide long-term safety evidence of saproterin treatment.

In addition, the sixth version of the Periodic Benefit-Risk Evaluation Report (PBRER), published on the 9th of February 2018, confirms the safety profile of the product and indicates that the benefit-risk balance of sapropterin remains positive (114).

Details of the adverse events in the studies presented in B.2.2 section are presented below.

Safety evidence from clinical trials

PKU-001

In PKU-001 study, patients were monitored for AEs by a combination of medical interview, physical examination and laboratory tests at baseline and on days 4, 8 and 36 (96).

A total of 482 AEs was reported in 48% of the 489 patients included in the safety analyses. Only 281 AEs were considered to be possibly or probably treatment related. AEs that occurred in >2% of patients are listed in

Table 28 (96).

The most common AEs included gastrointestinal disorders, such as abdominal pain and diarrhoea, and minor neurological symptoms, including headache. Most AEs were rated by the investigator as mild to moderate in severity. However, five AEs were rated as severe in 1% (4/489) of patients and included vomiting, headache and migraine, and thrombocytopenia. No patient discontinued the study for an AE (96).

No deaths occurred during the study. One patient developed appendicitis between the final dose of sapropterin and day 36, but the condition was not considered to be treatment related. No other serious AEs occurred (96).

Table 28. PKU-001. Adverse events that occurred in >2% of subjects

	Sapropterin group
	Patients N (%)
Diarrhoea	24 (5%)
Abdominal pain	23 (5%)
Nausea	16 (3%)
Flatulence	11 (2%)
Vomiting	9 (2%)
Decreased appetite	8 (2%)
Pharyngolaryngeal pain	9 (2%)
Upper respiratory tract infection	17 (3%)
Headache	50 (10%)
Hyperreflexia	10 (2%)
Tremor	9 (2%)
Fatigue	14 (3%)

Source: Burton 2007 (96)

PKU-003

Ninety-five AEs were reported by 34 (72%) of patients who received placebo and 53 adverse reactions were reported by 21 (51%) sapropterin-treated patients. 8/41 (20%) of patients in the placebo group and 11/47 (23%) of patients in the sapropterin group experienced AEs that might have been drug-related (p=0.80) (88).

Most adverse events were deemed to be unrelated to the study drugs. The most commonly reported adverse event was upper respiratory tract infection. Nervous system disorders (e.g., headache) were more frequent in the placebo group than in the sapropterin group. No SAEs were recorded in either group, and no patient died during the study (88).

Table 29. PKU-003. Adverse events observed by treatment group and for all subjects (ITT population)

	Placebo group (n=47)		Sapropterin group (n=41)		Total (n=88)	
	Patients	**Events**	**Patients**	**Events**	**Patients**	**Events**
Any adverse event on or after first dose	34 (72%)	95	21 (51%)	53	55 (63%)	148
Adverse events that occurred in 5% or more of patients						
Upper respiratory tract infections	13 (28%)	13	7 (17%)	7	20 (23%)	20
Headache	7 (15%)	10	4 (10%)	5	11 (13%)	15
Vomiting	4 (9%)	4	2 (5%)	2	6 (7%)	6
Abdominal pain	4 (9%)	4	1 (2%)	1	5 (6%)	5
Diarrhoea	3 (6%)	3	2 (5%)	2	5 (6%)	5
Pyrexia	2 (4%)	2	2 (5%)	2	4 (5%)	4
Back pain	3 (6%)	3	1 (2%)	1	4 (5%)	4

Source: Levy 2007 (88)
Notes: Only AEs with onset on or after first dose are summarised here. A patient was counted at most once for a given AE. Several events were counted if patients had the same adverse events with different onset dates or times.

No patients in the sapropterin group and controls had clinically significant changes in liver enzymes (alanine aminotransferase in one and aspartate transaminase in the other). One patient in the sapropterin group had a clinically significant low T4 at week 0 (before sapropterin exposure) and again at week 6. This patient had normal TSH concentration at week 0 and high TSH after 6 weeks (88).

No serious AE or death occurred during this study and no patient withdrew from the study due to an AE (88).

PKU-004

Sixty-eight (85%) patients had at least one AE during the study. All AEs, except one, were mild (53%) or moderate (31%) in severity. The most commonly reported AEs for this study were headache, nasopharyngitis, and vomiting. Importantly, there was no apparent relationship between the dose of sapropterin and incidence, frequency, or type of AE (101).

A total of 82 (32%) AEs in 31 (39%) patients were judged by the investigator to be possibly or probably related to sapropterin. 29 AEs that were considered to be probably related to sapropterin were upper abdominal pain (1 patient), nausea (2 patients), headache (1 patient), dizziness (1 patient), and increased alanine amino-transferase (1 patient); with the exception of one episode of moderate nausea, all of these were mild in severity. AEs that were considered to be possibly related to sapropterin and were reported by more than one patient included: urinary tract (2 patients) or streptococcal infections (2 patients), vomiting (4 patients), diarrhoea (2 patients), abdominal pain (2 patients), headache (8 patients), migraine (4 patients), pharyngolaryngeal pain (3 patients), cough (2 patients), decreased neutrophil counts (2 patients), and rash (2 patients). Thirty-one AEs possibly related to sapropterin were reported by 1 patient each (101).

Table 30. PKU-004. Adverse events observed in >5% of subjects (ITT population)

	Sapropterin group
	Patients N (%)
Headache	16 (20%)
Pharyngo-laryngeal pain	12 (15%)
Nasopharyngitis	11 (14%)
Vomiting	10 (13%)
Diarrhea	8 (10%)
Upper respiratory tract infection	8 (10%)
cough	7 (9%)
Dysmenorrhea	3 (9%)
Migraine	6 (8%)
Back pain	4 (5%)
Gastroenteritis	4 (5%)
Influenza	4 (5%)

source: Lee 2008 (101)

Three patients each experienced one serious AE during the study. Two of these events, urinary tract infection and spinal cord injury, occurred during the fixed-dose phase of the study. The third event, tibia fracture, occurred after the week-22 visit. The spinal cord injury and tibial fractures were accidental, sports-related injuries and the urinary tract infection occurred in a 13-year-old female with duplex kidney and a history of prior infection. None was considered related to sapropterin (92).

Two patients had plasma Phe concentrations that reached 2,000 mmol/L (33.3 mg/dl) or higher during the course of the study. One patient had plasma Phe concentrations >2,000 mmol/L at week 6, which decreased to 1,819 mmol/L (30.3 mg/dl) by week 10 and increased again to >=2,000 mmol/L at all visits between week 12 and week 22: this patient received the 20 mg/kg/day dose during the fixed-dose phase. The second patient had plasma Phe concentration >2,000 mmol/L at week 0, which decreased to 766 mmol/L (12.8 mg/dl) by week 2: this patient also received 20 mg/kg/day during the fixed-dose phase, during which time plasma Phe concentrations ranged between 476 mmol/L (7.9 mg/dl) and 873 mmol/L (14.6 mg/dl) (92).

No deaths occurred in this study and no patient withdrew from the study or discontinued treatment because of an AE (92).

The authors of this study concluded that sapropterin is effective in reducing plasma Phe concentrations in a dose-dependent manner and is well tolerated at doses of 5-20 mg/kg/day over 22 weeks in responsive patients with PKU (92).

PKU 016

Adverse events (AEs) that occurred in ≥5% in either treatment group included: abdominal pain, cough, diarrhoea, headache, nasal congestion, nasopharyngitis, nausea, oropharyngeal pain, pain in extremity, pyrexia, upper respiratory tract infection, vomiting. Most AEs were mild or moderate. One person withdrew from treatment due to heart rate increase classified as possibly or probably drug-related in a patient being treated with sapropterin (93).

Serious AEs (SAE) occurred in one patient each and included amino acid level increase (placebo patient before Week 13), animal bite (placebo patient after Week 13), concussion (placebo patient before Week 13), necrotising fasciitis (placebo patient before Week 13), and petit mal epilepsy (placebo patient after Week 13). The only SAE classified as possibly or probably related to treatment was the petit mal seizure, which occurred in a patient with a history of seizures (93).

No subjects withdrew due to SAEs.

Table 31: PKU-016. Adverse events occurring in all enrolled subjects (N=206)

Characteristic	Randomised trial baseline to week 13		Open-label treatment period weeks 13 to 26 (all subjects on sapropterin)	
	Placebo n=108	Sapropterin n = 98	Placebo/ sapropterin n = 104	Sapropterin n = 95
Adverse events occurring in ≥ 5% of subjects in either group, n (%)				
Abdominal pain, upper	5 (4.6%)	4 (4.1%)	2 (1.9%)	7 (7.4%)
Cough	8 (7.4%)	7 (7.1%)	8 (7.7%)	8 (8.4%)
Diarrhoea	4 (3.7%)	10 (10.2%)	8 (7.7%)	4 (4.2%)
Headach	28 (25.9%)	25 (25.5%)	16 (15.4%)	17 (17.9%)
Nasal congestion	11 (10.2%)	7 (7.1%)	4 (3.8%)	12 (12.6%)
Nasopharyngitis	9 (8.3%)	11 (11.2%)	12 (11.5%)	11 (11.6%)
Nausea	10 (9.3%)	4 (4.1%)	10 (9.6%)	7 (7.4%)
Oropharyngeal pain	10 (9.3%)	6 (6.1%)	11 (10.6%)	11 (11.6%)
Pain in extremity	3 (2.8%)	1 (1.0%)	3 (2.9%)	7 (7.4%)
Pyrexia	5 (4.6%)	1 (1.0%)	5 (4.8%)	7 (7.4%)
Upper respiratory tract infection	7 (6.5%)	4 (4.1%)	10 (9.6%)	3 (3.2%)
Vomiting	14 (13.0%)	4 (4.1%)	12 (11.5%)	3 (3.2%)
Serious adverse events n (%)				
Amino acid level increased	1 (0.9)	0 (0)	0 (0)	0 (0)
Animal bite	0 (0)	0 (0)	1 (1.0)	0 (0)
Concussion	1 (0.9)	0 (0)	0 (0)	0 (0)
Necrotising Fasciitis	1 (0.0)	0 (0)	0 (0)	0 (0)
Petit mal epilepsy	0 (0)	0 (0)	1 (1.0)	0 (0)

Source: Burton et al (93)
NOTE: Subjects who experienced more than 1 AE within a preferred term were counted once within that preferred term.

SPARK

At least one AE (Table 32) was experienced by the patients in the safety population (54 patients); in the sapropterin plus Phe-restricted diet group, eight out of 27 patients (29.6%) reported at least one treatment-emergent AE (TEAE) related to sapropterin. The proportion of patients reporting TEAEs was the same in the two groups, and no patients withdrew owing to AEs. None of the TEAEs were graded as severe. All patients

had at least one TEAE that was judged to be mild in severity. Seven (25.9%) patients in the sapropterin plus Phe-restricted diet group had nine TEAEs, and eight (29.6%) patients in the Phe-restricted diet group reported 18 TEAEs graded as moderate in severity, respectively (91, 103).

Table 32 Summary of safety data showing the proportion of patients reporting adverse events (AEs) (Safety population)

	Sapropterin + Phe-restricted diet (n = 27)		Phe-restricted diet alone (n = 27)	
	Patients, n (%)	Events, n	Patients, n (%)	Events, n
Treatment-emergent AEs	27 (100)	282	27 (100)	278
AEs related to sapropterin	8 (29.6)	31	NA	NA
Infections and infestations related to sapropterin	3 (11.1)	3	NA	NA
Gastrointestinal disorders related to sapropterin	3 (11.1)	8	NA	NA
Amino acid concentrations decrease related to sapropterin	6 (22.2)	20	NA	NA
SAEs	3 (11.1)	5	1 (3.7)	2
Gastroenteritis	1 (3.7)	1	0 (0.0)	0
Rash	1 (3.7)	1	0 (0.0)	0
Overdose[a]	1 (3.7)	2	0 (0.0)	0
Stomatitis	1 (3.7)	1	0 (0.0)	0
Bronchiolitis	0 (0.0)	0	1 (3.7)	1
Bronchopneumonia	0 (0.0)	0	1 (3.7)	1

Source: Muntau (91)

[a] On the day of first administration of study treatment, the subject had a sapropterin overdose (severity: mild; 80 mg/day instead of 75 mg/day by mistake). At 26 days after the first administration of study treatment, the subject had another sapropterin overdose (severity: mild; 80 mg/day instead of 75 mg/day by mistake). Both events were reported in accordance with the protocol and were therefore categorized as medically important. The subject recovered without sequelae from both events. The administration of sapropterin plus Phe-restricted diet alone was continued without change after the first overdose and the dose was reduced after the second overdose.

The most common TEAEs in the sapropterin plus Phe-restricted diet group and in the Phe-restricted diet group were:

- pyrexia (63.0 and 66.7%)
- cough (48.1 and 48.1%)
- nasopharyngitis (48.1 and 40.7%)

The most common TEAEs classified as related to sapropterin were:

- amino acid concentration decrease (six patients [22.2%])
- rhinitis (two patients [7.4%])
- vomiting (two patients [7.4%])
- pharyngitis, diarrhoea, abdominal pain, mouth ulceration and increased amino acid concentration (1 patient each). (91, 103)

Although the proportion of patients who reported a serious AE (SAE) was higher in the sapropterin plus Phe-restricted diet group compared with the Phe-restricted diet (11.1 vs. 3.7%), all SAEs were assessed as unrelated to sapropterin treatment (91, 103).

Extension Study

Overall, 96.1% of subjects experienced at least one treatment-emergent adverse event (TEAE): all 25 subjects in the “sapropterin continuous” group and 24/26 subjects in the “sapropterin extension” group:

- Only 47 of 1401 TEAEs (3.4%) were assessed by the Investigator as related to sapropterin, the most commonly reported (n, %) of patients were:
    - Amino Acid level decreased – 24 events occurring in 9 patients
    - Amino Acid level increased – 4 events occurring in 2 patients
    - Vomiting – 4 events occurring in 3 patients
    - Rhinitis – 3 events occurring in 3 patients

The proportion of subjects who were reported with a serious AE was similar between the treatment groups – 6 subjects (24.0%) with 12 events in the “sapropterin continuous” group and 7 subjects (26.9%) with 7 events in the “sapropterin extension” group.

All SAEs were assessed as unrelated to sapropterin treatment.

No subjects withdrew from the study during the Extension Period due to an AE (94).

PKU-008

In PKU-008, safety was the primary outcome, as mentioned in section B.2.3.2, and was assessed by monitoring every 3 months for AEs and SAEs, clinical laboratory evaluations, physical examinations, concomitant medications, and vital sign measurements (93).

Patient exposure to study drug

Mean (median, range) duration of exposure to sapropterin in PKU-008 was 658.7±221.3 (595, 56–953) days. The maximum exposure was 953 days (2.6 years).

The mean (range) duration of exposure during participation in multiple studies (parent study plus extension study or studies) was 799.0±237.5 (135-1151) days. The mean (median, range) daily amount of sapropterin taken was 16.4±4.4 (18.4, 4.8–22.1) mg/kg/day (93).

Safety results

Of all participants who received at least one dose of sapropterin, AEs were reported for 93 (83.8%) subjects and drug-related AEs were reported for 37 (33.3%) subjects. Most were considered mild or moderate.

Table 33 and Table 34 list AEs occurring in >5% of subjects. No drug-related AEs occurred at a frequency >5% (93).

Table 33. Treatment-emergent adverse events occurring in >5% of subjects.

	No. of subjects (%), no. of events				
System Organ Class	4–7 years (N=20)	8–11 years (N=24)	12–17 years (N=28)	≥18 years (N=39)	Total (N=111)
Infection and infestations	20 (100), 58	17 (70.8), 42	14 (50), 32	23 (59), 66	74 (66.7), 198
Upper respiratory tract infection	6 (30), 10	7 (29.2), 7	6(21.4), 7	3 (7.7), 4	22 (19.8), 28
Nasopharyngitis	2 (10), 4	1 (4.2), 1	5 (17.9), 8	12 (30.8), 17	20 (18), 30
Influenza	3 (15), 5	1 (4.2), 1	1 (3.6), 1	4 (10.3), 8	9 (8.1), 12
Viral infection	5 (25), 8	1 (4.2), 2	1 (3.6), 1	1 (2.6), 1	8 (7.2), 12
Gastroenteritis viral	2 (10), 2	3 (12.5), 4	2 (7.1), 2	1 (2.6), 1	8 (7.2), 9
Pharyngitis	1 (5), 1	4 (16.7), 10	0	2 (5.1), 2	7 (6.3), 13
Gastroenteritis	2 (10), 2	1 (4.2), 1	2 (7.1), 2	2 (5.1), 2	7 (6.3), 7
Bronchitis	2 (10), 2	1 (4.2), 1	0	3 (7.7), 4	6 (5.4), 7
Gastrointestinal disorders	11 (55) 16	9 (37.5), 16	8 (28.6), 12	15 (38.5), 29	43 (38.7), 73
Vomiting	6 (30), 6	5 (20.8), 6	4 (14.3), 5	5 (12.8), 7	20 (18), 24
Diarrhoea	1 (5), 1	3 (12.5), 6	1 (3.6), 1	5 (12.8), 8	10 (9), 16
Respiratory, thoracic, and midiastinal disorders	7 (35),18	9 (37.5), 26	8 (28.6), 17	12 (30.8), 16	36 (32.4), 77
Cough	4 (20), 8	6 (25), 8	4 (14.3), 5	7 (17.9), 7	21 (18.9), 28
Pharyngolaryngeal pain	0	6 (25), 11	2 (7.1), 2	2 (5.1), 2	10 (9), 15
Nasal congestion	2 (10), 2	2 (8.3), 4	3 (10.7), 5	2 (5.1), 2	9 (8.1), 13
Rhinorrhoea	3 (15), 4	1 (4.2), 2	2 (7.1), 2	0	6 (5.4), 8
General disorders and administration site conditions	8 (40), 9	6 (25), 12	5 (17.9), 6	6 (15.4), 6	25 (22.5), 33
Pyrexia	8 (40), 9	5 (20.8), 3	3 (10.7), 4	2 (5.1), 2	18 (16.2), 25
Nervous system disorders	2 (10), 3	4 (16.7), 7	4 (14.3), 8	6 (15.4) 35	16 (14.4), 53
Headache	2 (10), 3	3 (12.5), 6	3 (10.7), 7	5 (12.8), 32	13 (11.7), 48

Source: Burton 2011 (93)

Table 34. Drug-related treatment-emergent adverse events occurring in >5% of subjects.

	No. of subjects (%), no. of events				
System Organ Class	4–7 years (N=20)	8–11 years (N=24)	12–17 years (N=28)	≥18 years (N=39)	Total (N=111)
Infection and infestations	3 (15), 8	2 (8.3), 4	3 (10.7), 1	3 (7.7), 5	11 (9.9), 27
Upper respiratory tract infection	0	0	2 (7.1), 2	0	2 (1.8), 2
Nasopharyngitis	0	0	2 (7.1), 2	1 (2.6), 1	3 (2.7), 6
Influenza	0	0	0	1 (2.6), 2	1 (0.9), 2
Viral infection	1 (5), 1	0	0	0	1 (0.9), 1
Gastroenteritis viral	2 (10), 2	1 (4.2), 1	2 (7.1), 2	0	5 (4.5), 6
Pharyngitis	0	0	0	0	0

Gastroenteritis	0	0	0	0	0
Bronchitis	0	0	0	0	0
Gastrointestinal disorders	4 (20), 5	0	4 (14.3), 5	6 (15.4), 8	14 (12.6), 18
Vomiting	3 (15), 3	0	0	2 (5.1), 3	5 (4.5), 6
Diarrhoea	0	0	1 (3.6), 1	2 (5.1), 2	3 (2.7), 3
Respiratory, thoracic, and midiastinal disorders	1 (5), 2	2 (8.3), 6	0	1 (2.6), 2	4 (3.6), 5
Cough	1 (5), 2	1 (4.2), 2	0	1 (2.6), 2	3 (2.7), 5
Pharyngolaryngeal pain	0	1 (4.2), 4	0	0	1 (0.9), 1
Nasal congestion	0	0	0	0	0
Rhinorrhoea	0	0	0	0	0
General disorders and administration site conditions	2 (10), 2	2 (8.3), 3	0	0	4 (3.6), 5
Pyrexia	2 (10), 2	2 (8.3), 3	0	0	4 (3.6), 5
Nervous system disorders	1 (5), 1	0	0	5 (12.8), 24	6 (5.4), 25
Headache	1 (5), 1	0	0	4 (10.3), 22	5 (4.5), 6

Source: Burton 2011 (93)

The most common drug-related AEs were viral gastroenteritis, vomiting, and headache (each in 4.5% of subjects) (93).

Severe Adverse Events

Of the severe AEs reported for six subjects, one (difficulty concentrating and mood swings) was considered possibly related to study drug, which resolved when timing of sapropterin treatment was altered to not coincide with levothyroxine medication (93).

Serious Adverse Events

Of the serious AEs (SAEs) reported for 7 subjects, one (gastroesophageal reflux and concomitant use of ibuprofen) was considered probably drug-related. Most subjects' blood Phe levels stayed within recommended treatment range. 5 (4.5%) subjects had blood Phe levels ≤26 µmol/L on seven occasions. Low Phe levels were considered transitory, not treatment- related and resolved without intervention. Twenty-four subjects had transitory neutrophil counts <1.5 x 109/L at 35 time points that did not require intervention. Thirteen subjects had platelet counts below the lower limit of

normal that did not appear treatment related. One subject was withdrawn due to low platelet count (93).

Study discontinuations

Twenty-one (18.9%) of the 111 subjects discontinued the study early. Of these 21 subjects:

- 3 discontinued due to an adverse event (AE) which were deemed to be possibly drug-related (one each of difficulty concentrating, clinically significant decreased platelet count, and intermittent diarrhoea);
- 3 discontinued at the Investigator's discretion due to uncooperative or non-compliant behaviour;
- 9 subjects withdrew consent;
- 4 discontinued due to unresponsiveness; and
- 2 moved out of the country (93).

Study conclusions

Sapropterin was found to be safe and well tolerated in doses of 5 to 20 mg/kg per day for up to 2.6 years. These PKU-008 data represent the longest exposure to sapropterin with subjects receiving up to 2.6 years of treatment with a consistent safety profile to other clinical trials. Controlled blood Phe levels throughout the study also confirm the durability of long-term sapropterin response, regardless of dietary adherence (93).

Safety evidence from disease registries

In addition to the safety data reported in the sapropterin clinical development programme, registry data collected over time have and will continue to provide insight into the long-term safety of a large number of patients with PAH deficiency exposed to sapropterin. An overview of the 2 key registries and evidence of safety to date is as follows:

PKUDOS

The Longo publication presents safety data from 7 years of sapropterin exposure for 1189 PKU patients enrolled in the PKUDOS registry and demonstrates that sapropterin is well-tolerated in the longer-term and has a favourable safety profile (95).

- At 5 year follow up of patients in PKUDOS, drug-related AEs were reported in 6% of subjects, were mostly considered non-serious, and were identified in the gastrointestinal, respiratory, and nervous systems. Serious drug-related AEs were reported in ≤1% of subjects (95).

- Of the 113 drug-related AEs in PKUDOS, 73% were considered mild, 23% moderate, and 4% severe. Twelve percent of AEs culminated in permanent discontinuation of sapropterin, 10% in temporary discontinuation, 4% in dose reductions, and in the 62% the dose was not changed nor discontinued (95).

- In PKUDOS, 10 SAEs were reported as possibly related to sapropterin. Of these 10 SAEs, 3 were reported to be mild, 3 were moderate, and 4 were severe. The AEs were: cardiac system (arrhythmia, n = 1); gastrointestinal system (abdominal discomfort and gastroesophageal reflux, n = 2); hepatobiliary (cholecystitis, n = 1), metabolism and nutrition disorders (diabetes mellitus, n = 1); pregnancy, puerperium and perinatal conditions (spontaneous abortions n = 3; premature labour n = 1); and psychiatric system (conversion disorder, n = 1). Ten percent (n=1) of SAEs culminated in permanent discontinuation of sapropterin, 20% (n = 2) in temporary discontinuation, and in the 60% (n = 6) the dose was neither changed nor discontinued (95).

At the time of the most recent interim analysis (February 2017), AEs considered related to sapropterin occurred in 9 (2.4%) previously-treated patients and 116 (12.8%) continuously treated patients (see Table 35). There was a gradual decrease in the number of AEs reported over the years. The most common drug-related AEs in previously treated patients were gastrointestinal disorders (n=5; 1.3%), nervous system disorders (n=2; 0.5%), and respiratory, thoracic, and mediastinal disorders (n=1; 0.3%). Most common drug-related AEs in continuously treated patients were gastrointestinal

disorders (n=62; 36.8%), nervous system disorders (n=30; 3.3%), and psychiatric disorders (n=15; 1.7%) (5).

Table 35. PKUDOS. Most common AEs considered related to sapropterin from baseline to last follow-up

System Organ Class	Previously treated (n=381)		Continuously treated (n=908)	
	Patients n (%)	Events n	Patients n (%)	Events n
Patients with ≥1 reported drug-related AE	9 (2.4%)	9	116 (12.8%)	217
Gastrointestinal disorders	5 (1.3%)	5	62 (36.8%)	80
Nervous system disorders	2 (0.5%)	2	30 (3.3%)	40
Respiratory, thoracic and mediastinal disorders	1 (0.3%)	1	7 (0.8%)	10
General disorders	0	0	7 (0.8%)	10
Psychiatric disorders	0	0	15 (1.7%)	17
Skin and subcutaneous tissue Disorders	0	0	10 (1.1%)	16
Musculoskeletal and connective tissue disorders	0	0	4 (0.4%)	6
Infections and infestations	0	0	4 (0.4%)	5
Injury, poisoning and procedural Complications	0	0	2 (0.2%)	2

Source: Lilienstein et al (5)

KAMPER

The primary objective of the KAMPER registry is to assess the long-term safety in patients treated with sapropterin. A total of 627 patients were to be enrolled in the registry with a target patient enrolment target of 2019. However, the patient enrolment target was reached early on 20 May 2016. Interim results have been published which continue to show that sapropterin has a favourable safety profile. The Trefz 2015 publication was based on 325 patients (97, 108).

Data from the KAMPER registry (8th interim analysis) are now available and continue to show that sapropterin has a favourable safety profile (108). Table 36 below, lists the AEs by primary system organ class for PKU population.

Table 36. Frequency of Adverse Events for PKU Population (table below is AIC)

Source: CRS KAMPER 2018 (108)
a This is an interim analysis with a data cut-off on 29 January 2018. Those un-coded events will be coded for the following interim analysis.

The main findings from this 8th interim analysis (as yet unpublished) are:

As demonstrated in the clinical trial evidence, the 8th interim analysis results from the KAMPER registry continue to show that sapropterin has a favourable safety profile. In general, blood Phe levels were lower than Phe levels prior to treatment, and Phe tolerance was above pre-treatment values.

B.2.11 Ongoing studies

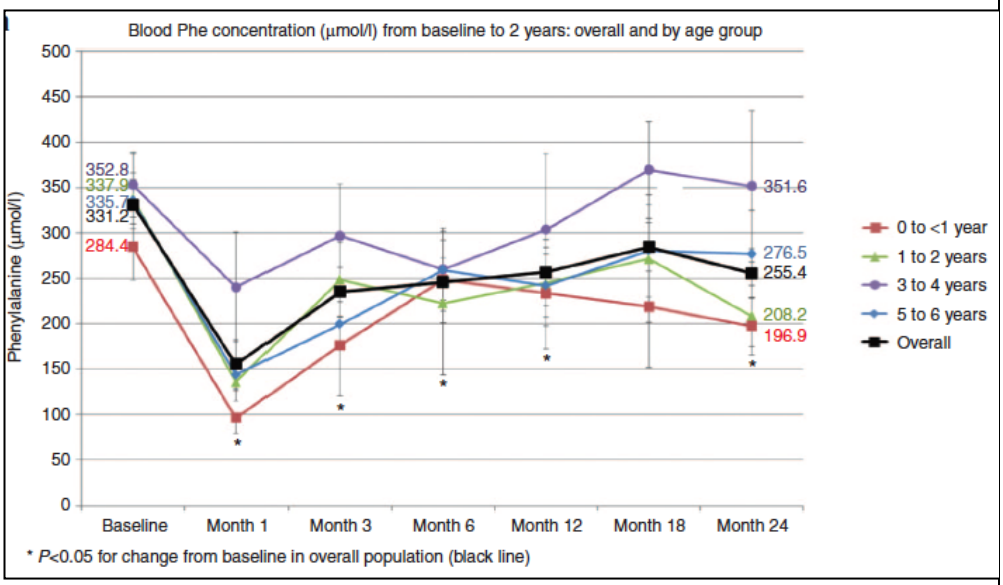
Currently, there are two ongoing Phase IIIb studies (SPARK Extension study and PKU 015) and 3 Phase IV observational studies (PKUDOS, KAMPER and KOGNITO). The extension of the SPARK study is presented with the rest of the SPARK study, Phase IV studies PKUDOS and KAMPER are presented throughout the sections B.2.2 to B.2.6 and KOGNITO is presented on Appendix F, as there are no published results yet for this study.

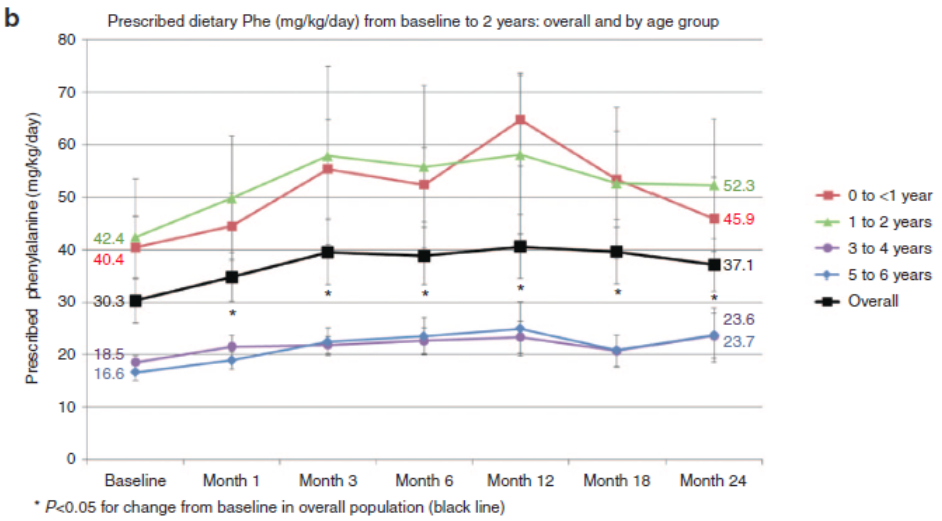
In the Table 37 below, follow the summary of design methodology and interim findings of PKU-015 study (99).

Table 37. PKU-015. Summary of design, methodology and interim findings

Title	A Phase 3 study to evaluate the effect of sapropterin on neurocognitive function in children ages 0 to 6 years of age with PKU (NCT00838435)

Study design	PKU-015 is an ongoing multicenter, international Phase 3b open-label study to evaluate the effect of sapropterin on neurocognitive function, maintenance of blood Phe concentrations, safety, and population pharmacokinetics in children between 0 to 6 years of age with PKU. Study design: In part 1: patients received a 4-week trial designed to identify BH4 responders. Sapropterin responsiveness was defined as a ≥30% average reduction in blood Phe concentration from baseline calculated from the average of phenyl-alanine levels at weeks 1, 2, 3, and 4. Sapropterin-responsive subjects received a baseline neurocognitive assessment within 6 weeks of confirmation of sapropterin responsiveness. Part 2 is the 7-year trial component to evaluate long-term effects on neurocognitive function. Subjects who responded to sapropterin and attained a score of ≥80 on the infant developmental test or an IQ ≥80 were eligible to enter part 2, which included a 6-month safety and efficacy evaluation followed by a long-term neurocognitive evaluation for 7 years of follow-up. Study visits occurred monthly up to 1 year and every 6 months thereafter through year 7. Interim assessments were conducted by telephone every 3 months to assess weight, adverse events (AEs), and concomitant medications.
Objectives	The primary objective is to determine the long-term efficacy of sapropterin in preserving neurocognitive function in PKU children when treatment is started at 0 to 6 years of age.
Inclusion criteria	• Established diagnosis of PKU with hyperphenylalaninemia (HPA) >= 360 micromol/L • Age 0 to 6 years old, inclusive, at Screening.
Exclusion criteria	• Established diagnosis of primary tetrahydrobiopterin (BH4) deficiency • Known hypersensitivity to sapropterin or its excipients • History of organ transplantation • Perceived to be unreliable or unavailable for study participation or to have parents or legal guardians who are perceived to be unreliable or unavailable • Use of methotrexate or other medications that inhibit folate metabolism • Serious neuropsychiatric illness (eg, major depression) not currently under medical control • Use of sapropterin or any investigational agent within 30 days prior to Screening, or known requirement for any investigational agent prior to completion of all scheduled study assessments • Concurrent disease or condition that would interfere with study participation or safety (eg, seizure disorder, oral steroid-dependent asthma or other condition requiring oral or parenteral corticosteroid administration, or insulin dependent diabetes) • Use of phosphodiesterase type 5 inhibitor, often shortened to PDE5 inhibitor (eg, sildenafil citrate, vardenafil, tadalafil, avanafil, lodenafil, mirodenafil, udenafil)

Intervention	Sapropterin dihydrochloride
Outcomes	**Primary:** Long-term efficacy in preserving neurocognitive function when treatment is initiated at 0-6 years **Secondary:** Long-term safety; Growth; Neurocognitive function; pharmacokinetics
Results	The study is ongoing with sites in the US and Canada, however 2-year interim analysis data is available. Results are reported in Longo N, Siriwardena K, Feigenbaum A, et al. Long-term developmental progression in infants and young children taking sapropterin for phenylketonuria: a two-year analysis of safety and efficacy. Genet Med 2014;17(5):365-73 (99) The results from a 2-year interim analysis demonstrate that sapropterin lowered blood Phe levels while allowing for increased prescribed dietary Phe. Mean blood Phe declined in all children in each age group from baseline to the week 4 visit, then increased to levels still below baseline by month 3, with the exception of 3- to 4-year-old children, in whom blood Phe increased to the baseline level (see Figure 34 below). **Figure 34. PKU-015. Blood Phe concentrations from baseline to 2 years, overall and by age group**  Source: Longo 2015 (99) Figure 35 below demonstrates that the prescribed dietary Phe (mg/kg/ day) increased from baseline to 2 year follow up in all age groups. **Figure 35. PKU-015. Prescribed dietary Phe from baseline to 2-year follow-up in all age groups**



Source: Longo 2015 (99)

In terms of IQ, the mean full-scale intelligence quotient was 103 ± 12 at baseline and 104 ± 10 at 2-year follow-up (p=0.50, paired t-test, n=25) and was therefore maintained. For children younger than 30 months of age, the cognitive composite score from the Bayley Scales of Infant and Toddler Development, Third Edition was also maintained within the normative range of 100+/-15. (99)

Safety

Sapropterin had a favourable safety profile and was well tolerated. AEs and drug-related AEs were consistent with adverse reactions listed on the sapropterin package insert. An analysis of long-term safety in an extension study of multiple phase III studies of sapropterin 5–20 mg/kg/day found that most AEs were mild or moderate in severity and were unrelated to treatment.

Table 38 presents nonserious AEs classified as possibly or probably related to sapropterin and occurring in >5% of individuals with PKU. These included abdominal pain, diarrhea, vomiting, infections of the ear and upper respiratory tract, nasal congestion, and headache. Six serious AEs were reported in five (9%) subjects. None of the serious AEs, which included constipation, croup, pneumonia, injury, anaesthesia complication, and seizure, was deemed by the investigator to be related to sapropterin.

The study authors concluded that sapropterin has a favorable safety profile and was well tolerated, based on dose adherence and absence of serious AEs, consistent with previous studies of sapropterin in subjects older than 4 and 8 years of age (Table 38). The reported AEs and drug-related AEs were consistent with adverse reactions listed on the sapropterin package insert. An analysis of long-term safety in an extension study of multiple phase III studies of sapropterin 5–20 mg/kg/day found that most AEs were mild or moderate in severity and were unrelated to treatment. All growth parameters in the current study were slightly above the 50th percentile of the Centers for Disease Control and Prevention reference values at baseline and did not

change significantly during the study, indicating that sapropterin therapy for up to 2 years does not affect growth in young children with PKU (99).

Table 38. PKU-015. Adverse events observed in >5% of subjects (ITT population)

	Sapropterin group
	Patients N (%)
Drug-related adverse events occurring in >5% of patients (overall for all age groups)	
Vomiting	7 (12.7%)
Diarrhoea	6 (10.9%)
Upper respiratory tract infection	6 (10.9%)
Abdominal pain	5 (9.1%)
Nasal congestion	5 (9.1%)
Upper abdominal pain	4 (7.3%)
Ear infection	3 (5.5%)
Headache	3 (5.5%)
Serious adverse events (all deemed unrelated to study drug) (overall for all age groups)	
Airway complication of anaesthesia	1 (1.8%)
Constipation	1 (1.8%)
Seizure	1 (1.8%)
Croup (infections)	1 (1.8%)
Injury	1 (1.8%)
Pneumonia	1 (1.8%)

Source: Longo 2015 (99)

Conclusion

Sapropterin use preserved developmental performance, intellectual quotient scores, and neurocognitive performance in children who started therapy between 0 and 6 years of age (99).

Furthermore, according to the systematic literature review conducted, of 116 hits, 3 studies of sapropterin were identified with primary completion date recently or occurring in the next 12 months (Table 39).

Table 39: Ongoing clinical trials from registry

NCT Number	Title	Status	Outcome Measures	Sponsor/Collaborators	Age	Phase	Enrollment	Study Type	Primary Completion Date	Completion Date
NCT02677870	The Effectiveness of Kuvan in Amish PKU Patients	Recruiting	Change in plasma Phe levels Change in Phe tolerance Executive function/QoL	University Hospitals Cleveland Medical Center|BioMarin Pharmaceutical	2 Years to 60 Years (Child, Adult)	4	25	Interventional	Jun-18	Aug-18
NCT00838435 PKU-015	Effect of Kuvan on Neurocognitive Function, Blood Phenylalanine Level, Safety, and Pharmacokinetics in Children With PKU	Active, not recruiting	Long term efficacy of sapropterin in preserving neurocognitive function in children with PKU. when tx is initiated at 0-6 years Effect of sapropterin on growth. BL neurocognitive function for all sapropterin -responsive subjects and 6 month Bayley III data for subjects who are 0-2 years old. PKs of sapropterin in young children	BioMarin Pharmaceutical	Up to 6 Years (Child)	3	230	Interventional	Aug-19	Jan-20
NCT00730080 PKU/Kuvan/ White- 201104287	Sapropterin in Individuals With Phenylketonuria	Completed	Diffusion tensor imaging of the brain|n-back task/ recognition span task/ list learning task/ verbal fluency task/ go/no-go task/ stimulus-response compatibility task/ structural MRI of the brain|WASI	Washington University School of Medicine| BioMarin Pharmaceutical|University of Missouri-Columbia	6 Years to 50 Years (Child, Adult)		45	Observational	May-18	May-18

Abbreviations: MRI, magnetic resonance imaging; PKs, pharmacokinetics; PKU, phenylketonuria; WASI, Wechsler Abbreviated Scale of Intelligence

B.2.12 Innovation

Sapropterin is the first approved pharmacological treatment for PKU, a synthetic form of chaperone enzyme BH4, which enhances the activity of the PAH enzyme. In responsive patients of all ages, sapropterin produces a significant and durable reduction in blood Phe.

Clinical trial evidence has demonstrated the reduction in blood Phe and improvement in Phe tolerance possible in patients responsive to sapropterin. As a result these studies suggest that sapropterin will allow patients to increase the natural protein in their diet:

- The Phase IIIb, SPARK extension study has shown that patients 0-4 years old taking sapropterin treatment are steadily increasing their protein intake by 38.74 mg/kg/day vs. Baseline (95% CI: 28.9, 48.6; p<0.0001) (94) The original SPARK study (Muntau 2017) showed an improvement in Phe tolerance from 50.1 mg/day to 80.6 mg/day of Phe. Those patients who remained on sapropterin plus diet showed their Phe-tolerance increased significantly vs. Baseline and significant increases were maintained throughout the 36- month duration of the study. Dietary Phe tolerance at the end of study increased by 38.74 mg/kg/day vs. Baseline (95% CI: 28.9, 48.6; p<0.0001).

- The Phase IV registries PKUDOS and KAMPER have shown even higher increases:

    - In the latest interim PKUDOS analysis published, continuously sapropterin treatment patients of all ages have increased their median Phe intake 1.7 times, consistently over the 6 year study period. (5)

    - In the latest interim KAMPER analysis published, dietary Phe and natural protein intakes increased in all age groups by 1.5 to 2 times their intakes prior to sapropterin treatment. (48)

Furthermore, sapropterin treatment has been related to improvements on neuropsychiatric and neuro-cognitive functions. As shown in section B.2.6. Clinical Trial Results, in PKU-016, sapropterin treatment was associated with a significant

improvement in ADHD inattention symptoms that were maintained throughout the study for individuals with PKU and ADHD symptoms (93). In PKU-015 sapropterin use had been shown to preserve developmental performance, intellectual quotient scores, and neurocognitive performance in children who started therapy between 0 and 6 years of age (99).

Finally, in addition to the clinical benefits of sapropterin, other benefits include:

- reduction in healthcare resource: improved Phe control will result in fewer GP and hospital outpatient appointments, fewer avoidable or emergency hospital admissions, and a reduction in the use of concomitant medicines used to treat some of the psychiatric and neurological symptoms of PKU, such as anxiety and depression based on clinical opinion

- reduction in the burden on caregivers: by reducing the reliance on a strict Phe-free diet, sapropterin treatment is expected to result in a reduction in the burden on caregivers

- improvement of the psychosocial aspects of PKU and health-related quality of life: treatment with sapropterin can help PKU patients reduce their Phe levels and in turn improve their executive function. Patients will then be able to see improvements in their planning, processing speed, working memory and quality of life.

- better social inclusion, improved work performance and educational outcomes: Given the impact elevated Phe has on cognition, treatment with sapropterin would reduce blood Phe, improve executive function, improve Phe tolerance and therefore eat a more natural diet and engage with family and friends on a more social and inclusive basis. In addition, one would expect to observe improvements in their ability to concentrate thus improving their academic and work performance.

B.2.13 Interpretation of clinical effectiveness and safety evidence

In the pivotal Phase III RCT in 89 patients aged 8 years and over (PKU-003), 18/41 (44%) of patients treated with sapropterin had a reduction in blood Phe concentration of 30% or more after 6 weeks (95% CI 28-60), compared to 4/47 (9%) of patients in the placebo arm (95% CI, 2-20) (p=0.0002).

In SPARK, a Phase IIIb RCT to evaluate the safety and efficacy of sapropterin in PKU patients aged under 4 years, the primary endpoint was Phe tolerance, or the amount of natural Phe patients with PKU can consume whilst maintaining their blood Phe levels. In the intention-to-treat population (n=56), at 26 weeks, the adjusted Phe tolerance was 80.6±4.2 in the sapropterin+diet group (n=27) (vs. 37.1±17.3 mg/kg/day at baseline) compared 50.1±4.3 mg/kg/day (vs. 35.8±20.9 mg/kg/day at baseline) in the diet-only group. 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).

Compelling long-term, real world data in more than 2,700 PKU patients from the ongoing registry studies PKUDOS and KAMPER highlight the long-term (up to 6-7 years of treatment) benefits of sapropterin treatment when used as an adjunct to a low Phe diet, including sustained and clinically meaningful Phe reduction and the ability to eat more natural protein.

In PKUDOS, subjects continuously exposed to sapropterin since registry enrolment had an average 34% decrease in blood Phe from baseline over a period of 5 years (p = 0.0009) and a 54% increase in their ability to consume, or tolerate, dietary Phe after 6 years.

As stated above, the relevant comparator is lifelong adherence to a restricted protein diet. Direct comparative clinical evidence is available from the Phase IIIb SPARK study, which compared the efficacy and safety of sapropterin administered in conjunction with a Phe-restricted diet vs. a Phe-restricted diet alone. Similarly, the PKUDOS registry provides a series of cross-sectional data cuts over the long-term comparing sapropterin treatment in responsive patients to a cohort of non-responders on diet only. Other data comparing the clinical benefits and adverse effects of sapropterin treatment vs. placebo

are also available from the Phase III, IIIb and IV studies. These data are used to populate the economic model and so no indirect treatment comparison has been performed.

The safety of sapropterin treatment has been evaluated across the full clinical development programme for a total period of period of more than 10 years; safety data continue to be collected in the ongoing studies.

In totality, the long-term real-world evidence and historical clinical trial data consistently demonstrate the benefits of sapropterin in both paediatric and adult patients across a range of outcomes, including clinically relevant improved and sustained Phe control and the ability to eat natural protein without affecting blood Phe levels. Continuous use of sapropterin is associated with improved and sustained Phe control and improved Phe control is associated with reduced neuropsychiatric complications. Sapropterin is well-tolerated with a manageable safety profile.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

Appendix G details the systematic searches performed to identify relevant economic data. The search strategies are provided within this appendix. Appendix G also describes and compares the methods and results of the identified cost-effectiveness analyses for the technology and/or the comparator.

The cost-effectiveness studies identified are summarised in **Error! Reference source not found.**.

Table 40: Summary list of published cost-effectiveness studies

Study, year, reference	Year	Summary of model	Patient population (average age in yrs)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER per QALY gained
Mlcoch et al. 2016a/b(115, 116) AB and POS	2016	Payer perspective, lifetime CUA Markov model, 1 yr cycle length, costs and outcomes discounted at 3%, 3 HSs (on diet, non-compliance to diet (mental retardation), death)	Pts with PKU requiring lifetime RPD, mean age NR	RPD reimbursed: 23.16 RPD non-reimbursed 22.35	RPD reimbursed: EUR €16.235 RPD non-reimbursed: EUR €0	€19.955
TLV 2017 HTA evaluation summary	2017	Payer perspective (no indirect costs), lifetime horizon, landmark model, 1 yr cycle length, 5 HSs (controlled, partially controlled, uncontrolled, asymptomatic, death)	Children and adults with HPA due to PKU with genetic conditions responding to Kuvan who do not achieve an adequate response to dietary treatment alone	NR	NR +	SEK 286,353 Accepted by TLV

NCPE 2017(117) HTA evaluation summary	2017	Payer perspective, 100-yr time horizon, decision analytic model, cohort-based Markov-type model, after BH4 response test responders move to recursive Markov part of model, 1 yr cycle length, 5 HSs (controlled, partially controlled, uncontrolled, asymptomatic, and death), half cycle correction applied	Pts with HPA due to PKU, uncontrolled or partially controlled (mean age NR)	Incremental QALY (sapropterin + Phe-RD vs Phe-RD): 252.59	Incremental cost (sapropterin + Phe-RD vs Phe-RD): EUR €8,749,188	34,638 (BC – 20% Phe toler.)
SMC 2018(118) SMC evaluation	2018	Payer perspective, 100-yr time horizon, decision analytic model (during 4-week period of testing responsiveness) and, for responders, Markov model, 1 yr cycle length, 5 HSs (controlled, partially controlled, uncontrolled, asymptomatic, and death)	Pts 0-18 yrs with HPA due to PKU, uncontrolled (elevated Phe with symptoms) & partially controlled (Phe in target with symptoms), sapropterin-responsive, & maternal PKU females	NR	NR	Not CE

+Incremental costs NR. Average cost of sapropterin: SEK 1,080,000/patient/year. Average cost of diet SEK 167,065/patient/year. Cost of visit to dietitians and specialists given per visit and number of visits per HS reported.
Abbreviations: AB, abstract; BC, basecase; CE, cost-effective; CUA, cost-utility analysis; EUR, euros; HPA, hyperphenylalaninaemia; HS, health states; ICER, incremental cost-effectiveness ratio; NCPE, National Centre for Pharmacoeconomics (Ireland); NR, not reported; Phe, phenylalanine; Phe-RD, phenylalanine restricted diet; POS, poster; pts, patients; QALYs, quality-adjusted life years; RPD, restricted protein diet; SMC, Scottish Medicines Consortium; toler., tolerance; uos, unless otherwise stated; yr, year; yrs, years

B.3.2 Economic analysis

Patient population

Conceptually, the patient population of interest is as stated in the SmPC and decision problem, namely for the treatment of HPA in patients of all ages, with phenylketonuria PKU who have been shown to be responsive to treatment with sapropterin dihydrochloride (119).

Based on the scope agreed with NICE, the following populations are captured in the economic model:

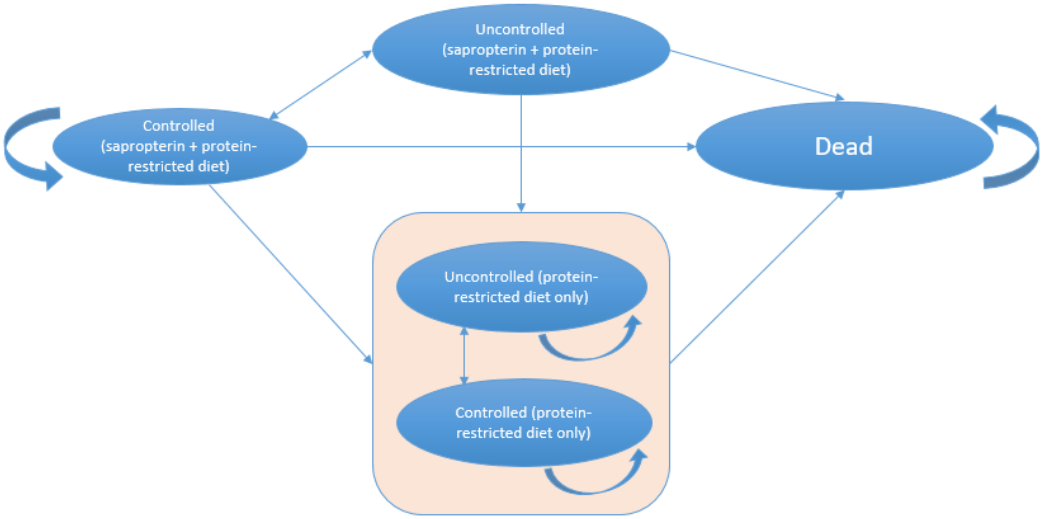
- 0 to 4 years old
- 0 to 12 years old
- 0 to 17 years old
- 5 to 12 years old
- 13 to 17 years old
- Adults (≥18 years old)
- Women of childbearing age (defined as 18 to 40 years old)
- All years (base case)

Of these, the base-case patient population considered in this economic evaluation comprises controlled PKU patients starting treatment from four weeks of age, who were shown to be responsive to sapropterin treatment during the response testing period and who are treated for the duration of their lifetime (i.e. the all years group). It was considered imperative to capture the cost-effectiveness of sapropterin treatment when taken immediately after the completion period, because PKU is diagnosed by newborn screening, and babies must begin treatment immediately to prevent irreversible brain injury (further information is provided in Section B.1.3). Cost-effectiveness results for all the other patient populations are also reported in this submission.

Model structure

A decision analytic Markov model was developed in Microsoft Excel®, with the overall structure shown in **Error! Reference source not found.**.

Figure 36: Schematic representation of the Markov model



The model uses a cycle length of one year to estimate the transition of a hypothetical cohort of PKU patients through the following five health states:

- Controlled (sapropterin in conjunction with a protein-restricted diet).
- Uncontrolled (sapropterin in conjunction with a protein-restricted diet).
- Controlled (protein-restricted diet only).
- Uncontrolled (protein-restricted diet only).
- Death.

As described in Section B.1.3, uncontrolled PKU is defined by Phe levels being above the target Phe levels described in the European PKU guidelines (9). Controlled PKU is defined by Phe levels being within the target range. Therefore, if a patient is within one of the 'uncontrolled health' states, their Phe is not in the target range and

symptoms are present. In contrast, a ‘controlled’ health state represents Phe within the target range, with no symptoms experienced.

Because all patients within the sapropterin treatment cohort are assumed to have been responsive to sapropterin treatment within the four-week testing period, they enter the model in the controlled state, and can potentially move between all health states (with or without sapropterin) or to the death state. It was assumed patients within the protein-restricted diet only cohort can move between the two diet only health states or to the death state.

The model was constructed from the perspective of the NHS and Personal Social Services (PSS) in England and Wales. A lifetime horizon was adopted to capture all relevant costs and health-related utilities, with all costs and utilities discounted at a rate of 3.5% per year in alignment with the NICE guide to methods of technology appraisal (120).

The key features of the economic model are summarised in **Error! Reference source not found.**. There have been no previous NICE appraisals in this indication, and therefore, a comparison with historical designs and outputs was not possible.

Table 41: Features of economic analysis

Current appraisal	Chosen values	Justification
Model structure	Markov model	The model structure captures the impact of distinct resource use and patient HRQoL associated with each health state and allows for a cost-utility analysis over an extended time horizon.
Time horizon	Lifetime	Considered long enough to reflect all important differences in costs or outcomes between the technologies being compared.
Half-cycle correction	A half-cycle correction was implemented	Compensates for the fact that transition between health states are modelled to occur at the beginning or end of a cycle, whereas on average, transition between health states occurs in the middle of a cycle.
Cycle length	One year	This was the shortest cycle length considered practical, given the lifetime time horizon of the model.
Treatment waning effect	Natural attrition is included in the model	Annual natural attrition rates were included in the controlled and uncontrolled state to reflect what was observed in routine clinical practice. Exclusion of these values was explored in a sensitivity analysis.
Source of utilities	Elicitation of values from a sample of the overall Swedish population	Sample size and scope of work as well as a paucity of published information meant this was the best available source.
Source of costs	NHS reference costs (121), PSSRU (122), BNF (123), MacDonald (32)	Consistent with the NICE reference case.
Treatment-related adverse events (TRAE)	Not included	The rate of adverse reactions in the clinical development programme for sapropterin was low (see Section B.2.10). Therefore, adverse events are not a key driver of cost-effectiveness.
Mortality	General population mortality with no adjustment.	Not enough evidence to support the hypotheisis that there is an impact of the underlying condition on overall survival.

Abbreviations: BNF: British National Formulary; EQ-5D: EuroQol five-dimension scale; HRQoL: health-related quality-of-life; NICE: National Institute for Health and Care Excellence; PSSRU: Personal Social Services Research Unit; TRAE: treatment-related adverse events.

Intervention technology and comparators

The interventions considered in all patient populations are:

- Sapropterin dihydrochloride in conjunction with a protein – restricted diet.
- A protein–restricted diet only.

Average sapropterin daily doses of 10mg mg/kg per day for paediatric patients (0-17 years of age) and 12.5mg/kg per day adult patients (≥18 years of age) was assumed for the purpose of costing. These doses were informed by the dosages used in the clinical trial programme and align with the content of the IIA report produced by NHS England (4).

Patients within the sapropterin cohort will take the treatment in conjunction with a restricted protein diet. This consists of Phe-free food items combined with protein supplements. Further information on the restricted protein diet is provided in Section **Error! Reference source not found.**.

As outlined in Section B.1.3, a protein restricted diet is the only current treatment for PKU available for patients in the UK. Therefore, the relevant comparator is a restricted protein diet only.

Starting age and treatment duration used in each of the patient populations

Each of the eight populations outlined above are subject to a specific starting age for sapropterin and treatment duration. The starting ages and treatment durations applied in the model for each population is outlined in **Error! Reference source not found.** below. As explained in Section B.1.3, it is imperative for PKU to be treated from birth in order to prevent intellectual disabilities and other health problems. For this reason, the lower bound age in each population category is assumed to be the starting age of sapropterin. The upper bound age of each population is assumed to be the age at which treatment is discontinued and all patients move to restricted diet only. For the adult and all years populations, treatment is assumed to be administered for life.

Table 42: Starting age and treatment duration

Population	Starting age	Treatment duration
0 to 4 years old	0	5 years
0 to 12 years old	0	13 years
0 to 17 years old	0	18 years

All years	0	Lifetime
5 to 12 years old	5	8 years
13 to 17 years old	13	5 years
Adults	18	Lifetime
Women of childbearing age	18	1 year

Quantification of non-health care related costs and benefits

As described in Section B.1.3, adherence to dietary treatment is essential, with careful planning, dietary supervision and monitoring required. Adherence to this treatment regimen is extremely demanding, with required tasks including planning daily Phe consumption, preparing low-Phe meals and monitoring Phe intake (82). This regimen is very time consuming for parents and caregivers who manage the PKU lifestyle on top of regular childcare, and often results in parents having to reduce working hours (32) (see Section B.1.3).

Furthermore, the productivity of adults with PKU may be hindered by their condition. Common PKU symptoms which may hinder ability to perform physical work include seizures, tremors, malformation of hands and eczema. Mental defects caused by PKU, such as ADHD may also prevent a patient with PKU from remaining within stable education and employment due to a lack of concentration, even when performing labour-orientated jobs (124).

The economic model has the functionality for the wider societal burden of PKU to be incorporated into the cost-effectiveness analysis. The disutility and productivity loss experienced by patients of whom have a child with PKU has been captured within the economic model, alongside the productivity loss of adults with PKU. These values are not included in the base case in order to comply with the NICE reference case and have been separately demonstrated as part of the DSA in Table 64.

B.3.3 Clinical parameters and variables

Treatment effectiveness

Transition probabilities for patients moving between different health states were derived from the PKUDOS registry (see Section B.2.3.3), with the methodology used to derive the values used in the model presented in Appendix M.

Annual transition probabilities over the six year treatment for each of the two treatment options are presented in **Error! Reference source not found.** to **Error! Reference source not found.**. For completeness, the economic model has the functionality to have different transition values for each treatment in years one to six. This functionality could become important in the future if more data emerged on which to base the transition values.

The transition probabilities from the PKUDOS registry for the age group 0 to 12 years are presented in **Error! Reference source not found.** below. These transition probabilities were applied to all patient populations where treatment starts at age zero, excluding the all years population.

Table 43: Annual transition matrices used in the base-case analysis (0 to 12 years)

	Sapropterin + restricted diet: Controlled	**Sapropterin + restricted diet: Uncontrolled**	**Restricted diet only: Controlled**	**Restricted diet only: Uncontrolled**
Sapropterin + restricted diet: Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Sapropterin + restricted diet: Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
Restricted diet only: Controlled	[redacted]	[redacted]	[redacted]	[redacted]
Restricted diet only: Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]

The transition probabilities from the PKUDOS registry for the age group 13 to 18 years are presented in **Error! Reference source not found.** below. These transition probabilities were applied to the 13 to 17 years population.

Table 44: Annual transition matrices used in base case analysis (13 to 18 years)

	Sapropterin + restricted diet: Controlled	Sapropterin + restricted diet: Uncontrolled	Restricted diet only: Controlled	Restricted diet only: Uncontrolled
*Sapropterin + restricted diet: Controlled	[redacted]	[redacted]	[redacted]	[redacted]
*Sapropterin + restricted diet: Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
*Restricted diet only: Controlled	[redacted]	[redacted]	[redacted]	[redacted]
*Restricted diet only: Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]

The transition probabilities from the PKUDOS registry for the age group ≥19 years are presented in **Error! Reference source not found.** below. These transition probabilities were applied to both adult populations.

Table 45: Annual transition matrices used in base case analysis (≥19 years)

	Sapropterin + restricted diet: Controlled	Sapropterin + restricted diet: Uncontrolled	Restricted diet only: Controlled	Restricted diet only: Uncontrolled
*Sapropterin + restricted diet: Controlled	[redacted]	[redacted]	[redacted]	[redacted]
*Sapropterin + restricted diet: Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
*Restricted diet only: Controlled	[redacted]	[redacted]	[redacted]	[redacted]
*Restricted diet only: Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]

Natural attrition rate (sapropterin)

The economic model includes a treatment attrition rate, whereby a given percentage of individuals in the controlled health state [redacted] of sapropterin patients stop taking treatment annually and transition to a protein-restricted diet only. The reasons for such natural attrition could include, for example, personal preference or sub-optimal clinical outcomes. This was based on the number of PKU patients discontinued from sapropterin at an interim point in the analysis from the KAMPER registry (2017) (110).

It was also assumed that if a patient starts a given model cycle in the 'uncontrolled (sapropterin in conjunction with a protein-restricted diet)' health state and remains uncontrolled for a year, they transition to 'Phe-diet only'. The distribution between controlled and uncontrolled aligned with the relevant transition probability for diet only in the relevant year.

Mortality

General population all-cause mortality was included in the model to capture the number of deaths, based on life tables for England and Wales (125). Age and gender stratified rates were used, such that the rates changed as the cohort included in the model aged. The patient cohort enter the model at birth, replicating the patient population described in Section **Error! Reference source not found.**. With the exception of the female of childbearing age cohort, the prevalence of PKU is balanced between genders so the mortality rates were based on a 50:50 split of males and females (126).

As the impact of PKU on the risk of mortality is unclear, given the relevant population of the analysis (i.e. patients who have be shown to be responsive to such treatment), no increased risk of mortality was modelled.

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

None of the clinical trials with sapropterin in Section B.2 measured health-related quality-of-life (HRQoL). HRQoL data has, therefore, been identified from a comprehensive systematic review of the literature.

Health-related quality-of-life studies

Published studies

Appendix H details the systematic searches performed to identify relevant HRQoL data. The results along with the search strategies are also provided within this appendix.

Unpublished studies

BioMarin undertook a time trade off (TTO) study in Sweden to elicit general population preferences for a range of health states relating to PKU. Overall, 3,096 individuals were contacted to take part in the study, with 1,016 (33%) completing the survey. The summary characteristics of these individuals is presented in **Error! Reference source not found.** below.

Table 46: Characteristics of the complete respondents

Characteristic	Mean value
Mean age (Std.Dev.)	50 (18)
Females	56%
More than one adult in household	65%
Child in household	31%
University education for at least 3 years	35%
Mean gross household income per month (SEK)	45,950
Experience of PKU	2%
Utility for PKU based on VAS rating	0.49
Utility for own health based on VAS rating	0.77
Expected difficulty following PKU diet on 5-point scale (5=very difficult)	4.07
Perceived difficulty answering the questionnaire on 5-point scale (5=very difficult)	3.38

Individuals were asked to choose between being in a less than perfect health state for the remainder of their lifetime (t) or choosing to be in a perfect health state for a shorter period of time (t-x). The utility of the less than perfect health state (e.g. PKU) is elicited by dividing time with perfect health by time with less than perfect health ((t-x)/t) when the respondent is indifferent between the two. The application of the TTO method in

this study is in line with the widely used and accepted guidelines for deriving utilities for the EQ-5D-5L (127, 128). The TTO approach has been found to be easier for the respondent to accept and understand compared to Standard Gamble (SG), since it does not involve the (hypothetical) immediate risk of death. The TTO approach is also less prone to upward bias compared to SG (129).

Full details of the methods used to elicit the values used in the model are presented in Appendix H.

The health state utilities elicited from this study are reported in **Error! Reference source not found.** below. The 'no symptoms, no diet restriction' health state was used as the basis for all decrement calculations.

Table 47: TTO based health state utilities derived from the Swedish general population

	Characteristic	Mean value	Decrement*
1	*No symptoms and no diet restriction	[redacted]	[redacted]
2	*No symptoms, partially restricted diet without medical food.	[redacted]	[redacted]
3	*No symptoms, partially restricted diet with medical food	[redacted]	[redacted]
4	*No symptoms, restricted diet with medical food	[redacted]	[redacted]
5	*Mild symptoms, restricted diet with medical food	[redacted]	[redacted]
6	*Moderate symptoms, restricted diet with medical food	[redacted]	[redacted]
7	*Severe symptoms, restricted diet with medical food	[redacted]	[redacted]

* relative to health state one, which has been used as the baseline for all of these calculations.

Health-related quality-of-life data used in the cost-effectiveness analysis

Sweden is broadly similar to the UK in terms of genetics, geographic closeness and ethnic composition. Thus, the Swedish data were used in the base case analysis.

The Swedish study described above provided information that could be used to inform health state utility values for adults with PKU but not directly for children. The information from Sweden was also of limited use in quantifying the impact of PKU on the parents/ caregivers of children with the condition. We therefore convened and

undertook a combination of expert panel meetings and clinician surveys whereby UK based experts were asked to provide insights into how different the utility values in these key groups would be compared to the Swedish adult data. Information on the participants in this expert elicitation activity, the methods used to elicit the values and the outputs from this study are presented in Appendix H.

The values derived for the group for children with PKU as well as their parents/ caregivers are presented in **Error! Reference source not found.** and **Error! Reference source not found.** below. As with the adult Swedish data, scenario 1 is used as the baseline for all utility decrement calculations.

Table 48: TTO based health state utilities for children with PKU

	Characteristic	Mean value	Decrement
1	*No symptoms and no diet restriction	[redacted]	[redacted]
2	*No symptoms, partially restricted diet without medical food.	[redacted]	[redacted]
3	*No symptoms, partially restricted diet with medical food	[redacted]	[redacted]
4	*No symptoms, restricted diet with medical food	[redacted]	[redacted]
5	*Mild symptoms, restricted diet with medical food	[redacted]	[redacted]
6	*Moderate symptoms, restricted diet with medical food	[redacted]	[redacted]
7	*Severe symptoms, restricted diet with medical food	[redacted]	[redacted]

Table 49: TTO based health state utilities for parents/ caregivers of children with PKU

	Characteristic	Mean value	Decrement
1	*No symptoms and no diet restriction	[redacted]	[redacted]
2	*No symptoms, partially restricted diet without medical food.	[redacted]	[redacted]
3	*No symptoms, partially restricted diet with medical food	[redacted]	[redacted]
4	*No symptoms, restricted diet with medical food	[redacted]	[redacted]
5	*Mild symptoms, restricted diet with medical food	[redacted]	[redacted]
6	*Moderate symptoms, restricted diet with medical food	[redacted]	[redacted]
7	*Severe symptoms, restricted diet with medical food	[redacted]	[redacted]

In order to map these values onto the two health states in the model we made the assumption that ‘controlled PKU’ would correspond to a mixture of scenarios 2,3,4 and

'uncontrolled PKU' would correspond to scenarios 5,6,7. In absence of any information on the proportion of individuals in each of the six scenarios in the UK population, we used the assumption that a simple average value for scenarios 2,3,4 would be used for the 'controlled PKU' health state. Similarly, a simple average value of scenarios 5,6,7 would be used for the 'uncontrolled PKU state'. The values used in the model are summarized in **Error! Reference source not found.** below, with functionality included to allow the user to select any of the individual scenarios for each of the health state. The model also contains the functionality to have no value assigned to parents/ caregivers for either controlled PKU, uncontrolled PKU, or both.

Table 50: Utility decrements used in the base case analysis

	Children[a]	**Adults[b]**	**Parents/ caregivers[a]**
*Controlled PKU	[redacted]	[redacted]	[redacted]
*Uncontrolled PKU	[redacted]	[redacted]	[redacted]

a) Value applied to patient groups 0-4, 4-12, 13-18; b) values applied to all adults as well as females of childbearing age.

Use of the other unpublished study in the cost-effectiveness model (scenario analyses)

Excluding information on patients with sapropterin treatment, for children, we assumed a 50%/50% spread across the Mild/moderate controlled and severe controlled health states leading to a decrement for controlled PKU of -0.07. The respondents showed additional benefits of sapropterin in both patient groups and so we used a simple average of the three increments in these groups in the model and applied this to all patient populations regardless of age. The values used to inform a sensitivity analyses are therefore as shown in **Error! Reference source not found.** below.

Table 51: Alernative utility decrements (scenario analysis only)

	Children[a]	Adults[b]	Parents/ caregivers[c]
*Controlled PKU	[redacted]	[redacted]	See footnote
*Uncontrolled PKU	[redacted]	[redacted]	See footnote
*Treatment with sapropterin	[redacted]		

a) Value applied to patient groups 0-4, 4-12, 13-18; b) values applied to all adults as well as females of childbearing age; c) values not elicited in study so base case values carried forward

Comparison of base case decrements with other values identified in the systematic review

As noted in Appendix G, five studies reported utility values within the PKU population. **Error! Reference source not found.** below reproduces these data and also the corresponding utility decrements for health states. Comparison of the controlled and uncontrolled decrements in this table, particularly the ones generated by Pastores et al. using the EQ-5D instrument are comparable to the values used in the model for in adults. The information from Pastores et al. for children leads to a higher decrement than being used in the economic model. Hence, the base case decrements appear aligned with the totality of the available literature.

Table 52: Utilities reported within the PKU population

Study	Health state - full description	Mean value	Decrement
Autti-Rämö et al. (130)	PKU - Best screening effect	0.92	N/A[a]
	PKU - Best current practice	0.64	-0.28
	PKU - Worst current practice	0.58	-0.34
Hatam et al. (131)	PKU - screened (detected & treated early)	0.85	N/A[a]
	PKU - unscreened (severe mental retardation)	0.40	-0.45
Pastores et al.(132)	PKU in adult, controlled (Phe in target range) and no symptoms	1.00	N/A[a]
	PKU in adult, controlled (Phe in target range) and no symptoms	0.84	N/A[b]
	PKU in adult, uncontrolled	0.54	-0.46
	PKU in adult, uncontrolled	0.57	-0.27
	PKU in child, controlled (Phe in target range) and no symptoms	0.92	N/A[a]
	PKU in child, uncontrolled	0.39	-0.53
Thiboonboon et al. (133)	PKU - screened (detected & treated early) without long-term complication	0.71	N/A[a]
	PKU - with mental retardation	0.13	-0.58

a) Used as the baseline for all calculations; b) used as the baseline for all SF-6D calculations

Adverse reactions

Adverse reactions, including the impact on HRQoL, were not explicitly modelled as part of the analysis.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Appendix I details the systematic searches performed to identify relevant cost and healthcare resource data.

Intervention and comparators' costs and resource use

Sapropterin dose used in the model

The daily dose of sapropterin is informed by patient body weight (see Appendix L). Therefore, a standard weight by age table has been used within the economic model using data from the British National Formulary. Within the base-case analysis, the number of tablets of sapropterin prescribed annually is based on the SmPC (3).

As per the product SmPC (3), there is not a fixed dose for each of the age groups but a recommended range (starting dose 10mg/kg per day and then titrated to 5 to 20mg/kg qd based on patient needs). There has been a range of doses used in relevant clinical studies with values representing the whole of this range reported. The average dose used in the KAMPER study was 12.7mg/kg per day (although this was based on a population with a mean age of 10.3 years, 42% of which were over 12 and 18% were adults). The dosing information from the SPARK study is also in the public domain. All patients in this study who received sapropterin began on a dose of 10mg/kg qd and 92.6% of particapants maintained that dose post four weeks.(48)

In order to align this submission with the contents of the integrated impact assessment report for clinical commissioning policies prepared by NHS England we have used average doses of 10 mg/kg per day for all pediatric groups (0 to 17 years of age) and 12.5 mg/kg for adults (≥18 years of age)(4). The model includes sapropterin in the form of a soluble tablet, rather than the powder, as this is the only formation of the drug with cost data available

In calculating the number of tablets used per year we have applied (in line with the SmPC for sapropterin) a rounding function with works out the nearest whole number of tablets required. This, if a patient needed 140mg of sapropterin they would receive one tablet for the purpises of costing whereas if they needed 160mg of sapropterin they would receive two tablets.

Drug acquisition costs

We have used a pack price of £597.22 for thirty tablets (100mg per tablet) in the model which corresponds to a tablet price of £19.91 as per the BNF. We have also included a commercial arrangement as part of this submission. The structure of which is a simple discount on the NHS list price of of sapropterin of [redacted]*.

Cost of protein-restricted diet

Protein supplements

The total cost of a restricted protein diet is made up of two components: the cost of the low protein food and the cost of protein supplements. This was calculated in December 2018 by Prof. Anita Macdonald. Based on the average cost of three brands, the cost per annum of protein supplements for adults with a daily requirement of [redacted] and [redacted] protein are [redacted] and [redacted], respectively. These costs were averaged to derive a cost of [redacted] which is used in the model.

Based on the average cost of two brands, the cost of protein supplements for a three-year-old child weighing [redacted], with a [redacted] daily protein substitute requirement is [redacted]. The corresponding cost for a seven-year-old child weighing [redacted], with a [redacted] protein substitute requirement was [redacted]. The cost for children up to four years old is more expensive due to gels and pastes being used as protein supplements rather than liquids (32).

The annual costs of protein supplement per patient are presented in **Error! Reference source not found.** to **Error! Reference source not found.**. It was assumed that the daily requirement of protein substitute remains constant from zero up to four years old (using the cost for a three-year-old), and then from four years up to 18 years old (using the cost for a seven-year-old).

Comparison of these values with published sources is challenging due to the lack of relevant papers, but a study by Belanger et al. does contain comparable information (41). Based on information generated relative to a cost year of 2009, the authors concluded that the mean annual cost of protein substitues for individuals who were two, eight, fifteen and thirty years old were €5,484, €9,519, €13,278 and €18,777 respectively. Allowing for differences in currency and the large amount of elapsed time, these values are broadly aligned with those calculated by Professor Anita Macdonald.

Table 53: Unit costs used to estimate the annual cost of protein supplements per patient: Adults (32) (Table below is AIC)

Daily requirement	Price per annum
[redacted]	[redacted]
[redacted]	[redacted]
Average cost for [redacted] requirement	[redacted]

Table 54: Unit costs used to estimate the annual cost of protein supplements per patient: Children (32) (Table below is AIC)

Daily requirement	Age	Price per annum
[redacted]	0 up to 4 years old	[redacted]
[redacted]	4 up to 18 years old	[redacted]

Low protein food

The annual costs for low protein foods for adults and children are presented in **Error! Reference source not found.** to **Error! Reference source not found.**. This is based on weekly requirements for bread, flour, milk, pasta, pizza base and sausage/burger mix for an adult, three-year-old child weighing 14kg, and a seven-year-old child weighing 22kg. It was assumed that the daily requirement of low protein food remains constant from zero up to four years old (using the cost for a three-year-old) and then from four years up to 17 years old (using a cost for a seven-year-old).

Table 55: Annual costs for low protein food – Children 0 up to 4 years old (32)

Low protein food	Weekly requirement	Price per annum
Bread	280g	£145
Flour	250g	£182
Milk	600ml per day (21 cartons a week)	£1,391
Pasta	125g	£112
Pizza base	0.5	£112
Sausage mix/burger mix	50g	£133

Table 56: Annual costs for low protein food – Children 4 up to 17 years old (32)

Low protein food	Weekly requirement	Price per annum
Bread	560g	£290
Flour	500g	£364
Milk	400ml a day (14 cartons a week)	£927
Pasta	250g	£224
Pizza base	1	£224
Sausage mix/burger mix	100g	£265

Table 57: Annual costs for low protein food - Adults

Low protein food	Weekly requirement	Price per annum
Bread	800g	£416
Flour	500g	£364
Milk	400ml a day (14 cartons a week)	£927
Pasta	250g	£224
Pizza base	1	£224
Sausage mix/burger mix	100g	£265

The impact of sapropterin on low protein food usage

It is anticipated that a proportion of patients within the 'Controlled (sapropterin in conjunction with a protein-restricted diet)' health state will relax this strict protein restricted diet and the use of protein supplements.

The parameter estimate was based on on a survey of 291 sapropterin responders in eight PKU centres across Europe. These individuals were spread across all age groups from infant to adult (134). Across these individuals 82 (28%) did not require any form of diet supplement following treatment and the average reduction in specialist diet usage across the remaining patients was 60%. Hence, we have used a value of 71.2% in all patient groups ([28%*100%] + [72%*60%]).

This value is aligned with information recorded in the PKUDOS study (97) where there was a consistent and statistically significant difference in diet usage in patients with short term and continuous sapropterin usage. Across all years, the mean reduction in food usage was 54%, with a value of 68% being recorded in year six. Hence, the value observed when comparing continuous use sapropterin with no active treatment should be higher than either of these values.

Health-state unit costs and resource use

Error! Reference source not found. presents the unit costs of resource use within the economic modelling. This includes the cost of a GP consultation, an outpatient appointment and a specialist outpatient appointment for both children and adults. The GP consultation cost was based on a 9.22 minute appointment and sourced from the PSSRU (122).

The cost of an outpatient appointment and specialist outpatient appointment was based on the cost of an average outpatient non-consultant led and consultant led appointment, respectively, sourced from NHS reference costs (135). An average cost was used due to a lack of a discrete outpatient specialty code to use as a proxy for adults. For children, however, service codes for a non-consultant led and consultant led paediatric metabolic disease consultation were available. These costs are considerably higher than the cost of an average adult appointment due to the higher resource use involved in treating children compared to adults. However, it was decided that the same costs would be used for both adult and children.

Table 58: Resource use unit costs

	Value	**Source**
GP consultation (122)	£39.23	PSSRU 2019
Specialist outpatient appointment (consultant led appointment)	£144.39	NHS reference costs 2018/19 (121)
Outpatient appointment (non-consultant led average)	£83.72	NHS reference costs 2018/19 (121)

Error! Reference source not found. and **Error! Reference source not found.** presents the mean annual number of healthcare visits used in the economic model for each population in the controlled and uncontrolled health states, respectively. These numbers were derived from a panel of clinical experts in England, conducted in June 2020 (136), for the paediatric (0 to 17 years) and adult (≥18 years) populations. The

frequency of appointments for the 0 to 17 years population was applied to all the paediatric populations.

Table 59: Mean annual number of healthcare visits for each population – controlled health state (136)

Population	GP	Outpatient appointment	Specialist outpatient appointment
0 to 4 years old	4.3	2.7	1.3
0 to 12 years old	4.3	2.7	1.3
0 to 17 years old	4.3	2.7	1.3
5 to 12 years old	4.3	2.7	1.3
13 to 17 years old	4.3	2.7	1.3
Adults	5.3	1.6	0.6
Women of childbearing age	3.0	2.0	3.0
All years	5.3	1.6	0.6

Table 60: Mean annual number of healthcare visits for each population – uncontrolled health state (136)

Population	GP	Outpatient consultant	Outpatient Specialist consultant
0 to 4 years old	4	3.3	4

0 to 12 years old	4	3.3	4
0 to 17 years old	4	3.3	4
5 to 12 years old	4	3.3	4
13 to 17 years old	4	3.3	4
Adults	6.0	2.3	0.9
Women of childbearing age	3.0	2.0	2.0
All years	6.0	2.3	0.9

Treatment related severe adverse reaction unit costs and resource use

As described previously, TRAEs have not been included in the analysis so no costing inputs relating to these events were modelled.

Miscellaneous unit costs and resource use

No other health care resources were included in the analysis.

Non-health care related costs and resource use.

As aforementioned (in Section **Error! Reference source not found.**), the economic model has the functionality for the wider societal burden of PKU to be incorporated in the cost-effectiveness analysis.

The productivity loss of both parents of children with PKU, and adults with PKU has been estimated to quantify the economic burden of PKU from a societal perspective. We have assumed that every PKU patient under the age of 18 requires day-to-day parental support to help manage their condition, and once a patient reaches the age of 18, they no will longer require this level of supervision.

A study estimating the personal burden for caregivers of children with PKU found that a proportion of parents will leave their employment completely in order to care for their child, whilst a proportion will reduce their working hours (82). It was assumed that the reduction in hours worked was dependent upon the PKU status of patients (i.e. uncontrolled or uncontrolled), but not treatment specific. The proportions of parents leaving employment or choosing to reduce working hours identified from this study were applied to patients in the uncontrolled health states. These values were decreased by 20% for patients in the controlled health states, to reflect the assumption that patients in the controlled health states would require less care and/or strict management.

Once an individual with PKU reaches the age of 18 years, and until they reach the national retirement age of 67, it has been assumed that they are eligible to work full time, and therefore the economic burden of leaving work, or reducing hours due to PKU has been estimated using the same values as for the parents. Mental defects caused by PKU, such as ADHD (53), reduced performance in working memory tasks, and cognitive flexibility (17, 18, 20) may prevent a patient with PKU from remaining within stable education and employment due to a lack of concentration, even when performing labour orientated jobs (124).

Productivity loss was derived using the average wage per hour, calculated using the median UK annual wage (£23,474) and the average hours worked a week (37.4), sourced from the Office for National Statistics ASHE estimates and the average actual weekly hours of work for full-time workers (137, 138). The proportion of parental carers (for patients under 18) and PKU patients (between 18 and 67) leaving work, reducing hours and the number of hours reduced is presented in **Error! Reference source not found.**. The calculated annual productivity cost per year is also shown in **Error! Reference source not found.**.

Table 61: Annual productivity loss for both parents (for patients under 18) and patients (between 18 and 65)

Health State	Parents leaving work	Annual productivity loss: left work	Parents reducing hours	Working hours reduced per week	Annual productivity loss: working hours reduced
Controlled	18.9%	£24,897	16.6%	14.8	£9,879
Uncontrolled	23.6%		20.8%	18.5	£12,348

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

The base-case model parameters are summarised in **Error! Reference source not found.**.

Table 62: Summary of variables applied in the economic model

	Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model settings	Discount rate (costs)	3.5%	N/A	B.3.2
	Discount rate (benefits)	3.5%	N/A	
Patient characteristics	Female	50.0%	N/A	
Transition probabilities (0 to 4 years, 5 to 12 years, 0 to 12 years, and 0 to 17 years populations)	Controlled to uncontrolled: Sapropterin treatment	18%	Dirichlet	B.3.3
	Controlled to uncontrolled: diet only	24%	Dirichlet	
	Uncontrolled to controlled: Sapropterin treatment	33%	Dirichlet	
	Uncontrolled to controlled: diet only	14%	Dirichlet	

Transition probabilities (13 to 17 years population)	Controlled to uncontrolled: Sapropterin treatment	14%	Dirichlet	B.3.3
	Controlled to uncontrolled: diet only	26%	Dirichlet	
	Uncontrolled to controlled: Sapropterin treatment	11%	Dirichlet	
	Uncontrolled to controlled: diet only	7%	Dirichlet	
Transition probabilities (≥18 years, women of childbearing age, and all years populations)	Controlled to uncontrolled: Sapropterin treatment	13%	Dirichlet	B.3.3
	Controlled to uncontrolled: diet only	22%	Dirichlet	
	Uncontrolled to controlled: Sapropterin treatment	17%	Dirichlet	
	Uncontrolled to controlled: diet only	8%	Dirichlet	
Disutility (paediatric populations*)	Controlled	0.124	Gamma	B.3.4
	Uncontrolled	0.347	Gamma	
Disutility (≥18 years and all years populations)	Controlled	0.115	Gamma	
	Uncontrolled	0.482	Gamma	
Disutility (women of childbearing age)	Controlled	0.136	Gamma	
	Uncontrolled	0.392	Gamma	
Disutility for parent/care giver	Controlled	0.177	Gamma	B.3.4
	Uncontrolled	0.463	Gamma	
Utility increment	Sapropterin	0	N/A (assumption)	B.3.4
Relative Risks	Sapropterin	1	Log normal	B.3.3
	Protein-restricted diet	1	Log normal	
Drug dose (paediatric populations*)	Sapropterin	10 mg/kg	N/A	B.3.5
Drug dose (≥18 years, women of childbearing age, and all years populations)	Sapropterin	12.5 mg/kg	N/A	

Drug costs	Sapropterin	£19.91 without PAS. [redacted]*with PAS	N/A	B.3.5
Protein-restricted diet for adults (protein low food plus supplements)	Annual cost	£15,973	N/A	
Protein-restricted diet for children aged 0 up to 4 (protein low food plus supplements)	Annual cost	£10,326	N/A	
Protein-restricted diet for children aged 4 up to 18 (protein low food plus supplements)	Annual cost	£11,820	N/A	
Unit costs: paediatric populations*	Specialist outpatient consultation	£144.39	Gamma	
	Outpatient consultation	£83.72	Gamma	
	GP consultation	£39.23	Gamma	
Unit costs: ≥18 years, women of childbearing age (8 to 40 years) and all years populations	Specialist outpatient consultation	£144.39	Gamma	
	Outpatient consultation	£83.72	Gamma	
	GP consultation	£39.23	Gamma	
Resource use: paediatric populations*	Specialist outpatient consultation controlled	1.3	Gamma	
	Specialist outpatient consultation uncontrolled	4.0	Gamma	
	Outpatient consultation controlled	2.7	Gamma	
	Outpatient consultation uncontrolled	3.3	Gamma	
	GP consultation controlled	4.3	Gamma	
	GP consultation uncontrolled	4.0	Gamma	
Resource use: ≥18 years and all	Specialist outpatient	0.6	Gamma	

years populations	consultation controlled			
	Specialist outpatient consultation uncontrolled	0.9	Gamma	
	Outpatient consultation controlled	1.6	Gamma	
	Outpatient consultation uncontrolled	2.3	Gamma	
	GP consultation controlled	5.3	Gamma	
	GP consultation uncontrolled	6.0	Gamma	
Resource use: Women of childbearing age	Specialist outpatient consultation controlled	3.0	Gamma	B.3.4
	Specialist outpatient consultation uncontrolled	2.0	Gamma	
	Outpatient consultation controlled	2.0	Gamma	
	Outpatient consultation uncontrolled	2.0	Gamma	
	GP consultation controlled	3.0	Gamma	
	GP consultation uncontrolled	3.0	Gamma	
	Reduction in Phe-free diet and protein supplement usage when on sapropterin with controlled PKU	71.2%	Gamma	B.3.5
Productivity loss	Uncontrolled % leaving work	23.6%	N/A	B.3.5
	Uncontrolled % reducing hours	20.8%	N/A	
	Reduction in parents leaving work/reducing hours when in a controlled state	20%	N/A	
	Number of reduced hours uncontrolled	18.5	N/A	

	Number of reduced hours controlled	14.8	N/A	
	Abbreviations: CI, confidence interval *Paediatric populations: 0 to 4 years, 5 to 12 years, 13 to 17 years, 0 to 12 years, 0 to 17 years.			

Assumptions

The assumptions adopted in the analysis are summarized and justified in **Error! Reference source not found.**.

Table 63: Summary of assumptions in base-case analysis

Assumption	Justification
If a patient on sapropterin treatment moved to a "Phe-restricted diet" only health state, they could not take sapropterin in the future.	If a patient chooses to stop taking sapropterin treatment, either due to a lack of effectiveness or by choice, it is unlikely they would start the treatment again.
A lifetime horizon was adopted.	Lifetime used to capture all costs and QALYs associated with each treatment.
No treatment-related severe adverse events were included in the analysis.	The rate of adverse reactions in the clinical development programme for sapropterin was low, with only mild and minimal treatment adverse reactions identified. Therefore, adverse events are not a key driver of cost-effectiveness.
Mortality of the population included in the analysis is not greater than the general population.	There is no evidence of increased mortality for patients with PKU.
Age related stopping rules are applied in each of the patient populations.	The use of different patient populations should lead to more targeted decision making and to ease alignment with clinical practice.

PKU has no impact on non-health care related costs or benefits (either in patients or parental carers).	This assumption has been tested within a scenario analysis.
The starting age of the cohort is 0 years in the base case analysis	PKU is a condition that is diagnosed at birth and needs to be treated with immediate effect to prevent long term brain damage.
PKU is gender agnostic in every patient population except females of childbearing age.	There is no different in likelihood of PKU occurring in boys and girls.
The rate of contact with health care professionals varies by age and control status but not by treatment arm.	Patients with PKU would receive the same monitoring regardless of the treatment they are receiving.
There is an additional HRQoL benefit associated with sapropterin above and beyond what was captured for diet management only.	This assumption has been tested within a sensitivity/scenario analysis.
The dietary requirements for protein supplements and protein low foods remain constant for children aged 0 up to 4 and from 4 up to 18.	Assumption was made to align the model with the only available up to date source of information.

Sensitivity analysis undertaken

Deterministic Sensitivity Analysis

In order to assess the uncertainty around the results, the model includes DSA whereby individual parameters are varied. The parameters varied in the DSA are summarised in **Error! Reference source not found.**. All parameters were varied within the 95% CI, or if this was not available from the original data source, or could not be estimated, then the parameter was doubled/halved, with exception of the number of healthcare visits, which were varied between zero and ten for outpatient and specialist outpatient visits, and zero and 20 for GP appointments.

Table 64: DSA parameter values

Parameter	Base-case	Lower value	Upper value
*Cost of sapropterin	[redacted]	[redacted]	[redacted]
Cost of protein supplements and diet for adults	£15,973	£7,987	£31,946
Cost of protein supplements and diet for children aged 0 up to 4	£10,326	£5,163	£20,652
Cost of protein supplements and diet for children aged 4 up to 18	£11,820	£5,910	£23,640
Reduction in food usage (controlled)	71.2%	50%	100%
Cost of child specialist outpatient visit	£144	£71.50	£289
Cost of adult specialist outpatient visit	£144	£71.50	£289
Cost of child outpatient consultation	£84	£42	£167
Cost of adult outpatient consultation	£84	£42	£167
Cost of GP appointment	£39	£20	£78
Number of GP visits adult controlled	5.30	1	20
Number of GP visits adult uncontrolled	6.00	1	20
Number of GP visits child controlled	4.3	1	20
Number of GP visits child uncontrolled	4.0	1	20
Number of outpatient visits adult controlled	1.60	0	10
Number of outpatient visits adult uncontrolled	2.30	0	10
Number of outpatient visits child controlled	2.7	0	10
Number of outpatient visits child uncontrolled	3.3	0	10
Number of specialist outpatient visits adult controlled	0.60	0	10
Number of specialist outpatient visits adult uncontrolled	0.90	0	10
Number of specialist outpatient visits child controlled	1.3	0	10
Number of specialist outpatient visits child uncontrolled	4.0	0	10
Sapropterin dose 0 to 12 years	10	5	20
Sapropterin dose 13 to 17 years	10	5	20
Sapropterin dose ≥18 years	12.5	6.25	25
Disutility of an uncontrolled state adult	0.482	0.240	0.960
Disutility of a controlled state adult	0.115	0.057	0.230
Disutility of an uncontrolled state child	0.347	0.170	0.690
Disutility of a controlled state child	0.124	0.060	0.250
Utility increment for sapropterin	0	0	0.4
Parent/ caregiver utility decrement - controlled	0.177	0.090	0.350
Parent/ caregiver utility decrement - uncontrolled	0.463	0.230	0.930
Societal burden reduction for controlled parents (vs uncontrolled)	20%	0%	40%
Societal burden reduction for controlled adults (vs uncontrolled)	20%	0%	40%
TP: Controlled to uncontrolled: Sapropterin treatment	12.5%	6.0%	25%
TP: Controlled to uncontrolled: diet only	21.8%	11%	44%

Parameter	Base-case	Lower value	Upper value
TP: Uncontrolled to controlled: Sapropterin treatment	17.4%	9.0%	35%
TP: Uncontrolled to controlled: diet only	7.8%	4.0%	16%
Reduction in productivity loss: uncontrolled to controlled (parents)	20%	0%	40%
Reduction in productivity loss: uncontrolled to controlled (adults)	20%	0%	40%

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis (PSA) was performed to account for multivariate and stochastic uncertainty in the model. A PSA was undertaken with 1,000 model simulations. A full list of all parameters included in the PSA is presented in **Error! Reference source not found.** to **Error! Reference source not found.**. Probability distributions were based on sampling error estimates from data sources, such as confidence intervals. In the absence of data on the variability around the sampling distribution of mean values, the standard error was assumed equal to 25% of the mean, except for disutility values and protein supplement costs where a tenth of the mean was used. Caps were introduced into the model programming to ensure logical consistency is maintained in all simulation runs (e.g. cannot have uncontrolled PKU being more preferential than controlled PKU in terms of utility decrements.)

Dirichlet distributions were used for treatment effectiveness such as transition probabilities, and gamma distributions were used for utility decrements and costs applied in the model.

Table 65: Disutility and utility parameters included in the PSA

Parameter	Base-case	Standard Error	Distribution
*Disutility controlled health state (0-17 years old)	[redacted]	0.012	Gamma
*Disutility controlled health state (≥18 years old)	[redacted]	0.012	Gamma
*Disutility uncontrolled health state (0-17 years old)	[redacted]	0.035	Gamma
*Disutility uncontrolled health state (≥18 years old)	[redacted]	0.048	Gamma

Table 66: Resource use parameters included in the PSA

Parameter	Base-case	Standard Error	Distribution
GP visit adult – controlled	5.300	1.325	Gamma
GP visit adult – uncontrolled	6.000	1.500	
GP visit child – controlled	4.300	1.075	
GP visit child – uncontrolled	4.000	1.000	
Outpatient appointment adult - controlled	1.600	0.400	
Outpatient appointment adult - uncontrolled	2.300	0.575	
Outpatient appointment child - controlled	2.700	0.675	
Outpatient appointment child - uncontrolled	3.300	0.825	
Specialist outpatient adult - controlled	0.600	0.150	
Specialist outpatient adult - uncontrolled	0.900	0.225	
Specialist outpatient child - controlled	1.300	0.325	
Specialist outpatient child - uncontrolled	4.000	1.000	

Table 67: Year one to six treatment arm transition probability parameters included in the PSA (0 to 12 years data)

Transition	Base-Case	Standard Error	Distribution
*TP treatment: Sapropterin controlled to sapropterin controlled	[redacted]	0.044	Dirichlet
*TP treatment: Sapropterin controlled to sapropterin uncontrolled	[redacted]	0.006	
*TP treatment: Sapropterin uncontrolled to sapropterin controlled	[redacted]	0.009	
*TP treatment: Sapropterin uncontrolled to sapropterin uncontrolled	[redacted]	0.041	
*TP diet only: Protein-restricted diet controlled to protein-restricted diet controlled	[redacted]	0.039	Dirichlet
*TP diet only: Protein-restricted diet controlled to protein-restricted diet uncontrolled	[redacted]	0.011	
*TP diet only: Protein-restricted diet uncontrolled to protein-restricted diet controlled	[redacted]	0.004	
*TP diet only: Protein-restricted diet uncontrolled to protein-restricted diet uncontrolled	[redacted]	0.046	

Table 68: other parameters included

Parameter	Base-case	Standard Error	Distribution
Reduction in food usage (controlled)	0.712	0.178	Gamma
Protein supplements child 0 up to 4 years	£10,326	£1,033	Gamma
Protein supplements child 4 up to 18 years	£11,820	£1,182	Gamma
Protein supplements adults	£15,973	£1,597	Gamma

Scenario analyses undertaken

HPA in patients with PKU is a rare condition, and the proportion of patients who are expected to be responsive to sapropterin a subset of these patients. Hence, there is some uncertainty around some of the parameters in the economic model. In addition, the condition is genetic and incurable.

In order to provide the Committee with a range of possible ICERs, the following scenario/ structural uncertainty analyses were performed:

- Using vignette specific utility values for controlled health state instead of average of vignettes
- Using vignette specific utility values for uncontrolled health state instead of average of vignettes
- Using vignette specific utility values for controlled health state instead of average of vignettes – parent/ caregivers
- Using vignette specific utility values for uncontrolled health state instead of average of vignettes – parents/ caregivers
- Inclusion of additional benefit associated with sapropterin
- Exclusion of attrition
- Using utility values from the unpublished UK study
- Varying Kuvan dose

- Altering years on treatment for women of childbearing population

B.3.7 Base-case results

Cost-effectiveness analysis results (base case population)

In the base case analysis, it was assumed that sapropterin is available for all ages and as such have assumed that treatment commences at age four weeks and continues for lifetime (with some individuals stopping treatment beforehand). The cost-effectiveness results for this patient population are presented in Table 69 below. BioMarin have submitted a commercial arrangement to the NHS PASLU of a [redacted] *off the NHS list price for sapropterin.

Sapropterin is more effective than the protein-restricted diet only in terms of quality-adjusted life year (QALY) gains and is associated with lower lifetime costs. Sapropterin is therefore the dominant intervention.

Appendix J contains the disaggregated results of base case incremental cost effectiveness analysis.

Table 69: Base-case results (All years, with PAS) (table below is CIC)

Treatment	Total costs	Total LYG*	Total QALYs	Δ costs	Δ QALYs	ICER (£/QALY gained)
*Sapropterin + Protein-restricted diet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protein-restricted diet	[redacted]	[redacted]	[redacted]			
* Undiscounted values; Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Cost-effectiveness results (all other patient populations)

As noted in section **Error! Reference source not found.**, a range of additional patient populations in the model to cover alternative uses of sapropterin in routine clinical practice was included. The key outputs from these patient populations are summarized in Table 71 below.

All populations where treatment is begun at age 0 generated dominant results (sapropterin plus diet offers more QALYs than diet alone at reduced overall cost). The ICER for 5-12 years was below the generally accepted NICE threshold of £20,000 per QALY gained. Treatment with sapropterin in the 13-17 years, adult, and women of childbearing age populations were above £20,000 per QALY gained, therefore not cost-effective.

Appendix J contains the disaggregated results for each of these patient populations.

Table 70: Base case cost-effectiveness results (other patient populations, with PAS) (table below is CIC)

Patient group	Δ costs	Δ QALYs	ICER (£/QALY gained)
*0-4 years	[redacted]	[redacted]	[redacted]
*0-12 years	[redacted]	[redacted]	[redacted]
*0-17 years	[redacted]	[redacted]	[redacted]
*5-12 years	[redacted]	[redacted]	[redacted]
*13-17 years	[redacted]	[redacted]	[redacted]
*All adults	[redacted]	[redacted]	[redacted]
*Women of childbearing age	[redacted]	[redacted]	[redacted]

Cost-effectiveness analysis results (alternative perspective)

Due to the clinical nature of PKU, and the fact that a substantive proportion of the impact of the condition is largely outside of the traditional scope of a STA, the model can also generate cost-effectiveness results using a wider societal perspective. The detailed results from this analysis for the base case population is presented in Table 71 and for all other patient groups in Table 72.

The base case ICER for sapropterin plus diet is again dominant against protein-restricted diet only with a higher incremental cost saving compared to the ICER without societal perspective [redacted]

As with the base case analysis, all populations where treatment is begun at age 0 generate dominant results (sapropterin plus diet offers more QALYs than diet alone at reduced overall cost). The ICER for 5-12 years was below the generally accepted NICE threshold of £20,000 per QALY gained. Treatment with sapropterin in the 13-17

years, adult, and women of childbearing age populations were above £20,000 per QALY gained.

Table 71: Base-case results (All years, with PAS, societal perspective) (table below is CIC)

Treatment	Total costs	Total LYG*	Total QALYs	Δ costs	Δ QALYs	ICER (£/QALY gained)
*Sapropterin + protein-restricted diet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protein-restricted diet	[redacted]	[redacted]	[redacted]			
* Undiscounted; Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 72: Base case cost-effectiveness results (other patient populations, with PAS, societal perspective) (table below is CIC)

Patient group	Δ costs	Δ QALYs	ICER (£/QALY gained)
*0-4 years	[redacted]	[redacted]	[redacted]
*0-12 years			
*0-17 years			
*5-12 years			
*13-17 years			
*All adults			
*Women of childbearing age			

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis (base case patient population)

A summary of the probabilistic results for sapropterin is presented in Table 73 below, without societal costs and QALYs. All values correspond to the mean and 95% credible intervals (CrI's) from the cost-effectiveness model.

Overall, the results of the PSA are similar to the base-case analysis. Graphical depictions of the simulations are presented in **Figure 37**. For the base case population, at a threshold of £20,000 per QALY gained, there is a 100% likelihood that sapropterin is cost-effective.

Table 73: **Probabilistic cost-effectiveness results (All years, with PAS, all values mean [95% CrI]) (table below is CIC)**

Treatment	Total costs	Total QALYs	Δ costs (£)	Δ QALYs	ICER (£/QALY gained)
*Sapropterin + protein-restricted diet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protein-restricted diet	[redacted]	[redacted]			

Figure 37: Cost-effectiveness plane (All years, with PAS): (graph below is CIC)

[redacted]

Probabilistic sensitivity analysis (additional patient populations)

The corresponding PSA outputs (mean) for the additional populations of interest as well as the likelihood of cost-effectiveness at threshold values of £20,000 and £30,000 per QALY gained are presented in Table 74 below.

Overall, the results of the PSA are similar to those observed in the base case with all populations being cost-effective at both thresholds except for 13-17 years, adults, and women of childbearing age populations. The results show that the adult population is not expected to be cost-effective at a threshold of £20,000 or £30,000 per QALY gained. All patient populations where treatment is begun at age 0 have the greatest likelihood of being cost-effective at both thresholds.

Table 74: Probabilistic cost-effectiveness results (all other patient populations, with PAS) (table below is CIC)

Patient group	Δ (£)	Δ QALYs	ICER (£/QALY gained)	Liklihood cost-effective	
				£20,000 per QALY gained	£30,000 per QALY gained
*0-4 years	[redacted]	[redacted]	[redacted]	83.20%	80.20%
*0-12 years	[redacted]	[redacted]	[redacted]	88.40%	87.90%
*0-17 years	[redacted]	[redacted]	[redacted]	91.8%	92.6%
*5-12 years	[redacted]	[redacted]	[redacted]	71.10%	74.40%
*13-17 years	[redacted]	[redacted]	[redacted]	16.10%	31.10%
*All adults	[redacted]	[redacted]	[redacted]	0.00%	0.00%
*Women of childbearing age	[redacted]	[redacted]	[redacted]	36.50%	43.50%

Probabilistic sensitivity analysis (societal perspective)

The relevant PSA outputs (mean) for all patient populations generated using a broader societal perspective is presented in Table 75 below.

Overall, the results of the PSA are similar to those observed in the base case with additional cost savings and lower ICERs generated for all populations. Apart from the 13-17 years, adults, and women of childbearing age populations, the ICERs for all other populations is under the £20,000 per QALY threshold. The results show that the adult population is not expected to be cost-effective at both thresholds considered. All patient populations where treatment is begun at age 0 have the greatest likelihood of being cost-effective at both thresholds.

Table 75: Probabilistic cost-effectiveness results (all patient populations, with PAS, societal perspective) (table below is CIC)

Patient group	Δ (£)	Δ QALYs	ICER (£/QALY gained)	Liklihood cost-effective	
				£20,000 per QALY gained	£30,000 per QALY gained
*All years (base case)	[redacted]	[redacted]	[redacted]	100.00%	100.00%
*0-4 years	[redacted]	[redacted]	[redacted]	79.60%	77.50%
*0-12 years	[redacted]	[redacted]	[redacted]	88.70%	87.80%
*0-17 years	[redacted]	[redacted]	[redacted]	90.50%	90.80%
*5-12 years	[redacted]	[redacted]	[redacted]	67.40%	70.90%
*13-17 years	[redacted]	[redacted]	[redacted]	23.80%	37.30%
*All adults	[redacted]	[redacted]	[redacted]	0.00%	0.00%
*Women of childbearing age	[redacted]	[redacted]	[redacted]	42.80%	47.70%

Deterministic sensitivity analysis (Univariate analyses)

The results of the univariate deterministic sensitivity analyses generated in the presence of our commercial arrangement for the base case population is presented in figure Figure 38 below.

A number of parameters had no meaningful impact on the results and, therefore, only the 10 parameters with the largest impact are presented here. The results indicate that the parameters with the largest impact on the ICER, for the base analysis without the consideration of societal burden are: the cost and dose (0-12 years) of sapropterin, the cost of protein supplements and the reduction in food usage (diet liberalisation). The only value that generated an ICER in excess of £20,000 per QALY gained was the upper estimate on the cost of sapropterin; this was still below the £30,000 per QALY gained threshold.

Figure 38: Tornado diagram (conventional NICE reference case) (graph below is CIC)

Deterministic sensitivity analyses (alternative modelling assumptions for key parameters).

1. Alternative choice of data for health state utility decrements

The model retains the functionality to use utility data from an unpublished UK based study using disutility values from **Error! Reference source not found.**, this includes an additional utility increment associated with sapropterin of 0.063. Table 76 outlines the results using the alternative utility source. The mean incremental QALY gain is lower compared to Swedish data [redacted]. * However, the ICER remains dominant against the restricted diet only comparator due to the same level of cost-savings.

Table 76: Cost-effectiveness results (All years, with PAS, alternative source for health state utility decrements) (table below is AIC)

Treatment	Total costs	Total QALYs	Δ costs (£)	Δ QALYs	ICER (£/QALY gained)
*Sapropterin + protein-restricted diet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protein-restricted diet	[redacted]	[redacted]			

2. Alternative choices for patients'-controlled health state decrement in the preferred source of information

The base case data source for patient disutilities was composed of three distinct vignettes for the controlled health state (as outlined in section B.3.4 Measurement and valuation of health effects). In the base an average of all three vignettes was used. Table 77 shows the impact of using disutilities for each individual vignette in the model. [redacted]; * however, the ICERs for sapropterin remained dominant against diet only treatment for all three vignettes.

Table 77: Cost-effectiveness results (All years, with PAS, alternative choice for patients in controlled health state utility decrement) (table below is CIC)

Vignette	Δ costs	Δ QALYs	ICER (£/QALY gained)
*Base case (Average of three vignettes)	[redacted]	[redacted]	[redacted]
*No symptom, partly restricted diet without medical food			
*No symptom, partly restricted diet with medical food			
*No symptom, restricted diet with medical food			

3. Alternative choices for patients uncontrolled health state decrement in the preferred source of information

The base case data source for patient disutilities was composed of three distinct vignettes for the uncontrolled health state (as outlined in section B.3.4 Measurement and valuation of health effects). In the base an average of all three vignettes was used. Table 78 shows the impact of using disutilities for each individual vignette in the model. [redacted]*; however, the ICERs for sapropterin remained dominant against diet only treatment for all three vignettes

Table 78: Cost-effectiveness results (All years, with PAS, alternative choice for patients in uncontrolled health state utility decrement) (table below is CIC)

Vignette	Δ costs	Δ QALYs	ICER (£/QALY gained)
*Base case (average of three vignettes)	[redacted]	[redacted]	[redacted]
*Mild symptoms, partly restricted diet, no medical food			
*Moderate symptoms, partly restricted diet, medical food			
*Severe symptoms, restricted diet, medical food			

4. Alternative choices for parents/ carer uncontrolled health state decrement in the preferred source of information

The base case data source for parent/ caregiver disutilities was composed of three distinct vignettes for the controlled health state (as outlined in section B.3.4 Measurement and valuation of health effects). In the base case an average of all three vignettes was used. Table 79 shows the impact of using disutilities for each individual vignette or none in the model. [redacted].* The ICERs for sapropterin remained dominant against diet only treatment for all three vignettes and none.

Table 79: Cost-effectiveness results (All years, with PAS, alternative choice for parents/ carers in controlled health state utility decrement) (table below is CIC)

Vignette	Δ costs	Δ QALYs	ICER (£/QALY gained)
*Base case (average of three vignettes)	[redacted]	[redacted]	[redacted]
*No symptom, partly restricted diet, no medical food			
*No symptom, partly restricted diet, medical food			
*No symptom, restricted diet, medical food			
*No decrement			

5. Alternative choices for parents/ carer uncontrolled health state decrement in the preferred source of information

The base case data source for parent/ caregiver disutilities was composed of three distinct vignettes for the uncontrolled health state (as outlined in section B.3.4 Measurement and valuation of health effects). In the base case an average of all three vignettes was used. Table 80 shows the impact of using disutilities for each individual vignette or none in the model. [redacted] however, the ICERs for sapropterin remained dominant against diet only treatment for all three vignettes and none.

Table 80: Cost-effectiveness results (All years, with PAS, alternative choice for parents/ carers in uncontrolled health state utility decrement) (table below is CIC)

Vignette	Δ costs	Δ QALYs	ICER (£/QALY gained)
*Base case (average of three vignettes)	[redacted]	[redacted]	[redacted]
*Mild symptoms, partly restricted diet, no medical food			
*Moderate symptoms, partly restricted diet, medical food			
*Severe symptoms, restricted diet, medical food			
*No decrement			

6. Inclusion of additional benefit associated with sapropterin

The model includes the functionality to input additional benefits of sapropterin which may not be captured within the model. In the base case this value was set to zero. The

impact of any such benefit on the results was explored using a dummy additional benefit of 0.05. [redacted]

[redacted].* The ICER for sapropterin remained dominant against diet only treatment.

Table 81: Cost-effectiveness results (All years, with PAS, additional patient benefit for sapropterin) (table below is CIC)

	Δ costs	Δ QALYs	ICER (£/QALY gained)
*Base case (no additional benefit)	[redacted]	[redacted]	[redacted]
*With additional benefit	[redacted]	[redacted]	[redacted]

7. Removal of attrition

The model includes the functionality to set the attrition rate to zero (to reflect an alternative hypothesis that all individuals will continue on treatment if symptoms are controlled). Table 82 shows that assuming no attrition increases the total incremental cost and QALYs. The ICER was higher than the base case [redacted] *However, sapropterin remained cost-effective at a threshold of £20,000 per QALY gained.

Table 82: Cost-effectiveness results (All years, with PAS, removal of 10% attrition) (table below is CIC)

	Δ costs	Δ QALYs	ICER (£/QALY gained)
*Base case (with 10% attrition)	[redacted]	[redacted]	[redacted]
*Without attrition	[redacted]	[redacted]	[redacted]

8. Varying maximum years on treatment for women of childbearing age (with PAS)

The impact of varying duration of treatment within the women of childbearing age population was examined. The base case assumes this population to receive sapropterin from the age of 18 and receive treatment for 1 year. The increased number of years on treatment resulted in additional costs. These costs were higher depending on the number of years you [redacted] *

Table 83: Cost-effectiveness results (women of childbearing age, with PAS, starting age 18) (table below is CIC)

Treatment duration	Δ costs	Δ QALYs	ICER (£/QALY gained)
*Base case (1 year on treatment)	[redacted]	[redacted]	[redacted]
*2 years on treatment	[redacted]	[redacted]	[redacted]
*3 years on treatment	[redacted]	[redacted]	[redacted]

9. Varying Kuvan dose

The impact of varying treatment dose for the base case population was examined. The base case assumes this population to receive a treatment dose of 10 mg/kg for paediatric population and 12.5 mg/kg for adults. The increased treatment dose resulted in increased incremental costs compared to the base case. These costs increased as dose increased [redacted] *. Treatment in this population is cost-effective for doses of 14.4 mg/kg and 18.7 mg/kg, in addition to the base case, at a threshold of £20,000 per QALY gained. Treatment with a dose of 20 mg/kg is only cost-efective at a threshold of £30,000 per QALY gained.

Table 84: Cost-effectiveness results (All years, with PAS) (table below is CIC)

Dose	Δ costs	Δ QALYs	ICER (£/QALY gained)
*10 mg/kg (paediatric), 12.5 mg/kg (adults)	[redacted]	[redacted]	[redacted]
*14.4 mg/kg (all years)	[redacted]	[redacted]	[redacted]
*18.7 mg/kg (all years)	[redacted]	[redacted]	[redacted]
*20 mg/kg (all years)	[redacted]	[redacted]	[redacted]

Deterministic sensitivity analyses (Threshold analyses)

In addition to the univariate and structural uncertainty analyses presented above, several threshold analyses around key model parameters, were performed, to inform discussions around the plausibility of input assumptions. All the results from these analyses were generated in the presence of the proposed commercial arrangement.

1. Truncation of time horizon

Figure 39 displays the impact of varying time horizons on the ICER for the base case population, with PAS. Sapropterin is cost-effective across all time horizons considered at a threshold of £20,000 per QALY gained.

Figure 39: Varying the time horizon (All years old, with PAS): (graph below is CIC)

2. Utility increment associated with sapropterin

Figure 40 shows the impact of varying the utility increment applied to patients on sapropterin treatment. The results of this indicate that the ICER increases as the utility increment increases for the conventional NICE reference.

Figure 40: Varying the utility increment associated with sapropterin treatment (All years old, with PAS): (graph below is CIC)

3. Utility decrement: parents of a child with controlled and uncontrolled PKU

The utility decrement applied to the parents of children with controlled PKU was varied within a threshold analysis. The results of this indicate that the ICER decreases as the utility decrement increases (Figure 41: Varying the utility decrement for parents of children with controlled PKU (All years old, with PAS) : (graph below is CIC), with [redacted]*). Sapropterin remains cost-effective at a threshold of £20,000 per QALY gained as utility decrement for parents of children with controlled PKU increases to [redacted] *.

Figure 41: Varying the utility decrement for parents of children with controlled PKU (All years old, with PAS) : (graph below is CIC)

The utility decrement applied to the parents of children with uncontrolled PKU was varied within a threshold analysis. The results of this indicate that the ICER decreases as the utility decrement increases (Figure 42, with [redacted]*. Sapropterin remains cost-effective at a threshold of £20,000 per QALY gained as utility decrement for parents of children with uncontrolled PKU increases to [redacted].*

Figure 42: Varying the utility decrement for parents of children with uncontrolled PKU (All years old, with PAS): (graph below is CIC)

hyperphenylalaninaemia in adults and paediatric patients of all ages with phenylketonuria who have been shown to be responsive to such treatment

4. Attrition rate

In the base-case, it was assumed that 90% of patients who take sapropterin will continue to be on treatment from one year to the next. Figure 43 shows the ICER when the attrition rate is varied across a range of values. The ICER decreases as the attrition rate increases in patients with controlled PKU.

Figure 43: Varying the attrition rate (patients with controlled PKU, All years old, with PAS) : (graph below is CIC)

5. Proportion of diet costs incurred by sapropterin patients

In the base-case, it was assumed that patients on sapropterin treatment will remain on an identical diet to patients only on the protein-restricted diet. As it is anticipated that that a proportion of patients on sapropterin treatment will be able to relax the strict Phe-restricted diet, the multiplier in the model has been varied, to decrease the proportion of diet costs incurred by sapropterin patients. The results of this analysis indicate that as sapropterin patients incur less Phe-diet and protein supplement costs, the ICER reduces (Figure 44).

Figure 44: Varying the proportion of diet costs incurred by sapropterin patients (All years old, with PAS): (graph below is CIC)

B.3.9 Subgroup analysis

All subgroup analyses are discussed in the main results sections above.

B.3.10 Validation

Validation of cost-effectiveness analysis

The internal validity of the model was examined via a two-step process. Firstly, a cell-by-cell check of all model formulae was undertaken to ensure they were both correct and appropriately applied. Secondly, a model verification checklist was used, which includes a range of tests, including sense checks, for instance, changing certain inputs to zero and checking that the observed effect was as expected (i.e. illogical results were not generated). This internal validation process was undertaken by a health economist who was not directly involved in the conceptualisation and development of the model.

B.3.11 Interpretation and conclusions of economic evidence

The economic evaluation considered both adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to sapropterin. This reflects the population included in the final NICE scope. The core economic model outputs for patients who started on sapropterin at the age of zero and continued on

treatment throughout their life, as well as all other populations covered by the NICE scope are presented in Table 85 and detailed breakdowns of the results are presented in Appendix J.

Looking across the patient populations, the ICERs for all populations which started treatment at age 0 was dominant against the comparator of diet only, with sapropterin plus restricted diet being cost saving compared to the restricted diet alone while offering increased benefits to patients. Of note, even when treatment is offered for the maximum time possible (i.e. lifetime), sapropterin is still cost saving, as observed for the base case population. Commencing treatment at age 5 and treating until at most age 12 was also cost-effective at a threshold of £20,000 per QALY gained. The incremental lifetime cost of treatment in this group was modest [redacted] and the benefits large [redacted].* Exploration of the drivers of these costs indicate that the large savings in food costs in sapropterin patients more than offsets the additional cost of treatment.

[redacted].* The results suggest that treatment within the paediatric population is associated with larger health benefits and cost savings. Within the paediatric population ealier treatment from birth and prolonged treatment up to 18 years or adulthood is associated with larger QALY gains, respectively.

Table 85: Cost-effectiveness results (all populations, with PAS) (table below is CIC)

Patient group	Δ costs	Δ QALYs	ICER (£/QALY gained)
*All years (base case)	[redacted]	[redacted]	[redacted]
*0-4 years	[redacted]	[redacted]	[redacted]
*0-12 years	[redacted]	[redacted]	[redacted]
*0-17 years	[redacted]	[redacted]	[redacted]
*5-12 years	[redacted]	[redacted]	[redacted]
*13-17 years	[redacted]	[redacted]	[redacted]
*All adults	[redacted]	[redacted]	[redacted]
*Women of childbearing age	[redacted]	[redacted]	[redacted]

The PSA estimated that the ICER for the all years population had a likelihood of being cost-effective of 100% at a threshold of £20,000 per QALY gained. For all populations where treatment began during a paediatric age there was a probability of the intervention being cost-effective, with the likelihood of being cost-effective at thresholds

of £20,000 and £30,000 per QALY gained being at least 83.2% and 80.2% in all these patient groups, respectively.

The addition of societal burden such as time off work led to increased cost savings for the all years population [redacted]. This was observed for all other populations modelled. As the results demonstrate, incorporating a societal perspective into the analysis makes a difference to the cost-effectiveness results. Clinical evidence has shown that carers and patients of children with PKU face significant losses to both productivity and quality of life.

The DSA demonstrated that for the base case population the key drivers of the economic model are the cost and dose (0-12 years) of sapropterin, the cost of protein supplements and the reduction in food usage (diet liberalisation).

Various scenario analyses were conducted to explore the impact of the inputs informing the model. The use of the UK specific utility data resulted in a lower incremental QALY gain compared to base case ([redacted])*. Furthermore, within the base case source for utility decrements there is the option to choose between vignettes instead of the average used in the base case for both the controlled and uncontrolled health states. This resulted in changes of total incremental QALYs ranging between [redacted] * for the controlled and uncontrolled health states, respectively. However, the ICER remained dominant in all scenarios explored.

Similar scenarios were explored for the parent/ caregiver disutilities. The choice of different vignettes resulted in incremental QALYs that ranged from [redacted] for the controlled health state and large variation for uncontrolled health state [redacted]). It is important to note that even when no impact on parent/ caregiver HRQoL was assumed, treatment with sapropterin still generated positive lifetime QALYs at lower lifetime costs (i.e. dominance was maintained).

Other sensitivity analyses explored included additional benefit associated with sapropterin, where the ICER remained dominant, and removal of attrition rate. Whilst the ICER was no longer dominant if attrition was removed, it resulted in an ICER that

was still cost-effective at the £20,000 per QALY gained threshold [redacted]). The threshold analysis for attrition shows that an addition of attrition will result in a decrease in the ICER.

Various other threshold analyses were conducted to explore the change in ICERs. For the base case population, sapropterin is estimated to remain cost-effective and dominant as the time horizon increases. Even when the natural attrition rate was set to zero, the ICER was less than £10,000 per QALY gained and as long as the impact of treatment on the need for the specialist diet was at least 60%, sapropterin was cost saving.

As a very rare disease, only affecting a small proportion of the population, a strength of the model is that six years of registry data were used to derive transition probabilities. Furthermore, although a small number of inputs were elicited from clinical experts rather than published literature, these were elicited from experienced, specialised clinicians who were able to provide information applicable to current practice.

A limitation of the base case results is that the 19+ transition probabilities were applied to the whole cohort of the all years population. However, there will be variation between the proportion of people who move between each health states between the adult and paediatric populations, as observed from the transition probability data. Since the majority of the cohort are still alive at age 18, the application of the 19+ transition probability to this population is reasonable.

The results of this analysis show that sapropterin has the potential to be cost-effective in multiple populations explored. Sapropterin is cost-effective particularly in those populations which start treatment from birth and continue treatment for as long as possible, as observed for the base case population.

B.4 References

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Supportive Phase IIIb and IV studies

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Sapropterin cost based on age and weight

Appendix M: Transition Probabilities

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sapropterin for treating phenylketonuria [ID1475]

Clarification questions

August 2020

File name	Version	Contains confidential information	Date
		Yes/no	

Section A: Clarification on effectiveness data

A1. PKUDOS clinical effectiveness data, February 2018 data-cut

If available, please provide the following clinical effectiveness data from the latest data-cut of the PKUDOS registry, by age group (ideally 0 to ≤12, 12 to ≤18 and 18+), for patients responding to sapropterin, for the following outcomes, at baseline and follow-up:

a) mean (standard deviation) and median sapropterin dose

Please see data below from the PKUDOS registry, according to the set age groups in the registry. Two sets of figures are provided to reflect the Strict Adherence set and the Safety Analysis Set.

The Safety Analysis set included all patients who enrolled in the study and had received Kuvan during the study. The Strict Adherence set which included patients in the Safety Analysis set who received Kuvan during the study without dose interruptions of > 28 days and recorded Phe assessment(s) prior to the reference date (defined as the date of enrolment plus 120 days or the initial date of Kuvan exposure after the enrolment date, whichever is first.

	Strict Adherence Set		Safety Analysis Set	
Age	Mean (SD) – mg/kg/day	Median (mg/kg/day)	Mean (SD) – mg/kg/day	Median (mg/kg/day)
< 4 years	18.52 (2.804)	19.73	18.74 (3.641)	20
<12 years	18.46 (3.206)	19.59	18.79 (3.505)	20
<18 years	18.48 (2.897)	19.57	18.82 (3.729)	20
>=18 years	18.40 (2.879)	20	18.54 (3.729)	20

b) mean blood phenylalanine (Phe) levels

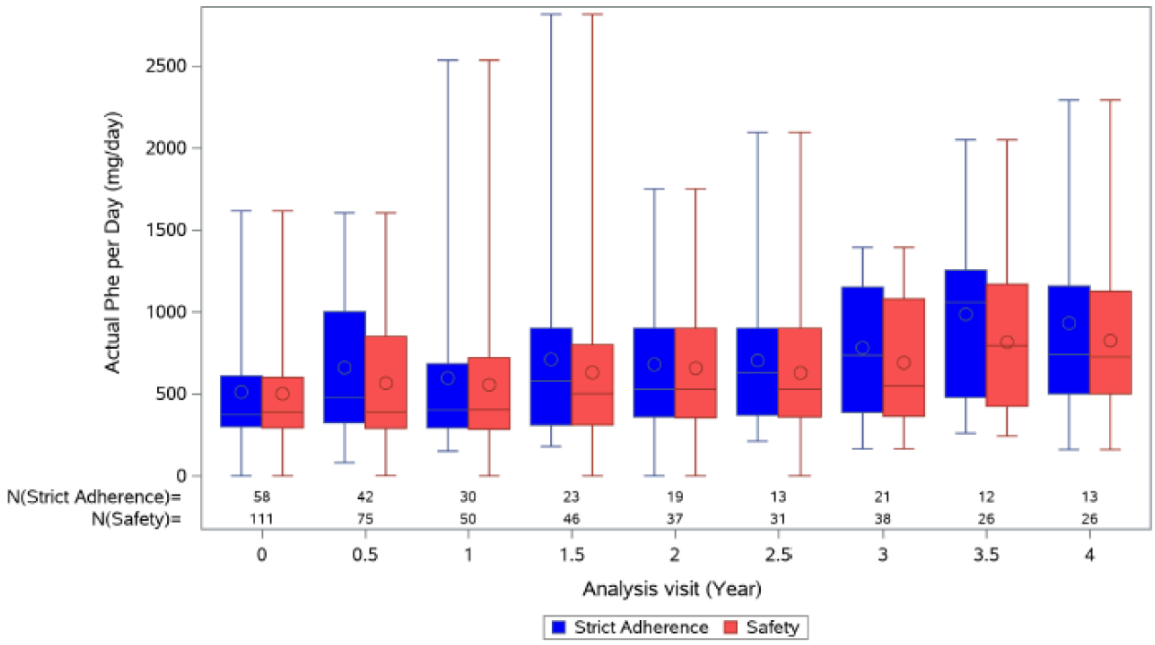
	Strict Adherence Set		Safety Analysis Set	
Age	Mean (µmol/L)		Mean (µmol/L)	
< 4 years	268.7		267.2	
<12 years	319.5		347.1	
<18 years	345.8		393.7	
>=18 years	662.6		720.9	

The Safety Analysis set included all patients who enrolled in the study and had received Kuvan during the study. The Strict Adherence set which included patients in the Safety Analysis set who received Kuvan during the study without dose interruptions of > 28 days and recorded Phe assessment(s) prior to the reference date (defined as the date of enrolment plus 120 days or the initial date of Kuvan exposure after the enrolment date, whichever is first).

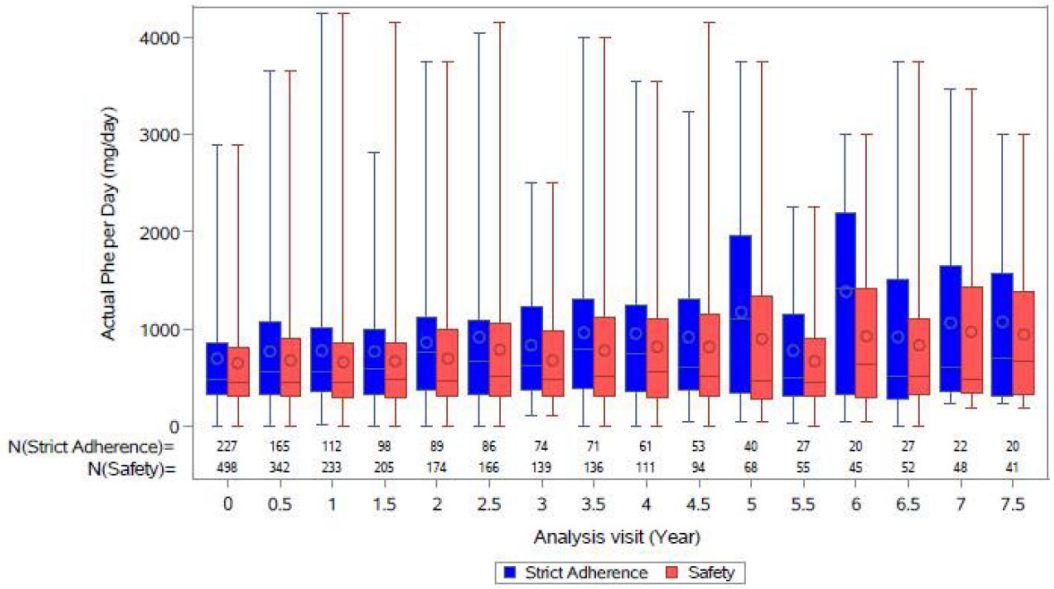
c) dietary Phe intake

The standard baseline for dietary Phe intake was defined as the average of the respective intake prior to enrolment and up to enrolment date plus 120 days. Data for actual dietary Phe intake was derived from recordings made by the patients in food diaries. Using the standard Phe baseline definition, actual dietary Phe intake was higher in the Strict Adherence set than in the Safety Analysis set This was observed in all age cohorts with the exception of patients < 4 years, in which actual dietary Phe intake was similar between the analysis sets.

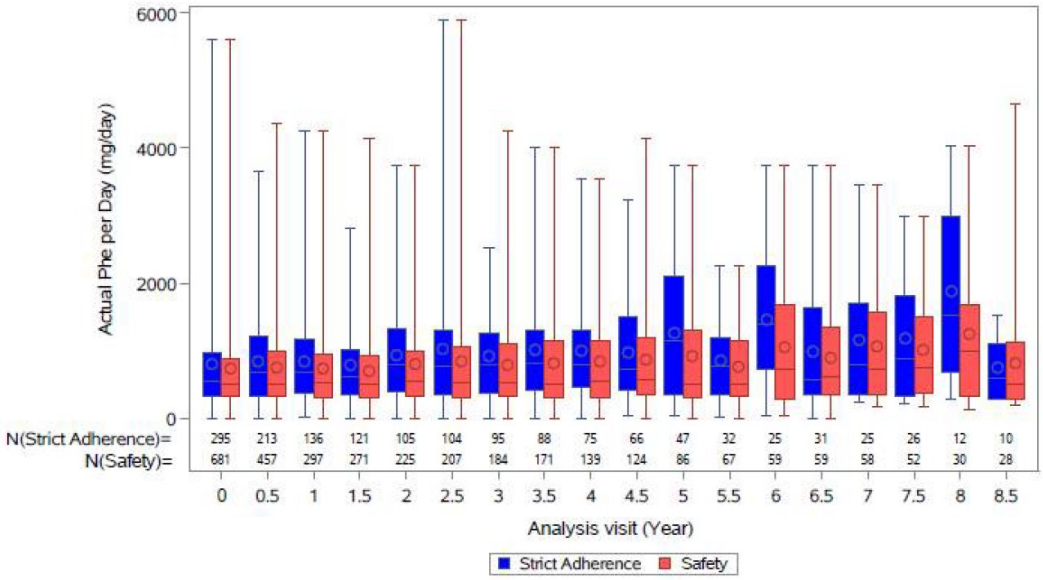
Actual Dietary Phe Intake per Day Over Time, Standard Baseline (Patients < 4 years at Time of Enrolment)



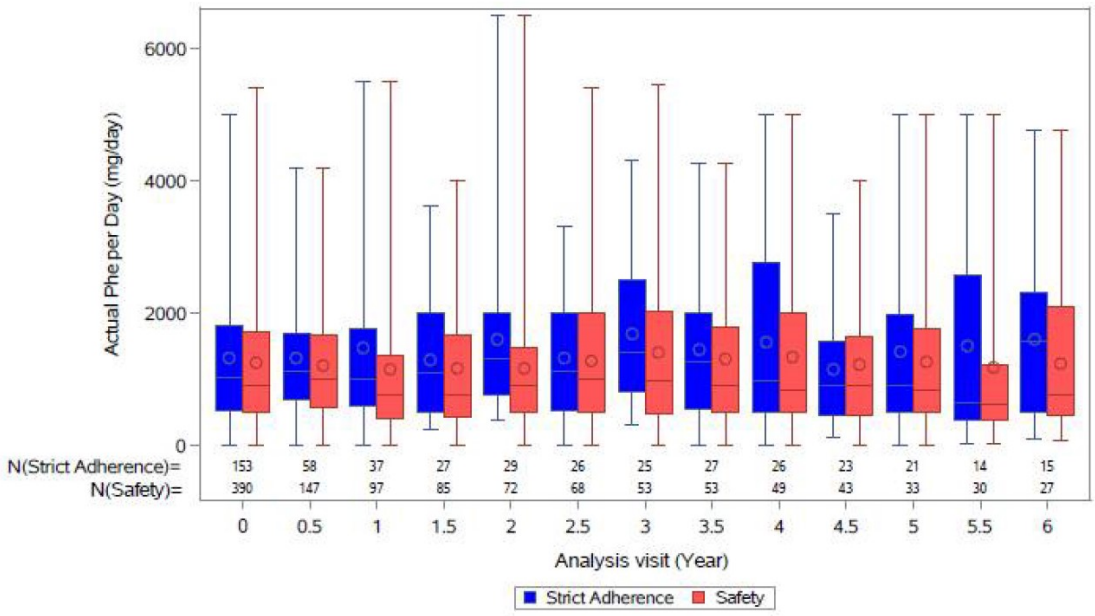
Actual Dietary Phe Intake per Day Over Time, Standard Baseline (Patients < 12 years at Time of Enrolment)



Actual Dietary Phe Intake per Day Over Time, Standard Baseline (Patients < 18 years at Time of Enrolment)



Actual Dietary Phe Intake per Day Over Time, Standard Baseline (Patients ≥ 18 years at Time of Enrollment)



d) reduction in protein supplements and specialist foods.

The increase in natural protein intake as evidenced in the submission comes from a poster presented by the ESPKU in 2018 (Yilmaz et al 2018) relating to a cross

sectional survey of 8 European PKU centres and 291 sapropterin responsive patients. The aim of this study is to report the dietary management and use of Foods for Special Medical Purposes in sapropterin responsive patients with PKU, from 8 European PKU centres. This study highlighted that:

- More than half (n=163, 56.0%) of the sapropterin treated patients achieved WHO/FAO/UNU safe levels of protein intake.

- Of 291 sapropterin responsive patients, 82 (28%) did not require a L-AA supplement and in the remaining patients L-AA dosage was reduced by 60%.

The reduction in amino acid supplement use is the average of the above 2 values i.e. [1-0.72*0.6] =71.2%.

The graph below illustrates Median dose of protein substitute recommended to patients managed with diet only vs sapropterin ± diet.
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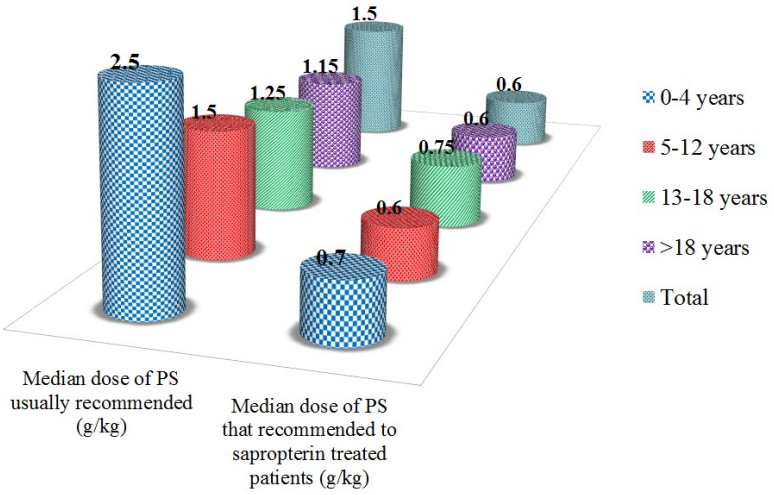

The reduction in the use of amino acid supplemented by clinicians in the United Kingdom at an advisory board held in June 2020 (report will be uploaded as part of this submission response).

The increase in natural protein intake observed in the Yilmaz et al 2018 poster is also referred to by Lilienstein et al 2017 in a poster presented at ICIEM, Rio in 2017 (Interim Analysis of the Phenylketonuria (PKU) Patients Enrolled in the PKUDOS Registry). The data shows the continuously treated sapropterin group had prescribed

median dietary Phe intakes about 1.7 times that of the previously treated group (500-550 mg/day vs 295-333 mg/day).

This is also consistent with a paper published by Evers et al 2018 (Molecular Genetics and Metabolism 124 (2018) 238–242) which highlights the reduction in prescribed amino acid mixture (AAM) following 5 years of treatment with sapropterin. The paper states that after 5 years of BH4 treatment, there was a significant decrease in prescribed amino acid mixture in the treatment group (0.32 ± 0.34 vs. 0.99 ± 0.51 g/kg/day, p < 0.001). This translates to a 68% decrease in prescribed AAM. This reference will be uploaded to the NICE platform.

This is further supported by a publication by Singh et al 2010 (J Inherit Metab Dis (2010) 33:689–695). The paper reports medical food protein intake reducing from 0.96g/kg/day to 0.15g/kg/day over 2 years, representing an 84% decrease (see below).

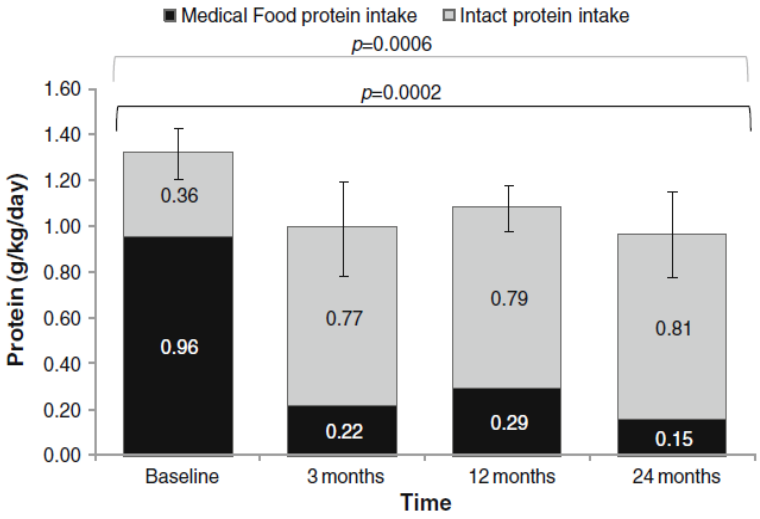

Fig. 2 Total protein intake in six tetrahydrobiopterin (BH_4)-responsive patients over the course of 24 months. Total protein did not significantly change over time, but the source of protein did. Intact protein intake significantly increased (p=0.0006), whereas medical-food intake significantly decreased (p=0.0002)

A2. Clinical effectiveness evidence

In the company submission (CS), there are several inconsistencies between the studies listed in Section B.2.2 '*list of relevant clinical effectiveness'*, and Section B.2.3 '*summary of methodology of relevant clinical effectiveness evidence*'.

a) Two studies, the SPARK extension study (94) and Burton 2010 (45) were identified as relevant studies in Section B.2.2 (Tables 5 and 6). However, further details of these studies were not provided in Section B.2.3 (Table 7). Please explain the reasons for this or provide the study details.

b) In Section B.2.3 and CS Appendix F, the methodological characteristics of four studies were described but these were not listed in Section B.2.2 as relevant clinical effectiveness evidence. These studies are: PKU-015 (99), ENDURE (100), PKUMOMS (21), and KOGNITO. Please explain why these four studies were not listed in Section B.2.2 as relevant clinical effectiveness evidence.

(a) [Data from the SPARK Extension study is available as a poster (Rutsch et al, 2018 - presented at SSIEM, Athens 2018) and is awaiting formal publication. For this reason it was not included in Table 7. The Burton 2010 study captures an outcome that is not captured in clinical practice and not featured in clinical guidelines hence we do not consider this a relevant study. It was included in Table 5 and 6 in error. The poster from Rutsch et al 2018 will be submitted (uploaded) as part of our response.

(b) This was an omission and these 4 studies (PKU-015, ENDURE, PKUMOMS and KOGNITO) should be captured in section B.2.2.]

Section B: Clarification on cost-effectiveness data

B1. Priority request: company model populations

Please provide the following information from the PKUDOS registry:

a) the detailed criteria that were used to select the 'sapropterin treatment+diet' population

b) the detailed criteria that were used to select the ‘diet only’ population

c) the number of patients in each group

d) the demographic characteristics (including, age, sex, ethnicity and weight) for the sapropterin treatment+diet and diet only model populations.

a) The “sapropterin + diet” group was selected based on the following criteria:

- Intended to initiate sapropterin within 90 days of enrolment (i.e. new users of sapropterin),
- ≥1 recorded sapropterin-naïve (i.e. pre-treatment) blood Phe value,
- Available information on sapropterin dosing while enrolled.
- The patients in this subgroup, regardless of sapropterin dose (range 5-20 mg/kg/day), were considered to be actively managed with diet in conjunction with sapropterin, as indicated in the sapropterin label [Kuvan SmPC].

b) Selection criteria for the “diet alone” group were those who had previously received sapropterin before enrolling in PKUDOS or discontinued sapropterin while in the registry.

c) The PKUDOS registry was initiated in 2008 and currently includes 1997 patients. At the last data-cut in February 2018, there were 1,867 patients that had been followed for up to 10 years.
Total exposure at the time of the last data cut in February 2018 are shown below in Table 1.

Table 1: Patients exposure in PKUDOS (February 2018 data cut)

Patient that agrees to commence Kuvan within 90 days	221
Patients that have previously received Kuvan	557
Patients that are currently receiving Kuvan	1069
Missing	20
Total	**1867**

d) Table 2 below shows the demographics of patients on 'sapropterin+Diet' and 'diet only'

Table 2: Patients demographics

		Diet only	**Sapropterin+Diet**	**Total**
Age (Years)	n	160	191	351
	Mean	16.7	18.1	17.5
	SD	12.6	14.7	13.7
Sex, n (%)	Female	78(48.8%)	113(59.2%)	191(54.4%)
Ethnicity, n (%)	Hispanic or Latino	5(3.1%)	8(4.2%)	13(3.7%)
	Non-Hispanic or Latino	150(93.8%)	175(91.6%)	325(92.6%)
	Missing	5(3.1%)	8(4.2%)	13(3.7%)
Baseline blood Phe ($\mu molL^{-1}$)				
	n	160	190	350

	Mean	630.7	701.6	669.2
	SD	407.9	462.9	439.4

B2. Priority request: attrition rate

The company model uses transition probabilities generated from the PKUDOS registry data and an attrition rate generated from the KAMPER registry data.

a) Please provide evidence to show that the two populations are comparable.

b) Please explain why it was not possible to calculate transition probabilities and the attrition rate using a single source.

c) Please provide additional detail on the calculation of the attrition rate. This should include patient numbers, the interim analysis time point, the median and the range of time points that treatment stopped and whether the attrition rate included patients who were no longer controlled with sapropterin treatment+diet.

The PKU Demographics, Outcome and Safety (PKUDOS) registry is a US-based, voluntary, multicentre, observational registry to track individuals with PKU on sapropterin. The study design is published in Longo et al. 2015. The PKUDOS registry was initiated in 2008 and currently includes 1997 patients, of whom 351 patients had been selected for the transition probability analysis shown below.

The KAMPER registry is a European registry undertaken across 85 clinical sites in 9 EU countries. KAMPER is an observational, multi-centre, multi-national, drug registry that tracks the outcomes of Kuvan therapy for patients with HPA due to PKU or BH4 deficiency. The detailed study design is reported in KAMPER_IA10_CSR_final v1.0_29Jun2020.

The subject demographics of PKUDOS (the analysis set for transition probability) and KAMPER is reported in Table 3 below.

Table 3: Patients demographics in PKUDOS and KAMPER

Parameters		**PKUDOS**	**KAMPER**
Age	N	351	572
	Median (min, max)	13 (0,68)	10.1 (1,47)
Sex, n (%)	Female	191 (54.4%)	291 (50.9%)
Ethnicity, n (%)	White	305 (86.9%)	550 (96.2%)
	Non-whites	30 (8.5%)	18 (3.1%)
	Missing	16 (4.6%)	4 (0.7%)
Baseline blood Phe ($\mu molL^{-1}$)	N	350	318
	Mean (SD)	669.2 (439.4)	378.8 (169.8)

PKUDOS is the best source of evidence for comparative analysis of sapropterin treatment+diet versus diet only. Evidence from the clinical trials are limited in sample size and duration of treatment. However, given the size of the PKUDOS registry (close to 2000 patients data) and data spanning 6 years this provides a reliable source of evidence to determine the transition probabilities.

KAMPER is a European registry with a comparatively limited sample size (close to 600) and shorter duration than PKUDOS. The main reason for not using the KAMPER registry for the calculation of transition probabilities is due to the lack of a comparator arm. PKUDOS has a sapropterin treatment + diet and diet only arms thus making it a more suitable evidence base to determine transition probabilities.

However, it may be noted that KAMPER is a European registry and the management of the disease itself in the United Kingdom is closely reflected by KAMPER. Usage of Phe restricted diet, dietary supplement, the target blood Phe thresholds (e.g. ≤600 µmolL-1 for >12-year olds, and ≤360 µmolL-1 for ≤12 year olds and maternal PKU) in PKU population is more closely aligned in KAMPER. Hence the treatment itself

(sapropterin treatment+diet and diet only), and thereby the dose and patients' adherence to treatment would be more closely reflected in KAMPER. This is further accentuated by the opinion from clinical experts (attached report from the advisory board).

d) Please provide additional detail on the calculation of the attrition rate. This should include patient numbers, the interim analysis time point, the median and the range of time points that treatment stopped and whether the attrition rate included patients who were no longer controlled with sapropterin treatment+diet.

The attrition rates were taken from the KAMPER registry (7th interim analysis in 2017) and is detailed in Table 4 below. KAMPER, being a drug registry, only included patients who were responsive to sapropterin treatment (i.e. ≥30% reduction in blood Phe level). The attrition rate calculation shown did not specifically include patients who were not controlled with sapropterin+diet treatment. At the time of this analysis, patients were followed up for 6 years.

The registry data below highlights the reasons for discontinuation:

Table 4: Reasons for discontinuation

Total n	575	
Number of patients discontinued, n (%)	59(10.3%)	
	Withdrawal of consent	2(3.4%)
	Lost to follow-up	13(22%)
	Inappropriate enrolment	4(6.8%)
	Investigator decision	12(20.3%)
	Adverse event	0(0%)

	Death	1(1.7%)
	Other/ unspecified	26(44.1%)
	Missing	1(1.7%)

We have supporting evidence from different sources which corroborates the rate of 10.3% observed from KAMPER. We will collate this supporting evidence from other countries (e.g. Germany), along with a review of previous CSRs for KAMPER (a review of previous CSRs is ongoing). Please allow up to two weeks for this to be completed but we will endeavour to share as soon as we can.

B3. Priority request: model transition probabilities (controlled to uncontrolled)

Please provide the detailed calculations used to calculate the transition probabilities used in the company model (i.e., please ensure there is sufficient detail to allow the ERG to validate the company calculations).

As discussed in response to section B1, transition probabilities of patients moving between health states on different treatments (Phe-restricted diet alone or Kuvan®+ Phe-restricted diet) were calculated from PKUDOS [Longo et al. 2015]. The PKU Demographics, Outcome and Safety (PKUDOS) registry is a US-based, voluntary, multicenter, observational registry to track individuals with PKU on sapropterin. Patients enrolled in this registry were receiving sapropterin at the time of enrolment, had previously received sapropterin but stopped treatment before enrolment into the registry, or intended to initiate sapropterin therapy within 90 days of enrolment [Longo et al. 2015]. The PKUDOS registry was initiated in 2008 and currently includes 1997 patients. At the last data-cut in February 2018, there were 1,867 patients that had been followed for up to 10 years.

Total exposure at the time of the last data cut in February 2018 are shown below in Table 5.

Table 5: Patients exposure in PKUDOS (February 2018 data cut)

Patient that agrees to commence Kuvan within 90 days	221
Patients that have previously received Kuvan	557
Patients that are currently receiving Kuvan	1069
Missing	20
Total	1867

The “sapropterin + diet” group was selected based on the following criteria:

- Intended to initiate sapropterin within 90 days of enrolment (i.e. new users of sapropterin),
- ≥1 recorded sapropterin-naïve (i.e. pre-treatment) blood Phe value,
- Available information on sapropterin dosing while enrolled.

The patients in this subgroup, regardless of sapropterin dose (range 5-20 mg/kg/day), were considered to be actively managed with diet in conjunction with sapropterin, as indicated in the sapropterin label [Kuvan SmPC].

A second comparator population of patients on a Phe-restricted diet alone, referred to as the “diet alone” group, and was also derived from the PKUDOS registry. Selection criteria for the “diet alone” group were:

- Had previously received sapropterin before enrolling in PKUDOS or discontinued sapropterin while in the registry

For the purpose of this analysis parients that were selected to be on treatment (sapropterin+diet and diet only) are shown in Table 6 below.

Table 6: Treatment allocation

Treatments	n
Sapropterin+diet	221
Diet only	557

Of these patents in Table 6 above, patients with baseline blood Phe values were 191 (for sapropterin+diet) and 160 (for diet only). These were the patients from which transition probabilities could be worked out. Table 7 below shows the demographics of these patients on ‘sapropterin+Diet’ and ‘diet only’

Table 7: Patients demographics

		Diet only	Sapropterin+Diet	Total
Age (Years)	n	160	191	351
	Mean	16.7	18.1	17.5
	SD	12.6	14.7	13.7
Sex, n (%)	Female	78(48.8%)	113(59.2%)	191(54.4%)
Ethnicity, n (%)	Hispanic or Latino	5(3.1%)	8(4.2%)	13(3.7%)
	Non-Hispanic or Latino	150(93.8%)	175(91.6%)	325(92.6%)
	Missing	5(3.1%)	8(4.2%)	13(3.7%)
Baseline blood Phe (µmolL-1)	n	160	190	350
	Mean	630.7	701.6	669.2
	SD	407.9	462.9	439.4

Over the 6 years period, number of patients were as shown in Table 8 below.

Table 8: Number of patients over 6 years

	n
Patients with baseline Phe	351
Patients with blood Phe at Y1	344
Patients with blood Phe at Y2	238
Patients with blood Phe at Y3	194
Patients with blood Phe at Y4	163
Patients with blood Phe at Y5	136
Patients with blood Phe at Y6	111

Transition probabilities were calculated based on actual counts of patients moving from one of the two health states (controlled and uncontrolled) over the period of 6 years for the 2 arms (saproptetin+diet and diet only) to the destination health states (controlled and uncontrolled). Uncontrolled PKU is defined by Phe levels being above the target Phe levels described in the European PKU guidelines. Controlled PKU is defined by Phe levels being within the target range.

Table18: Target Phe levels by subgroup.

Population	Target range
Treated PKU patients up to the age of 12 years	120 – 360 micromol/L
Treated PKU patients aged >12 years	120 - 600 micromol/L
Treated pregnant PKU women	120-360 micromol/L

The transition probabilities were derived from this dataset using frequency tables. Transition probabilities were available for three age categories: 0 to 12 years, 13 to 18 years and ≥ 19 years. Transition probabilities for 0-12 years was applied to the following three subgroups: 0 to 4 years, 5 to 12 years and 0 to 12 years. 13 to 18 years transition probabilities were applied to the 13 to 17 subgroup and the ≥19 year

transition probabilities applied to the adult and women of child bearing age populations.

Although different transition values were available for the first six years of a PKU patient's lifetime (as displayed in 9 to 14), the patient counts for individuals who responded to sapropterin therapy in each year were extremely small, with the majority of cases under 20. Therefore, a weighted average over the six- year period was performed in order to calculate a common transition matrix. Annual transition probabilities used in the economic model are presented in Table 9 to Table 14 below. The weighted average (of 6 years) for the 3 age categories is displayed in Table 15 to Table 17.

Table 9: Annual transition probabilities (controlled to uncontrolled) – (0 to 12 years old)

Year	Diet only		Sapropterin treatment	
	N (Total)	%	N (Total)	%
0 to 1	3 (35)	8.6%	3 (35)	8.6%
1 to 2	6 (27)	22%	16 (51)	31%
2 to 3	5 (20)	25%	6 (36)	17%
3 to 4	4 (14)	29%	5 (34)	15%
4 to 5	4 (11)	36%	4 (28)	14%
5 to 6	5 (7)	71%	3 (22)	14%
Weighted Average	N/A	24%	N/A	18%

Table 10: Annual transition probabilities (uncontrolled to controlled) – (0 to 12 years old)

Year	Diet only		Sapropterin treatment	
	N (Total)	%	N (Total)	%

0 to 1	5 (40)	13%	28 (51)	55%
1 to 2	5 (23)	22%	5 (20)	25%
2 to 3	2 (20)	10%	6 (27)	22%
3 to 4	1 (19)	5.3%	6 (21)	29%
4 to 5	4 (19)	21%	1 (17)	5.9%
5 to 6	2 (14)	14%	4 (15)	27%
Weighted Average	N/A	14%	N/A	33%

Table 11: Annual transition probabilities (controlled to uncontrolled) – (13 to 18 years old)

Year	Diet only		Sapropterin treatment	
	N (Total)	%	N (Total)	%
0 to 1	1 (12)	8.3%	0 (0)	0.0%
1 to 2	3 (10)	30%	1 (10)	10%
2 to 3	1 (5)	20%	0 (0)	0%
3 to 4	1 (2)	50%	3 (5)	60%
4 to 5	2 (2)	100%	1 (3)	33%
5 to 6	0 (0)	0.0%	0 (0)	0.0%
Weighted Average	N/A	26%	N/A	28%

Table 12: Annual transition probabilities (uncontrolled to controlled) – (13 to 18 years old)

Year	Diet only		Sapropterin treatment	
	N (Total)	%	N (Total)	%

0 to 1	1 (16)	6.3%	3 (9)	33%
1 to 2	1 (12)	8.3%	0 (0)	0.0%
2 to 3	0 (0)	0.0%	0 (0)	0.0%
3 to 4	1 (2)	50%	0 (0)	0.0%
4 to 5	0 (0)	0.0%	0 (0)	0.0%
5 to 6	0 (0)	0.0%	0 (0)	0.0%
Weighted Average	N/A	10%	N/A	33%

Table 13: Annual transition probabilities (controlled to uncontrolled) – (≥19 years old)

Year	Diet only		Sapropterin treatment	
	N (Total)	%	N (Total)	%
0 to 1	2 (19)	11%	0 (0)	0.0%
1 to 2	7 (15)	47%	3 (17)	18%
2 to 3	0 (0)	0.0%	2 (14)	14%
3 to 4	1 (6)	17%	2 (13)	15%
4 to 5	1 (4)	25%	3 (11)	27%
5 to 6	1 (4)	25%	0 (0)	0.0%
Weighted Average	N/A	25%	N/A	18%

Table 14: Annual transition probabilities (uncontrolled to controlled) – (≥19 years old)

Year	Diet only		Sapropterin treatment	
	N (Total)	%	N (Total)	%
0 to 1	4 (38)	11%	13 (59)	22%
1 to 2	0 (0)	0.0%	3 (26)	12%

2 to 3	2 (12)	17%	2 (17)	12%
3 to 4	0 (0)	0.0%	4 (15)	27%
4 to 5	1 (13)	7.7%	2 (12)	17%
5 to 6	1 (12)	8.3%	0 (0)	0.0%
Weighted Average	N/A	11%	N/A	19%

Table 15 Annual transition matrices used in the base-case analysis (0 to 12 years)

	Sapropterin + restricted diet: Controlled	Sapropterin + restricted diet: Uncontrolled	Restricted diet only: Controlled	Restricted diet only: Uncontrolled
Sapropterin + restricted diet: Controlled	82.0%	18.0%	0.0%	0.0%
Sapropterin + restricted diet: Uncontrolled	33.1%	66.9%	0.0%	0.0%
Restricted diet only: Controlled	NA	NA	76.3%	23.7%
Restricted diet only: Uncontrolled	NA	NA	14.1%	85.9%

The transition probabilities from the PKUDOS registry for the age group 13 to 18 years are presented in Table 16 below. These transition probabilities were applied to the 13 to 17 years population.

Table 16: Annual transition matrices used in base case analysis (13 to 18 years)

	Sapropterin + restricted diet: Controlled	Sapropterin + restricted diet: Uncontrolled	Restricted diet only: Controlled	Restricted diet only: Uncontrolled

Sapropterin + restricted diet: Controlled	85.7%	14.3%	0.0%	0.0%
Sapropterin + restricted diet: Uncontrolled	10.7%	89.3%	0.0%	0.0%
Restricted diet only: Controlled	NA	NA	74.2%	25.8%
Restricted diet only: Uncontrolled	NA	NA	7.3%	92.7%

The transition probabilities from the PKUDOS registry for the age group ≥19 years are presented in Table 45 below. These transition probabilities were applied to both adult populations.

Table17: Annual transition matrices used in base case analysis (≥19 years)

	Sapropterin + restricted diet: Controlled	Sapropterin + restricted diet: Uncontrolled	Restricted diet only: Controlled	Restricted diet only: Uncontrolled
Sapropterin + restricted diet: Controlled	87.5%	12.5%	0.0%	0.0%
Sapropterin + restricted diet: Uncontrolled	17.4%	82.6%	0.0%	0.0%
Restricted diet only: Controlled	NA	NA	78.2%	21.8%
Restricted diet only: Uncontrolled	NA	NA	7.8%	92.2%

B4. Specialist consultations

Table 62 and Table 63 in the CS include details of the mean annual number of outpatient and specialist outpatient visits that are modelled. Please provide details of the type of health care professionals, in each case, who are expected to deliver this care.

The type of healthcare professionals involved in the management of PKU would include paediatricians, adult metabolic disorder physicians, specialist dietitians and psychologists.

B5. Corrections to provided references

a) An estimated reduction of 71.2% in specialist diet usage with sapropterin is applied in the company model (CS, p173). Please provide: i) the correct publication reference to support the estimated reduction and ii) confirm that the reduction is for protein supplements and specialist food.

The correct reference for this is the following: Yilmaz O, Quintana A, Rossi A, Dam E, Özel H, Rocha J, et al. Use of Special Medical Foods with Sapropterin in PKU, ESPKU 2018. It has been corrected in Document B and will be uploaded to the NICE platform with the rest of the documentation. The reduction does relate to protein supplements and specialist foods.

b) In the CS (CS, p173), the company reports a mean reduction in food usage of 54% with sapropterin use. The data are derived from the PKUDOS study. Please provide: i) the correct publication reference that includes the 54% reduction in food usage and ii) confirm that the reduction is for protein supplements and specialist food.

The publication capturing the 54% reduction is from Longo 2015 (Molecular Genetics and Metabolism 114 (2015) 557–563). The 54% reduction relates to an increase in dietary Phe intake which means that protein intake is now being provided by natural sources whereas prior to the introduction of sapropterin, the source of protein available for PKU patients was from Phe-free protein supplements. This reference will be uploaded to the NICE platform with the rest of the documentation.

Section C: Textual clarification and additional points

C1. Hand-searching of conference proceedings during the literature searches

Please confirm whether SSIEM annual symposium 2018 and International Congress of Inborn Errors of Metabolism (includes SSIEM 2017) were the only two conference proceedings that were hand-searched for the 25th September 2018 and 13th July 2020 searches (i.e., no proceedings from any other conferences or from any other years, except 2017 and 2018, were searched).

[**Please see table below with our responses:**

Conference	Notes
SSIEM	• Abstracts presented at SSIEM 2018 were searched as part of the original SR. • In addition, abstracts presented at SSIEM 2019 were accessed during the updated SR [abstracts accessed on July 15th 2020 via Journal of Inherited Metabolic Disease. 2019 vol 42 (suppl 1) [https://onlinelibrary.wiley.com/doi/epdf/10.1002/jimd.12153] • SSIEM 2020 was scheduled for September 2020 and was therefore outside the scope of the update SR (now postponed to 2022)
ICIEM	• Abstracts presented at ICIEM 2017 were searched as part of the original SR. • The next ICIEM Congress will be held in 2021.
ISPOR	• The International, European, Asia Pacific, and Latin American ISPOR congresses were also searched on 15th July 2020 (last three years availability) via the presentations database portal (https://www.ispor.org/heor-resources/presentations-database/search)

Abbreviations: ICIEM, International Congress of Inborn Errors of Metabolism; ISPOR, International Society for Pharmacoeconomics and Outcomes Research;

SSIEM, Society for the Study of Inborn Errors of Metabolism]

C2. Quality assessment

Please clarify how many reviewers were involved in the quality assessment of RCTs and key single-arm studies (CS, Appendix D.1.3) and whether the assessments were independent of each other.

[The Quality assessment (QA) was performed by 1 reviewer and their assessment was then QC'd by a second (senior) reviewer. (It was not 2 independent assessments done separately and then discussed).
Single arm QA was performed by 1 senior reviewer.

In the update of the SLRs, the quality assessment of eligible studies using the appropriate checklist was conducted by two independent analysts. Any differences were resolved by discussions between the two analysts and remaining differences addressed by the project manager.]

C3. Latest interim analysis reports for PKUDOS and KAMPER

Please confirm whether the following reports reflect the latest interim analyses of the PKUDOS and KAMPER registries:

a) PKUDOS: PKUDOS-01-interim-report 2018 (reference 107 of the CS)

b) KAMPER: KAMPER_IA10_CSR_final v1.0_29Jun2020 (reference 109 of the CS)

c) PKUMOMS: Grange DK, Hillman RE, Burton BK, et al. Sapropterin dihydrochloride use in pregnant women with phenylketonuria: an interim report of the PKUMOMS sub-registry. Mol Genet Metab 2014;112(1):9-16. (reference 21 of the CS).

If more recent interim results are available, please provide them.

We confirm that these are the most recent reports containing the interim results for a) PKUDOS, b) KAMPER and C) PKUMOMS.

C4. Protocols of PKUDOS and KAMPER and statistical analysis plan of KAMPER

Please provide the latest version of the protocols of the PKUDOS (version 5, 19 May 2010) and KAMPER registries (version 4, Appendix 16.1.1 of the KAMPER_IA_10_CSR) and the latest statistical analysis plan of the KAMPER registry (version 10, Appendix 16.1.9 of the KAMPER_IA_10_CSR).

The requested documents will be uploaded with the rest of the documentation.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sapropterin for treating phenylketonuria [ID1475]

Clarification questions

October 2020

File name	Version	Contains confidential information	Date
		Yes/no	

B2. Priority request: attrition rate

The company model uses transition probabilities generated from the PKUDOS registry data and an attrition rate generated from the KAMPER registry data.

a) Please provide additional detail on the calculation of the attrition rate. This should include patient numbers, the interim analysis time point, the median and the range of time points that treatment stopped and whether the attrition rate included patients who were no longer controlled with sapropterin treatment+diet.

The attrition rates were taken from the KAMPER registry (7th interim analysis in 2017) and is detailed in Table 4 below. KAMPER, being a drug registry, only included patients who were responsive to sapropterin treatment (i.e. ≥30% reduction in blood Phe level). The attrition rate calculation shown did not specifically include patients who were not controlled with sapropterin+diet treatment. At the time of this analysis, patients were followed up for 6 years.

The registry data below highlights the reasons for discontinuation:

Table 4: Reasons for discontinuation

Total n	575	
Number of patients discontinued, n (%)	[redacted]	
	Withdrawal of consent	[redacted]
	Lost to follow-up	[redacted]
	Inappropriate enrolment	[redacted]
	Investigator decision	[redacted]
	Adverse event	[redacted]
	Death	[redacted]

	Other/ unspecified	26(44.1%)
	Missing	1(1.7%)

We have supporting evidence from different sources which corroborates the rate of [redacted] observed from KAMPER. We will collate this supporting evidence from other countries (e.g. Germany), along with a review of previous CSRs for KAMPER (a review of previous CSRs is ongoing). Please allow up to one week for this to be completed but we will endeavour to share as soon as we can.

Update October 2020

Following further analysis of various data sources, we observe there is some variance in the range of discontinuation rates observed in the real world. For example, we see a rate from the most recent CSR for KAMPER (European registry) calculated [redacted] (see Section *1* below) and data from Rohr et al, 2014 (attached) stating a figure of 29% (Table 1). In addition, anecdotally we are aware of real-world data from the US suggesting a figure closer to 10%.

Given this variance, our original submission figure of [redacted] reflects a mid-point of rates observed.

We have applied the rates of [redacted] and 29% discontinuation as sensitivity analyses in

Section *2* below.

Table 1 Rohr et al 2014

Table 1
Characteristics of patients with PKU who responded to sapropterin therapy.

	Remained on drug	Discontinued drug
Number of sapropterin responders	29	12
Mean age (years)	19.7	19.9
Age range (years)	0.5–54	3–47
Male	17	4
Female	12	8
Experienced side effects	8	10
Severity of PKU		
Mild hyperphenylalaninemia	1	0
Mild PKU	9	2
Moderate PKU	16	7
Severe PKU	3	3
Diet		
Tolerated more dietary PHE	24	7
Mean protein intake (SD) before sapropterin therapy (g/day)	11.3 (7.7)	8.8 (1.8)
Mean protein intake (SD) after sapropterin therapy (g/d)	31.8 (17.4)	17.2 (4.6)

Section 1 KAMPER data

[redacted]

[redacted]

[redacted]

Figure 1: Reasons for discontinuation


[redacted]

Section 2 Updated Economic Analyses

The revised deterministic ICER for the base case as reported in Table 72 in the main *ID1475 Sapropterin Company evidence submission Final* is presented below with a [redacted] discontinuation rate.

Table 2 base-case results (All years, with PAS, discontinuation rate 4.1%)

Treatment	Total costs	Total LYG*	Total QALYs	Δ costs	Δ QALYs	ICER (£/QALY gained)
Sapropterin + Protein-restricted diet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protein-restricted diet	[redacted]	[redacted]	[redacted]			
* Undiscounted values; Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Updated with 29% discontinuation rate

The revised deterministic ICER for the base case as reported in Table 72 in the main *ID1475 Sapropterin Company evidence submission Final* is presented below with a 29% discontinuation rate.

Table 3 base-case results (All years, with PAS, discontinuation rate 29%)

Treatment	Total costs	Total LYG*	Total QALYs	Δ costs	Δ QALYs	ICER (£/QALY gained)
Sapropterin + Protein-restricted diet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protein-restricted diet	[redacted]	[redacted]	[redacted]			
* Undiscounted values; Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Reference

NICE National Institute for Health and Care Excellence

Professional organisation submission

Sapropterin for treating phenylketonuria [ID1475]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Dietetic Association**

3. Job title or position	**Consultant Dietitian in Inherited Metabolic Disorders**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Dietetic Association (BDA) is a professional association and trade union for dietitians in the United Kingdom. It was founded in 1936. It has over 9000 members, many of who provide clinical dietetic services to hospitals and the community. It is self-funded by annual membership fees from dietitians.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Phenylketonuria (PKU) is an autosomal recessive inborn error of phenylalanine (Phe) metabolism. Mutations in the phenylalanine hydroxylase gene lead to PAH deficiency, which results in an inability to convert Phe into tyrosine (Blau 2010). Without treatment, Phe will cross the blood brain barrier and cause many detrimental effects. High toxic blood and brain Phe concentrations causes irreversible intellectual

or prevent progression or disability.)	disability, motor deficits, eczematous rash, autism, seizures, developmental problems, aberrant behaviour, low mood, depression and anxiety, psychiatric symptoms and impact on executive function. All treatments are aimed at decreasing the blood Phe concentration, which is considered a surrogate marker for brain Phe concentrations. The current recommendations are that children up to 12 ≥years of age maintain blood Phe between 120 to 360 µmol/l and patients aged ≥12 years and over between 120 to 600 µmol/L. This is above '**normal'** blood reference Phe levels (30 to 70 µmol/l) in the healthy population. However, on current management it is considered unsafe to reduce the lower blood Phe target limit in PKU, as a low Phe diet leads to considerable variability/fluctuations in blood Phe over 24 hours and may lead to Phe deficiency. In the USA, they recommend that blood Phe is maintained between 120 to 360 µmol/L for all age groups of patients. Several studies have demonstrated that using current management strategies, that many patients struggle to meet target blood Phe ranges on a conventional low Phe diet (Walter et al 2002, Jurecki et al 2017). There are several published studies that have concluded that higher blood phenylalanine levels (above target range of 360 µmol/L) are associated with lower IQ, and even well controlled children with PKU have an IQ that is 5 to 7 points lower than unaffected siblings. There have been 2 important meta-analysis that have examined the impact of IQ and Phe levels.

	1. Waisbren et al. (2007) performed a meta-analysis examining the correlation between IQ and Phe levels reported in 40 different publications. She concluded that a difference of 100 µmol/l between birth to 6-12 years predicted a difference in IQ between 1.3 to 3.1 points in patients whose blood Phe levels ranged from 423-750 µmol/l. Regarding lifetime Phe levels an increase of 100 µmol/l predicted an average 1.9 to 4.1-point reduction in IQ over a range of Phe from 394-666 µmol/l. For example, a patient with a Phe level of 500 µmol/l, on average had a 1.9 to 4.1-point lower score on an IQ-test compared to someone with a Phe level of 400 µmol/L. 2. Fonnesbeck et al. (2013) performed a meta-analysis of 17 studies (432 individuals with PKU, aged 2-32 years) and addressed the relationship between the probability of an IQ less than 85 and Phe levels. The healthy population probability of an IQ less than 85 was approximately 15%. For PKU patients the probability was 14% when the mean blood Phe level during the time frame of ≥6 years of age was 400 µmol/L but increased to 20% when the mean Phe level was 600 µmol/L. In addition, children may have problems with working memory, reasoning and planning, processing speed, fine motor skills, and perception and visual-spatial abilities (Albrecht, et al 2006, DeRoche et al 2008, Janzen et al 2010). Sustained attention and reaction time are reduced (Anjema et al 2011). In adolescents' results of meta-analysis indicate that any relaxation of blood Phe concentrations >600 µmol/L is associated with slower processing speed (Albrecht et al 2009). In adults, similar defects have been reported (Bilder et al 2016).

	Albrecht J, Garbade SF, Burgard P. Neuropsychological speed tests and blood phenylalanine levels in patients with phenylketonuria: a meta-analysis. Neurosci Biobehav Rev. 2009, 33: 414-21. Anjema K, van Rijn M, Verkerk PH, Burgerhof JG, Heiner-Fokkema MR, van Spronsen FJ. PKU: high plasma phenylalanine concentrations are associated with increased prevalence of mood swings. Mol Genet Metab. 2011, 104: 231-4. Bilder DA, Noel JK, Baker ER, et al. Systematic Review and Meta-Analysis of Neuropsychiatric Symptoms and Executive Functioning in Adults With Phenylketonuria. Dev Neuropsychol. 2016 May-Jun;41(4):245-260. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. Lancet. 2010, 376(9750): 1417-27. DeRoche K, Welsh M.Twenty-five years of research on neurocognitive outcomes in early-treated phenylketonuria: intelligence and executive function. Dev Neuropsychol. 2008;33(4):474-504. Fonnesbeck CJ, McPheeters ML, Krishnaswami S, Lindegren ML, Reimschisel T. Estimating the probability of IQ impairment from blood phenylalanine for phenylketonuria patients: a hierarchical meta-analysis. J Inherit Metab Dis. 2013 Sep;36(5):757-66. Janzen D, Nguyen M. Beyond executive function: non-executive cognitive abilities in individuals with PKU. Mol Genet Metab. 2010, 99 Suppl 1:S47-51. Jurecki ER, Cederbaum S, Kopesky J, et al. Adherence to clinic recommendations among patients with phenylketonuria in the United States. Mol Genet Metab. 2017 Mar;120(3):190-197. Waisbren S.E., Noel K., Fahrbach K., Cella C., Frame D., Dorenbaum A., Levy H. Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. Mol Genet Metab. 2007, 92: 63-70. Walter JH, White FJ, Hall SK, et al. How practical are recommendations for dietary control in phenylketonuria? Lancet. 2002 Jul 6;360(9326):55-7.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	For all patients with PKU, it is important to maintain blood Phe levels within target range as recommended by the European Guidelines, 2017 (van Spronsen et al 2017). For sapropterin, it is well accepted that a clinically effective response is a 30% reduction in blood phenylalanine levels following a sapropterin loading test. This is likely to occur in a subset of patients with PKU who are responsive to sapropterin – around 20 to 30% of the PKU population). The loading test is followed by a sapropterin treatment trial. It is expected that sapropterin should at least double dietary Phe intake whilst maintaining blood Phe within target range.

	Many sapropterin responsive patients will achieve safe levels of protein intake (≥ 20g/day natural protein compared with <10g/day on diet). Practically this is a significant relaxation of diet. Around 15 to 20% of sapropterin responsive patients would be expected to stop dietary treatment. It is also expected that protein substitute will be reduced by 50%. With sapropterin, it is likely that growth and IQ would be maintained. van Spronsen FJ, van Wegberg AM, Ahring K, et al. Key European guidelines for the diagnosis and management of patients with phenylketonuria. Lancet Diabetes Endocrinol. 2017 Sep;5(9):743-756.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	A low Phe diet is so restrictive that it is almost incompatible with a contemporary lifestyle. The diet is very strict, and few foods can be eaten without severe limitation. It requires good caregiver/patient knowledge, excellent organisation and cooking skills, and extraordinary will power. Many factors such as frequent illnesses, poor appetite causing low energy intake, and inability to take protein substitute all negatively impact on blood Phe control. There are some children whose parents are unable to adhere to the severity of the dietary restrictions. Therefore, their children have poor blood Phe control which results in low IQ. Children should not be disadvantaged because of their parents' skills and ability to administer the dietary treatment appropriately. It is recommended by the European Guidelines, 2017 that in children under the age of 12 years that they should be referred to social services if 100% of their phenylalanine levels are above target range. In addition, children have been taken into care through safe guarding procedures when dietary restrictions are not adhered to, highlighting both the seriousness of the condition and the difficulty in maintaining dietary treatment.

	There are many adult patients (potentially up to 50% of all adults with PKU) who are unable to follow dietary treatment. They may be bored with their food choices on a low Phe diet or do not have the skills to manage their own diet. Many adults have good intention and try to return to diet but commonly this is unsuccessful (Ford et al 2017a). Evidence from systematic reviews demonstrates that in early treated adults with PKU (ETPKU) significant suboptimal outcomes exist including deficits in executive functioning, attention problems, decreased verbal memory, expressive naming and verbal fluency, as well as social and emotional difficulties (Bilder et al 2016). Adults who have not been treated early and continuously have been reported to develop neurological complications such as leukoencephalopathy, spastic paraparesis, brisk reflexes, tremor, poor mental health, psychiatric symptoms (Daelman et al 2014) and vision loss (Anwar 2013, Rubin 2013). Tremors have also been detected in ETPKU, although they are more frequent and severe in late treated patients. Many adults with PKU have a vegan-like diet but may not take Phe-free protein substitute (Trefz et al 2011) and consequently may be at risk of micronutrient deficiencies (Rohde et al 2014) such as vitamin B12 deficiency. There is increasing documentation of women with PKU being overweight and obese (Gokmen Ozel 2014, Robertson, 2013). The risk of comorbidities makes dietary management more complex (MacDonald et al 2015). The risk of low bone density has widely been acknowledged but the risk of bone fractures is still unclear (Demirdas et al 2015). Also, maternal PKU is particularly challenging to manage. A recent NSPKU survey (Ford et al 2018b) indicated that some women were very frightened about pregnancy; they feared they would damage their baby due to their perceived inability to manage their diet in pregnancy. Thereby they chose not to have

	sexual relations in order to avoid the chance of pregnancy. The use of sapropterin should significantly ease the difficulties associated with dietary management to enable women to have a more normal family life.

Anwar MS, Waddell B, O'Riordan J. Neurological improvement following reinstitution of a low phenylalanine diet after 20 years in established phenylketonuria. BMJ Case Rep. 2013 Jul 12;2013.
Bilder DA, Noel JK, Baker ER, et al. Systematic Review and Meta-Analysis of Neuropsychiatric Symptoms and Executive Functioning in Adults With Phenylketonuria. Dev Neuropsychol. 2016 May-Jun;41(4):245-260.
Daelman L, Sedel F, Tourbah A. Progressive neuropsychiatric manifestations of phenylketonuria in adulthood. Rev Neurol (Paris). 2014 Apr;170:280-7
Demirdas S, Coakley KE, Bisschop PH, Hollak CE, Bosch AM, Singh RH. Bone health in phenylketonuria: a systematic review and meta-analysis.Orphanet J Rare Dis. 2015 Feb 15;10:17.
Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community. Mol Genet Metab Rep. 2018a Oct 18;17:57-63.
Ford S, O'Driscoll M, MacDonald A. Reproductive experience of women living with phenylketonuria. Mol Genet Metab Rep. 2018b Nov 2;17:64-68.
Gokmen Ozel H, Ahring K, Bélanger-Quintana A, Dokoupil K, Lammardo AM, Robert
M, Rocha JC, Almeida MF, van Rijn M, MacDonald A. Overweight and obesity in PKU: The results from 8 centres in Europe and Turkey. Mol Genet Metab Rep. 2014 Nov 16;1:483-486.
MacDonald A, Ahring K, Almeida MF, Belanger-Quintana A, Blau N, Burlina A,Cleary M, Coskum T, Dokoupil K, Evans S, Feillet F, Giżewska M, Gokmen Ozel H, Lotz-Havla AS, Kamieńska E, Maillot F, Lammardo AM, Muntau AC, Puchwein-Schwepcke A, Robert M, Rocha JC, Santra S, Skeath R, Strączek K, Trefz FK, van Dam E, van Rijn M, van Spronsen F, Vijay S. The challenges of managing coexistent disorders with phenylketonuria: 30 cases. Mol Genet Metab. 2015 Dec;116(4):242-51. Nutr Diet. 2013 Jul;26 Suppl 1:1-6.
Robertson LV, McStravick N, Ripley S, Weetch E, Donald S, Adam S, Micciche A, Boocock S, MacDonald A. Body mass index in adult patients with diet-treated phenylketonuria. J Hum Nutr Diet. 2013 Jul;26 Suppl 1:1-6
Rohde C, von Teeffelen-Heithoff A, Thiele AG, Arelin M, Mütze U, Kiener C, Gerloff J, Baerwald C, Schultz S, Heller C, Müller AS, Kiess W, Beblo S. PKU patients on a relaxed diet may be at risk for micronutrient deficiencies. Eur J Clin Nutr. 2014 Jan;68:119-24.
Rubin S, Piffer AL, Rougier MB, Delyfer MN, Korobelnik JF, Redonnet-Vernhet I, Marchal C, Goizet C, Mesli S, Gonzalez C, Gin H, Rigalleau V. Sight-threatening phenylketonuric encephalopathy in a young adult, reversed by diet. JIMD Rep. 2013;10:83-5.
Trefz F, Maillot F, Motzfeldt K, Schwarz M. Adult phenylketonuria outcome and management. Mol Genet Metab. 2011;104 Suppl: S26-30.

What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	The treatment of PKU is by a very strict low Phe diet (10 to 20% of a normal diet). This consists of three main principles: 1) exclusion of high Phe foods e.g. meat, fish, eggs, cheese, bread, flour, pasta and aspartame; 2) provision of Phe requirement from weighed amounts of foods such as potatoes, peas, cauliflower and broccoli and 3) administration of a synthetic protein substitute to give 80 to 90% of protein requirements. It is also supplemented with vitamins and minerals. Therefore, the diet involves calculation of daily Phe intake from food, taking synthetic protein three to four times daily, and preparing home-made

	meals from specialist low protein flour. Special low Phe food looks, smells and tastes different from normal. Every mealtime is a challenge as food choices are very limited and unpalatable and the diet restricts social activities. Overall this treatment is very difficult for patients and carers. Dietary adherence decreases with age (research indicates that up to 30% of children under the age of ten years and 80% by the age of 15 do not achieve acceptable Phe levels) (Walter et al 2002). Adherence to dietary control and treatment recommendations is a long-standing concern to clinicians involved particularly with the care of adult and adolescent PKU patients. The synthetic protein substitute is poorly tolerated and failure to take prescribed amounts of this adversely affects blood Phe control and causes vitamin and mineral deficiencies. Overall patients require significant support, including practical and psychosocial support. Adults who do manage a low Phe diet are often dependent on partners or parents for dietary support and motivation. Walter JH, White FJ, Hall SK, et al. How practical are recommendations for dietary control in phenylketonuria? Lancet. 2002 Jul 6;360(9326):55-7.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	European PKU Guidelines 2017: van Wegberg AMJ et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis. 2017 Oct 12;12(1):162.
• Is the pathway of care well defined? Does it vary or are there	The pathway of care for PKU should be consistent in England although this is always some clinical variation depending on the position and attitude of clinician. 1. All infants are diagnosed by newborn screening.

differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	2. All patients are treated with a low Phe diet if blood Phe levels are consistently >360 µmol/L following newborn screening. The application of the diet therapy is the same. 3. All patients are treated lifelong. 4. All patients are recommended to perform regular blood Phe monitoring by taking blood Phe spots at home and sending them to the hospital for analysis. 5. There are slight differences between the target upper blood Phe recommendations for adults with PKU nationally (UK historical upper Phe target is 700 µmol/L). This was revised and lowered to 600 µmol/L in the European Guidelines 2017. The new European guideline is applied by most centres except possibly London. 6. All clinics recommend strict pre-conception diets prior to and during pregnancy. 7. All clinics have a similar transition process between adult and paediatric centres. 8. Resources for dietitians and psychologists vary between clinics which affects the quality of care that some clinics can deliver.
• What impact would the technology have on the current pathway of care?	Considering that only 20 to 30% of patients respond to sapropterin, the use of sapropterin does involve an extra testing procedure to see if individual patients respond to it. This involves the following additional processes: • Stage 1: Mutation analysis. This is not routinely done in the UK. The European guidelines recommend that if mutation analysis is performed the following guide is followed: ▪ If a patient has two null mutations: then there will be no benefit from conducting a sapropterin test responsive test; so patients are managed by a low Phe diet only.

	▪ If a patient has two responsive mutations: they should be treated with sapropterin without an additional sapropterin loading test. ▪ If a patient has one responsive mutation or the genotype is not identified: then they should undertake a sapropterin loading test. NB: it is unknown what the mutation landscape is of the English PKU population, although there is suggestion that he North of England is more associated with classical/severe PKU (likely to have two null mutations) and the south of England milder PKU. Therefore, an unknown proportion of the PKU population will require a sapropterin loading test; but the rest of the population (with 2 null mutations) will receive no change in treatment or if there are 2 responsive mutations, sapropterin can be given directly. There are different ways of performing a sapropterin loading test, but NHS England have recommended that this is performed over 7 days and if the results are suggestive of sapropterin responsiveness, then a treatment trial should be conducted over 30 days. A suggested guide to how this should be performed and the steps involved is as follows: **Procedure for pre- sapropterin loading test (Home)**

	Blood Phe concentration should be **> 360 µmol/L** at the **commencement** of the sapropterin loading test, so in the week prior to the test, it is usually necessary to double the Phe intake for 7 days prior to the test. This requires at least twice weekly blood Phe monitoring. A daily dietary record should be maintained during this time. **Procedure for sapropterin loading test (Hospital visit day 1, home day 2 to 7)** ▪ baseline fasting blood Phe. ▪ administer BH4 (20 mg/kg/day) once daily with breakfast. ▪ continue same dose of BH4 for 7 days with the same amount of additional Phe administered in the pre- sapropterin loading test. ▪ perform at least alternate day blood Phe concentrations by blood spots. ▪ maintain 7-day diet record. ▪ On day 7, if ≥30% reduction in Phe has been observed, this is associated with BH4 responsiveness **Procedure for 28 day treatment trial to help establish protein tolerance** ▪ continue daily dose of sapropterin and increase natural protein intake using the following guide: ▪ *if 3 consecutive blood Phe are < 360 µmol/L*: *increase Phe intake by 20% (step wise)* ▪ if 2 consecutive blood Phe are > 360 µmol/L: *reduce Phe intake by approx. 20%, depending on the degree of elevation of the blood value* ▪ if mean blood Phe concentrations are around 360 µmol/L: *do not change Phe intake*

	▪ Blood Phe by blood spots should be conducted twice weekly at home. ▪ If dietary Phe intake is increasing but ≥75% of blood Phe concentrations are maintained within target range, then Phe intake should continue to be increased. Patients should have a clinic review, assessing the overall efficacy of sapropterin every 6 months. The dietitians will continue to modify the diet, and potentially increase natural protein intake in between formal clinic visits.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No but it is only the procedures associated with establishing responsiveness that will require additional work load. This should be conducted once for each patient with PKU. However, this procedure needs to be carefully conducted. It requires diligence from the PKU team as well the patient and family with good monitoring and record keeping required. It is important to have good knowledge about the natural protein intake at the time of testing.
• How does healthcare resource use differ between the technology and current care?	More resource will be necessary for: ▪ Patient mutation identification: blood sampling, analysis and interpretation. ▪ Dietetic time for pre-sapropterin loading (challenge with additional protein – 2-3 hours of dietetic time per patient). ▪ Nursing and dietetic time for 7-day loading testing: 2 hours nursing time; 3 hours dietetic time per patient. ▪ 28-day trial to help establish protein tolerance: 3 hours dietetic time per patient. ▪ Additional blood Phe monitoring (at least 12 blood samples inclusive of 28-day treatment trial).

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist PKU clinics with access to specialist dietitians and nurses.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	• Patient mutation identification: blood sampling, analysis and clinical interpretation. • Hospital day facility to undertake day 1 of Phe loading test. • Approx. 2 days of additional dietetic time per loading test for dietetic education, supervision and interpretation of blood Phe. • 2 hours nursing time to supervise day 1 administration of drug. • Medical time: prescription of drug and monitoring of drug efficacy and safety.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Increase in dietary Phe tolerance Sapropterin has been shown to significantly increase the Phe tolerance of children with PKU. In a study conducted by Trefz et al 2009, Phe tolerance increased by 20 to 30 mg/kg/day. In practical terms this would enable patients to tolerate foods such as ordinary bread, flour, pasta, pulses and all vegetables without measurement. This is more similar to a vegan diet, allowing a considerable easing of dietary restrictions which improves social inclusion. Belanger-Quintana et al. (Belanger -Quintana et al 2012) showed in 7 patients who were given sapropterin over 5-18 months that they at least doubled their Phe tolerance and 4 patients tolerated a normal protein intake without requiring Phe-free amino acid supplement. Similarly Burlina et al. (Burlina and Blau 2009)

	reported a 2-3 fold increase in Phe tolerance with sapropterin treatment and 12 patients discontinued Phe-free amino acid supplements. Reduction in the use of 'Foods for Specialist Medical Purposes' There should be significant reduction in the use of 'Foods for Specialist Medical Purposes' with sapropterin. This includes both protein substitute and low protein special foods. ' Protein substitute is an essential part of a low Phe diet and is reported to provide anything from 52-80% of the total protein intake in patients with PKU on diet (van Wegberg et al 2017). However, acceptance and administration of Phe-free amino acid substitute is particularly challenging. They are bitter tasting, the volume required is high and they are given evenly throughout the day (at least 3 times) to avoid amino acid oxidation and minimize blood Phe fluctuation. In addition, the rigorous regimen of 3 times daily dosing is demanding and dosages are commonly missed or partly given. They may also cause gastrointestinal upset, particularly if taken very concentrated or without extra fluid (Van Wegberg et al 2017). It is well established that protein substitute supplementation is problematic for many patients due to poor palatability, so any change/reduction in dosage associated with saproterin usage is advantageous. Data from 8 PKU centres from 8 countries reported the dietary management of 291 sapropterin responsive patients. Fifty-six per cent (n=163) achieved WHO/FAO/UNU safe levels of protein intake. Eighty-two (28%) did not require Phe-free protein substitute and in the remaining patients, the protein substitute dosage was reduced by 60% (Yilmaz et al poster, ESPKU 2018). Lambruschini et al. (Lambrushini et al 2005) in 11

saproterin responsive patients with mild/moderate PKU, completely removed protein substitute from the diet while maintaining good metabolic control after 1 year of treatment with sapropterin. In the USA, in 15 responsive patients, all but one required less than 50% of original dose of protein substitute and 5 of 15 (33%) subjects were able to stop the protein substitute intake. The energy intake provided by protein substitute decreased from 20 to 5% of energy intake (Brantley et al 2018).

Low protein special foods are important to provide variety and adequate energy to meet requirements in a low Phe diet. Despite significant development in their taste, presentation and variety, families still struggle with adherence due to their dry starchy presentation, lack of flavour, limited availability, financial cost and difficulties in their preparation (Bilginsoy et al 2005, MacDonald et al 2010). They also have poor nutritional quality and some have a higher energy, fat and carbohydrate profile than their equivalent regular products. There is data to show that their use is minimal in sapropterin responsive patients. In a carefully conducted a longitudinal study, energy intake supplied by low protein foods decreased from 39% of intake to 3% of energy intake (Thiele et al 2015).

Special protein substitutes and low protein foods are expensive. The annual estimated costs on diet treatment only are given in the table below.

Cost of low phenylalanine diet for adult with PKU: calculated Dec 2018

Daily requirement	Cost per annum		Cost per annum

60 g protein equivalent from protein substitute *Based on the average cost of 3 brands*	11,617	80g protein equivalent from protein substitute *Based on the average cost of 3 brands*	15,489
Weekly requirement		**Weekly requirement**	
114g low protein bread /day (800g/week)	416	114g low protein bread /day (800g/week)	416
500g low protein flour per week	364	500g low protein flour per week	364
400 ml low protein milk day (14 cartons per week)	927	400 ml low protein milk day (14 cartons per week)	927
250g pasta week	224	250g pasta week	224
1 pizza base week	224	1 pizza base week	224
100g sausage mix/burger mix week	265	100g sausage mix/burger mix week	265
Total cost	£14,037	Total cost	£17,909

Adult requirements for protein substitute will vary between 60 to 80g/day of protein equivalent which will affect cost.

Cost of low phenylalanine diet for children with PKU: calculated Dec 2018

3 y old child weighing 14 kg		**7 y old child weighing 22kgb**	
Daily requirement	**Cost per annum**		**Cost per annum**
40 g protein equivalent from protein substitute* *Based on the average cost of 2 brands*	8,251	50g protein equivalent from protein substitute *Based on the average cost of 2 brands*	9526
Weekly requirement		**Weekly requirement**	

40g low protein bread /day (280g/week)	145	80g low protein bread /day (560g week)	290
250g low protein flour per week	182	500g low protein flour per week	364
600 ml low protein milk day (21 cartons per week)	1391	400 ml low protein milk day (14 cartons per week)	927
125g pasta week	112	250g pasta week	224
0.5 pizza base week	112	1 pizza base week	224
50g sausage mix/burger mix week	133	100g sausage mix/burger mix week	265
Total cost	£10,326	Total cost	£11,820

*Protein substitute gels/pastes are used for children usually up to 4yrs. These are more expensive because the demand for these is smaller than for liquid protein substitutes.

Improved blood phenylalanine control: with an expectation that blood phenylalanine levels should be mainly within target range and stay consistent over time.

Improved nutritional outcome

Vitamin and mineral status: Vitamin B12 deficiency is commonly reported in the adult population, requiring vitamin B12 injections. Women with PKU have been observed to have thinning hair and poor skin, possibly associated with nutritional deficiencies. Sapropterin will increase natural protein intake which will improve

overall nutritional status. In contrast and associated with excessive supplementation of synthetic protein, blood folate above upper reference range is commonly observed and this may increase cancer risk.

Growth and obesity

The results of longitudinal growth studies on diet treatment only indicate that men miss their final height target by 5 cm and women by 3 cm (Thiele et al 2017), and % fat mass is decreased when a higher amount of natural protein is tolerated (Evans et al 2017). Overweight (55%) and obesity (33%) are particularly high in women with PKU (Burrage et al 2012). This observation has been validated in many studies. Obesity in adulthood may be associated with low IQ, poor organisational skills, inability to menu plan, poor cooking skills and low self-esteem. However, a low Phe diet is also abnormally high in carbohydrate, this may be associated with a lower thermal effect of feeding and post prandial fat oxidation and may be a physiological factor leading to higher overweight and obesity (Alfheeaid et al 2017).

Gastrointestinal intolerance

Gastrointestinal intolerance (gastritis, constipation, abdominal pain, and diarrhoea) occur in PKU (Ford et al 2018a) are associated with protein substitute intake in PKU, particularly its high osmolality. Any reduction in protein substitute intake is seen as advantageous as it should avoid or diminish unpleasant side effects associated with protein substitute intake.

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Bilginsoy C, Waitzman N, Leonard CO, Ernst SL.Living with phenylketonuria: perspectives of patients and their families. J Inherit Metab Dis. 2005;28:639-49.

	Brantley KD, Douglas TD, Singh RH. One-year follow-up of B vitamin and Iron status in patients with phenylketonuria provided tetrahydrobiopterin (BH4). Orphanet J Rare Dis. 2018 Oct 30;13: 192. Burlina A, Blau N. Effect of BH(4) supplementation on phenylalanine tolerance. J Inherit Metab Dis. 2009 Feb;32(1):40-5. Burrage LC, McConnell J, Haesler R, O'Riordan MA, Sutton VR, Kerr DS, McCandless SE. High prevalence of overweight and obesity in females with phenylketonuria. Mol Genet Metab. 2012 Sep;107(1-2):43-8. Evans M, Truby H, Boneh A. The relationship between dietary intake, growth and body composition in Phenylketonuria. Mol Genet Metab. 2017 Sep;122(1-2):36-42. Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community. Mol Genet Metab Rep. 2018a Oct 18;17:57-63. Lambruschini N, Perez-Duenas B, Vilaseca MA, et al. Clinical and nutritional evaluation of phenylketonuric patients on tetrahydrobiopterin monotherapy. Mol Genet Metab. 2005 Dec;86 Suppl 1:S54-60. MacDonald A, Gokmen-Ozel H, van Rijn M, Burgard P. The reality of dietary compliance in the management of phenylketonuria. J Inherit Metab Dis. 2010 33: 665-70. Thiele AG, Rohde C, Mütze U, Arelin M, Ceglarek U, Thiery J, Baerwald C, Kiess W, Beblo S. The challenge of long-term tetrahydrobiopterin (BH4) therapy in phenylketonuria: Effects on metabolic control, nutritional habits and nutrient supply. Mol Genet Metab Rep. 2015 Jul 26;4:62-7. Thiele AG, Gausche R, Lindenberg C, Beger C, Arelin M, Rohde C, Mütze U,Weigel JF, Mohnike K, Baerwald C, Scholz M, Kiess W, Pfäffle R, Beblo S. Growthand Final Height Among Children With Phenylketonuria. Pediatrics. 2017 Nov;140(5). Trefz FK, Burton BK, Longo N et al. Efficacy of sapropterin dihydrochloride in increasing phenylalanine tolerance in children with phenylketonuria: a phase III, randomized, double-blind, placebo-controlled study. J Pediatr 2009; 154:700-7. van Wegberg AMJ, MacDonald A, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, Burlina A, Campistol J, Feillet F, Giżewska M, Huijbregts SC, Kearney S, Leuzzi V, Maillot F, Muntau AC, van Rijn M, Trefz F, Walter JH, van Spronsen FJ. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis. 2017 Oct 12;12(1):162 WHO/FAO/UNU. Protein and amino acid requirements in human nutrition. Report of a joint WHO/FAO/UNU Expert Consultation. 2007. WHO Technical Report Series 935, United Nations University.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	The burden of care of a low Phe diet is severe and intense and consensus opinion would suggest that this is particularly difficult when compared with other dietary and pharmaceutical treatments. It is a more demanding treatment than administering medication or injections. A low Phe diet is associated with anxiety, psychological distress, stigmatisation, and disordered eating. Patients on dietary treatment require

	significant support, including practical, motivational, counselling and psychosocial support which are all costly. People with PKU on a low Phe diet face constant challenging situations about food choices; their diet is regimented, isolating and patients are expected to exercise remarkable discipline as well as cope with dietary adversity. Catering establishments do not provide or understand how to prepare very low protein food. Not surprisingly many patients struggle to adhere to this treatment and some children with poor blood Phe control are taken into care through safe guarding procedures because of parental incapacity to apply treatment. Poor patient blood control requires considerable extra health professional intervention and time. In adulthood, maintaining a lifelong low phenylalanine diet is not a realistic option for many adult patients; they commonly must compromise their treatment and follow partial diet only or even stop diet.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	A subset of patients with PKU who are responsive to sapropterin identified by mutation analysis or by sapropterin responsiveness testing. This is expected to be about 20 to 30% of all the English patients with PKU.
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	After sapropterin responsiveness testing has been established, the drug therapy will be much easier to administer than a low Phe diet only for the following reasons: 1. Less use of protein substitute: this will substantially improve the acceptability of the diet, minimise gastro-intestinal effects, minimise stress, upset and tensions between caregivers and children associated with its administration. It will reduce the need for dietary prescriptions, home delivery and access issues. 2. Minimal use of low protein special foods. Overall there should be less use of 'low protein food' prescriptions, specialist cooking, reduced planning associated with mealtimes, lower rate of feeding problems and disordered eating. 3. In the long term, it will reduce professional time by reducing the need for additional dietary counselling when trying to gain adherence with patients/caregivers who struggle with strict dietary treatment. 4. Help women with pre-conception and maternal dietary management in pregnancy. Women may not be as frightened by the thought of pregnancy as less rigorous dietary restrictions should be easier to follow. 5. Reduced anxiety for patients and caregivers.

	A more normal life for patients associated with less planning of meals and food preparation, increased ability to socialise and 'eat out,' going on holiday, eating school and nursery meals, and less teasing or bullying by peers at schools and less dependence on caregivers. 1. Overall, sapropterin therapy is easy to administer. The tablets are dissolved in a small amount of water and taken once daily with breakfast.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes: **Starting treatment** Considering that only 20 to 30% of patients respond to sapropterin, the use of sapropterin does involve an extra testing procedure to see if individual patients respond to it. This involves the following additional processes: ▪ Mutation analysis. - If a patient has two null mutations: then there will be no benefit from conducting a sapropterin test responsive test; so patients are managed on a low Phe diet only. - If a patient has two responsive mutations: they should be treated with sapropterin without an additional sapropterin loading test. - If a patient has one responsive mutation or the genotype is not identified: then they should undertake a sapropterin loading test.

	If a patient does only have one responsive mutation or an unidentified genotype, they will undertake a 7 day loading test (with aim of achieving ≥30% reduction in blood Phe levels), and if this is achieved it will be followed by a 28 day treatment trial. The aim of the treatment trial is to increase dietary Phe intake but still maintain ≥75% of blood Phe within target range. If this is achieved, daily sapropterin should continue to be administered and monitored, with a review of overall efficacy sapropterin occurring each year. It is expected that sapropterin should at least increase natural protein tolerance by 100%. **End treatment** If a patient does not have a reduction of blood Phe associated with ≥30% reduction following the 7-day loading test, the drug should be stopped. If the drug is continued, but at 6-month review if there is evidence that natural protein tolerance has not substantially increased (by 100% of prescription at sapropterin commencement) or there are < 75% of blood Phe levels within target range (without explanatory reasons such as illness), then the drug treatment should be stopped.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year wer without (QALY) calculation?	This is difficult to answer without knowledge of what has been included in the QALY calculation. However, it is important that nutritional outcome, growth, obesity and any cost savings associated with less use of 'Medical Foods for Special Purposes' are considered.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Treatment adherence is low with dietary management in all age groups. By adulthood, it is known that 79% of adults fail to control their blood phenylalanine levels within target range even though lifelong treatment is recommended. Some patients describe moving in and out of dietary treatment but struggle to recommence dietary treatment. Probably 50% of adult patients have stopped diet completely because they are unable to adhere to it. It is unrealistic to expect patients to maintain such a restrictive diet when this is so difficult to apply on a day to day basis. Therefore for 20-30% of patients with PKU, sapropterin will offer an alternative treatment that is easy to administer and will substantially lessen the need for 'Foods for Special Purposes.' For these patients it will ensure that they can be prescribed a treatment they are able to adhere to, maintain their blood Phe within target reference range for their age and substantially increase their natural protein tolerance.

• Is the technology a 'step-change' in the management of the condition?	This is a long-awaited improvement in the management of patients with PKU. Many people struggle with dietary management evidenced by the deteriorating blood phenylalanine control with age. They find it tedious, difficult and impractical
• Does the use of the technology address any particular unmet need of the patient population?	Sapropterin will benefit a sub section (20 to 30%) of the PKU population who have mild or moderate PKU who are proven to be responsive to this drug.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Sapropterin appears to be a safe drug. It has been widely used for 10 years in Europe. In clinical trials in children aged 4 years and above, adverse events with an incidence of ≥10% were headache and rhinorrhea; those occurring with an incidence of ≥1% to < 10% were pharyngolaryngeal pain, nasal congestion, cough, diarrhoea, vomiting, abdominal pain and hypophenylalaninemia. In children aged below 4 years who received treatment with sapropterin (10 or 20 mg/kg/day), the most commonly reported adverse reactions were hypophenylalaninemia, vomiting and rhinitis. Hypersensitivity reactions, including serious allergic reactions and rash, were also reported.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes: the UK contributed to most of the Clinical trials on sapropterin in all age groups of patients.

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	1. Continuous use of sapropterin is associated with a significant and persistent decrease in blood Phe. 2. Increase in natural protein tolerance, lowering of phenylalanine-free protein substitute dosage, reduced need for low protein special foods, and in some patients, it will lead to a normal diet. 3. Improved quality of life. This was not so well demonstrated in the clinical trials, but I care for 9 patients on long term Kuvan (mainly as part of clinical trials). The quality of their lives and their caregivers as improved beyond recognition. 4. The drug is well tolerated and appears safe. 5. Longitudinal data show that neurocognitive function and development are maintained within the normative range, and no children appear at risk of developmental delay.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not relevant.
• Are there any adverse effects that were not apparent in clinical trials	No

but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Data from The Kuvan® Adult Maternal Paediatric European Registry (KAMPER) PKUDOS registry Data from The PKUDOS registry experience
20. How do data on real-world experience compare with the trial data?	Sapropterin lowers blood Phe concentrations and improves Phe tolerance. We care for 9 children either on the 7-year sapropterin study (Kognito) or funded by IFR's. All children tolerate more than 20g/day natural protein (usual amount <10g/day), they have maintained consistent blood Phe levels over many years, and their quality of life has undoubtedly improved. The children are less dependent on parents, there are few issues at school or nursery with provision of meals and snacks, protein substitute dose is usually reduced by at least 50% of the previous dose, families are more likely to travel abroad on holiday, there is much less stress associated with food and mealtimes and the children and their families are usually less anxious and overall happier. Children have a better life- it is more normal.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	• Late treated/untreated patients with PKU: who may be neglected and seen as a low priority for treatment needs. Many of these patients are already brain damaged but could receive considerable improvement in their quality of life /and require less carers time in 'care homes'.

	• Patients with low IQ and poor executive functioning/communication skills who may be unaware, fail to understand or unable to articulate why they need this treatment. • Patients who had their diets discontinued by their hospitals in their childhood and are longer in the hospital system. Some of these patients may be suffering significant health problems but are unaware that the problems they have may be linked to PKU. It is not the fault of these patients that they were discharged from the hospital system years ago and there has been no active attempt to identify these patients. • There are a high number of travelling families with children/adults with PKU living in caravans who have no access to sterile water supplies or regular electricity. This leaves patients very vulnerable and at risk of sub-optimal treatment. • Patients with co-morbidities such as autism, diabetes, gut disorders. There is a need to identify adult patients lost to follow up – a national register of patients should be maintained by the NHS.
21b. Consider whether these issues are different from issues with current care and why.	If sapropterin is approved by NICE, it is possible that some of these patients would benefit from sapropterin. It may enable many of these vulnerable patients to have a more practical treatment for their PKU, which they can adhere to. However, these patients may be considered a low priority compared with other patients during any sapropterin testing phase.

Key messages
22. In up to 5 bullet points, please summarise the key messages of your submission. • Sapropterin is an adjunct treatment that is effective and will help 20 to 30% of sapropterin responsive patients with PKU. • It is well established that it will lower blood Phe levels and maintain blood Phe levels within target ranges over time; it substantially increases natural protein tolerance and reduces the need for 'Foods for Special Medical Purposes.' • Sapropterin has been shown to be safe in clinical trials and there is extensive experience with its use • Sapropterin responsive testing requires careful management by treatment centres. • From practical experience of caring for patients on trials using sapropterin, this drug substantially reduces the burden of care and will enable more patients with PKU to maintain a blood Phe within target range, which should lead to better neurocognitive outcome.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Sapropterin for treating phenylketonuria [ID1475]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Inherited Metabolic Disease Group**

3. Job title or position	**Paediatric Inherited Metabolic Disease Consultant**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	Charitable organisation representing multidisciplinary health professionals involved in the care of children and adults with inherited metabolic disease within the UK. Funded by membership and receives industry sponsorship for annual symposia.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	The aim of treatment is to prevent moderate-severe intellectual disability – the hallmark of untreated phenylketonuria (PKU). Intellectual disability results from elevation of the dietary amino acid phenylalanine (Phe). In PKU, elevated Phe results from deficiency of the enzyme phenylalanine hydroxylase which would normally convert Phe into tyrosine (Tyr).

or prevent progression or disability.)	The long-established recognised treatment for PKU is a medically prescribed protein-restricted diet which reduces dietary Phe intake, and which, when started early in life, prevents intellectual disability. A PKU diet entails severe dietary protein restriction. Many patients will be recommended not to eat any foods of high protein value eg. meat, fish, eggs, dairy at all. Others will also need to restrict their intake of foods that contain some protein eg. standard flour, pasta, bread, cakes, biscuits etc. Such a diet requires requires daily supplementation with specific prescribed amino acid, vitamin and mineral supplements (2-3 times per day). Alternative synthetic low protein medical foods such as bread, pasta, flour are prescribed and require skill and time to prepare palatable meals. Lifelong, this PKU diet is challenging, impacts on all aspects of living (home / school / work / social) and commonly results in reduced adherence, particularly from adolescence onwards. Low protein foods look and taste different from ordinary foods. Individuals with PKU have reduced food choices. Reported long-term clinical complications of higher Phe concentrations include decreased neurocognition, reduced executive function, school difficulties and problems with social integration. The aim of treatment with Sapropterin is to increase Phe tolerance and reduce or remove the burden of the PKU diet. This will support achievement of optimum Phe levels and improve the quality of life in those patients who are Sapropterin responsive. Optimum Phe levels within recommended targets will prevent PKU-related intellectual disability.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	A significant clinical response can be defined in terms of increased intake of natural dietary protein and / or in improved phenylalanine control. A pragmatic approach to this is taken by the ESPKU European guidelines (2017). A significant increase in natural protein intake is defined as a 100% increase in natural dietary protein intake. Improved phenylalanine control is defined as >75% of phenylalanine levels within the (NHS) recommended target range (100-360 umol/L for children up to 12 years; up to 600 umol/L for individuals 12 years of age and older).

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. The PKU diet is currently the only treatment modality available to control phenylalanine levels. Although this will continue to be the treatment of choice for the majority of PKU patients, treatment with Sapropterin for those individuals who are Sapropterin-responsive provides the first alternative therapy to reduce the burden of the dietary regimen, improve Phe tolerance and may remove the need for the PKU diet in some individuals.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	PKU is treated by a prescribed low protein diet, supplemented by amino acids, vitamins and minerals, and with (synthetic) low protein prescription foods. Phenylalanine is an essential amino acid and therefore in order to avoid deficiency, a measured amount of phenylalanine is allowed in the diet - foods such as potatoes, cereals, rice have to be weighed and given in measured portions throughout the day. In order to achieve adequate nitrogen for growth a protein substitute containing all the other essential amino acids, vitamins and minerals has to be taken a minimum of two-three times a day. These protein substitutes are based on pure amino acids and are often unpalatable making adherence to diet an extra burden In order to achieve adequate calories and variety in the diet low protein foods are prescribed. These foods offer an alternative to standard foods but they look and taste different. Skill and time are needed to prepare foods to ensure palatability.

	There are additional hidden and unquantified burdens associated with this chronic dietary restriction - some of these have been studied - psychological, emotional, social and clinical consequences, affecting both the person with PKU and the wider family.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	UK based guidelines (Medical Research Council working party on PKU – 1993) are available and, more recently, european guidelines on PKU have also been published (Lancet / Orphanet Journal of Rare Diseases – 2017). Uptake of the European Guidelines in England has not been ascertained.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In England, pathways for screening and diagnosis are well defined. There is good consensus for the main principles of long-term management, in particular the need for tight control and regular monitoring of phenylalanine levels during childhood, adolescence / young adulthood and pregnancy. Treatment for life is recommended (US, European & UK guidelines) – though it is recognised that some adults may choose to return to an unrestricted liberalised diet. It is recommended that these adults also remain under long-term follow-up if possible. In practice, there is some variability in some of the more detailed aspects of management – an example of this includes the precise defined target range for Phe during pregnancy. There is already an NHS policy on the use of Sapropterin during pregnancy.
• What impact would the technology have on the current pathway of care?	An additional stream would need to be added to the current pathway of care to cater for patients who wanted to access Sapropterin, to adequately assess whether individual patients are responsive (see section 10) and define the ongoing criteria for treatment. The proportion of patients that would be Sapropterin responsive depends on genotype prevalence, which is unknown in the UK. Based on the known response rates in Europe, where Sapropterin is commonly used,

	response rates would be expected to be between 20-40% [Southern European countries tend to have higher response rates, so the UK population is expected to have a response rate nearer 20%]. This technology may have an impact on the newborn screening programme. Part of the recommended assessment for Sapropterin responsiveness (see the NHS England Interim Clinical Policy for Sapropterin) includes sequence analysis of the gene involved in PKU (*PAH*). This is to identify patients who are genetically predetermined to NOT respond to Sapropterin. If genetic testing comes into routine practice, then addition of genetic testing into the newborn screening programme would seem a logical progression. Furthermore, testing for sapropterin responsiveness (and for Biopterin disorders) with a trial of Sapropterin in the newborn period could then be considered as part of the newborn screening programme.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Patients who use Sapropterin successfully are expected to have an increase in Phe tolerance (ie. natural dietary protein intake) and therefore, • a decrease in the need for prescribed low-protein foods • a decrease in the need for prescribed amino acid, vitamin and mineral supplements
• In what clinical setting should the technology be used? (For example,	Specialist inherited metabolic disease clinics, generally outpatient setting.

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Testing should be coordinated by specialist inherited metabolic disease centres managing individuals with PKU. A clear and agreed protocol for response testing is recommended to be part of any future Sapropterin policy to ensure equity across different metabolic services. Response testing should include genotyping of individuals. It will be important to ensure resources are in place to conduct genetic testing in a timely manner and to support clinical teams who may face a large number of parent / patient requests for response testing. Genetic testing is not routinely funded for all individuals with PKU at present. The process of Sapropterin response testing will require additional clinician & dietitian time and increased patient monitoring (laboratory bloodspot tests). Once a clinician has prescribed Sapropterin, the week-to-week management of dietary manipulation will be managed by the specialist dietetic services in close liaison with the clinical team. The initial response testing is time consuming and a limit to the number of people per month who could be tested would have to be agreed (ideally nationally by all specialist inherited metabolic disease services). If Sapropterin is successful, management after this initial phase would be less intensive.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	For those patients who are Sapropterin responsive, management with Saproterin and diet instead of PKU diet alone is likely to result in a reduction in the burden of the current PKU diet. Those with poor adherence to diet may have a clinically significant improvement in phenylalanine control and stability of phenylalanine concentrations.
• Do you expect the technology to increase	No

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Published studies to date have reported variable improvements when comparing Sapropterin to current PKU diet alone – but in those individuals who find the PKU diet very burdensome and are Sapropterin-responsive, then an improvement in quality of life would be expected.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are *PAH* genotypes known not to be responsive to Sapropterin. Sapropterin would be ineffective in individuals with these genotypes.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	Sapropterin tablets can be dissolved in water or juice and taken once a day, and should therefore be easier for patients than the current PKU diet. The initial practical implications of assessing Sapropterin responsiveness will involve extra commitment for patients and healthcare professionals and include genetic testing (see section 10).

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Once established on Sapropterin therapy, standard phenylalanine and dietary monitoring would continue. In some Sapropterin-responsive individuals, longer-term Phe concentration may be more stable and not require such frequent monitoring, and therefore reduce the healthcare professional workload also. The technology will bring additional benefits – improving Phe tolerance, decreasing the need for protein substitute and low protein prescribed foods and giving individuals with PKU the freedom to eat a more liberal diet.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, there is general agreement among the UK IMD centres that appropriate 'start and stop' criteria will be recommended. These criteria will include a nationally agreed response testing protocol (see section 10) that would incorporate additional genetic testing, dietary and phenylalanine monitoring.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	A recently published article (Mol Genet Metab Rep. 2018 Oct 18;17:57-63) reports the practical, social and psychological issues of patients, parents and carers, related to PKU.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Overall, the benefits expected are chiefly in reduction in the burden of the current PKU diet therapy and hence improved quality of life. For some patients these benefits might be significant, as might be the improvement in Phe control, particularly if adherence to current PKU diet is very difficult.
• Is the technology a 'step-change' in the management of the condition?	Although there have been significant improvements in the tolerability of the standard dietary therapy, for those PKU patients who are Sapropterin responsive, this would represent the first major innovation in therapy in 50 years since dietary therapy was introduced.
• Does the use of the technology address any particular unmet need of the patient population?	For some patients (& parents who are providing the diet for their children), the daily burden and complexity of the current PKU diet is high. Sapropterin would offer an alternative therapy for those that are responsive, with potential to improve Phe control and increase natural dietary protein intake (ie. return to a more normal liberalised diet).
17. How do any side effects or adverse effects of the technology affect the	Minor side-effects including gastrointestinal upset and headaches have been reported. One small recent study suggested around 15% of patients started on Sapropterin stopped because of such side-effects.

management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Clinical trials looking at the safety and efficacy of Sapropterin were conducted on patient populations that reflect / are applicable to UK clinical practice in the treatment of PKU.
• If not, how could the results be extrapolated to the UK setting?	N / A
• What, in your view, are the most important outcomes, and were they measured in the trials?	1) Safety – trials have assessed the safety of Sapropterin. 2) Efficacy (increase in natural protein tolerance / intake) – trials have assessed whether Sapropterin increases natural protein intake in responsive patients. 3) Long-term improvement in quality of life, comparing treatment with Sapropterin vs PKU diet alone – although the improvement in individual cases is apparent, trials providing long-term data are limited. 4) Long-term improvement of phenylalanine control with Sapropterin vs PKU diet alone – this has been addressed by the PKUDOS registry (section 19 below).

	5) Neurocognitive / neuromotor performance - preserved in children treated with Sapropterin (Genet Med. 2015 May;17(5):365-73; Orphanet J Rare Dis. 2017 Mar 9;12(1):47).
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	PKUDOS register. Large US based register of PKU patients treated with Kuvan, co-ordinated by BioMarin. Ongoing - previously published data in 2015 (Mol Genet Metab. 2015 Apr;114(4):557-63). Demonstrated that Sapropterin has a tolerable safety profile and that continuous use is associated with a significant and persistent decrease in blood Phe and improvements in dietary Phe tolerance. A recently published article (Mol Genet Metab Rep. 2018 Oct 18;17:57-63) reports the practical, social and psychological issues of patients, parents and carers, related to PKU.
20. How do data on real-world experience compare with the trial data?	Registry data above (section 19) is assumed to reflect the real world experience.

Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Sapropterin has been shown to be safe in clinical trials
- Sapropterin, in responsive patients, has been shown to be effective in lowering phenylalanine, improving metabolic control and increasing natural protein tolerance (hence liberalising the restrictive PKU diet)
- Neurocognitive / neuromotor performance is preserved in children treated with Sapropterin
- Although improvement in quality of life by reducing the burden of the PKU diet is apparent in individual cases, long-term evidence of improvement in quality of life is currently lacking
- Careful consideration needs to be taken to ensure that Sapropterin-responsive patients are correctly identified, and that responsiveness testing is structured, equitable and resourced in dedicated specialist inherited metabolic disease clinics.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Sapropterin for treating phenylketonuria [ID1475]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	Metabolic Support UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who	Metabolic Support UK (formerly known as Climb) is the leading umbrella patient organisation for all Inherited Metabolic Disorders and continues to be committed to improving the lives of those affected. The

funds it). How many members does it have?	aims of the charity remain as true today as it was when first founded in 1981. This is whilst evolving with the changing landscape of the rare disease community. The small and dedicated team work hard to: • Providing patients and families with bespoke support tailored to their needs, from point of diagnosis through to young people's transition adulthood and beyond • Connecting families worldwide to reduce isolation and enable them to share experiences • Funding research to develop treatments and support early diagnosis • Working closely with medical professionals to stay ahead in innovations such as new-born screening and treatments • Raising awareness of these conditions amongst the medical, health, social care and teaching professions, as well as the general public. The charity is funded by donations, fundraising and some corporate sponsorship and currently supports over 2,000 patients.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	An online survey was generated in the form of questions derived/rephrased from the questions in this submission form. The survey was sent out to all PKU patients and their families on the Metabolic Support UK database. The questions were open ended and with no word limits to allow patients write their submissions freely in narrative form. The naturalistic approach was decided on to help describe the reality of people's lives as they see and experience them. This was to help explore and comprehend true meanings related to events and complexities caused by PKU, current treatment option(s) and the patients' (and carers') thoughts on Sapropterin. Total number of submissions received was 110; out of which 2 were duplicates and hence excluded. The responses received were from patients (25), carers (80) and patients caring for their PKU children (3). Of the 108 total submissions, 92 stated that they have not submitted their inputs for this appraisal elsewhere and 16 mentioned they've had sent theirs through other means and charities. The data collected was then analysed through a mixed thematic method including both deductive and inductive element. The analysis was based on identifying common themes and issues submitted by patients and carers. A

	manual qualitative analysis was preferred due to the page limitation of this form and to adhere to the timeframe provided by NICE.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with PKU affects both patients and their carers to various degrees. Common themes among patients who responded are: -It's difficult to keep juggling work/studies/family commitments with controlling their diets appropriately, sense of being constantly dependant, social isolation, complex health issues, hard to maintain PHE levels, mental health issues and having to constant worry about the availability and cost of food. A subtle theme that appeared was uncertainty about the level of support that can be obtained through the healthcare system if at all. Also, there there's a confusion whether patients should come off diet altogether after a certain age. "*I struggle being a mum to two young children along with working and studying. As with any mum your priorities are feeding your children/family and often I struggle cooking PKU friendly foods and so I suffer.*" "*I am frequently fatigued, have headaches, can't think clearly, have mood swings, tremors and I deal with depression and anxiety as a consequence.*" "*As an adult who came off diet in my teens, I am noticing the effects of phenylalanine on my brain. I suffer anxiety, forgetfulness, fogginess, fatigue, confusion, severe depression and struggle with organisation and concentration. I have been trying to get my levels back down for a good couple of years now and I'm really struggling."* "*I eat the same things day in day out and cannot fully engage socially as it usually revolves around food.*" "A*ll 'free from' food that is also low in protein is ridiculously expensive and vegan food ALWAYS has protein supplements*" Carers responded in great length describing the challenges faced by their children on their daily life. Children face isolation and social limitations (school trips, festivities, travels). They feel like outcasts. Carers agree that children should be under constant vigilance regarding what the child is offered to eat/eating. When it comes to supplements, feeding them is a challenge, making them understand their health issues is another and the main one is dealing with symptoms of high PHE and the side effects of the supplements. Teenagers with PKU are known to

	feel hungry during their growth spurt. Some children need more attention if they have additional health issues specially if they affect the gastrointestinal system. *" …as my twin girls have multiple food allergies and are also under a gastro consultant and have been since 6 months of age. My daughters have NO prescription foods as they all contain either dairy proteins/potato proteins or wheat proteins."* *"At times for weeks sometimes months it feels we are force feeding her a drink she hates 3 times a day. A drink that at times makes her physically sick."* *"The supplements give gastro issues, and he suffers day to day from stomach pains and diarrhoea."* *"My son is nearly 13, he is going through a growth spurt... he is always hungry! The PKU diet just doesn't fill him up."* *"My daughter was watching a nature programme when she was seven years old. In it a lion was lying dying because there was no food. She started to cry and told me that was how she felt every day."* As for carers, they have additional challenges to face. Most of the responses from carers described in detail how lengthy is the process of purchasing food and preparing meals and how costly it is as well. If they have children who have PKU and other who don't then this usually means double the time for everything. On top of that having to take blood samples all the time, send them away and wait for results adds to the stress. They have to deal with a myriad of mental health issues ranging from anxiety and stress to depression. Time is a common theme, for all aspects of caring for the children. Setting appointments, meeting healthcare professionals, ordering prescription/supplement ordering and getting them delivered and correctly takes time and effort. Another theme constantly present in all replies, is they have to educate professionals about the children's conditions, the teachers, other students' parents, their families and other carers as well about the condition and the diet restrictions. Carers often have to leave their work or take on part time jobs, face difficulties in maintaining healthy relationships, lack support and struggle with getting the support needed. *"Staying up till 2am sometimes preparing food ahead of time to last the next few days. Checking every single food label for hidden dangers such as aspartame"*

	"Food shopping journeys can take 2-3 times longer than they used to before PKU, with visits to multiple outlets (often buying more expensive food ranges) to attempt to broaden and vary the diet as much as possible." *"Not only has it strained my relationship of nearly ten years it…"* *"You have to do blood checks regularly and wait on some cases for 3 -5 days before you get the result."* *"But I have no family support or help. And it's extremely scary that if I don't get her food and supplement right, it causes permanent brain damage"* *"I work part time, but have to work less because he can't eat dinners at school/after school club, so I am worried that he is not eating enough"* *"I gave up work after maternity leave ended as I couldn't trust that someone else who was to care for him would understand the complexity of the dietary controls."* *"Following my son's birth, I was diagnosed with post-natal depression as a consequence of having a child with PKU. I have suffered with depression ever since he was born and have been on medication for years for this. The shock, anger, confusion and guilt about my son not being "normal" in the early days was unbearable."* *"CCG don't even know what's available, we've been told a psychologist is available locally which is not true"* "*He was first told at 16 that he no longer needs the diet, he stayed on diet till 18 before eventually being told to come off….he was told would not affect him at all! His mood/health slowly deteriorated until he ended upon antidepressants and had now had to go back on diet for life! He is now under xxxx, who have stated that it was known all along that being off diet affects most PKU sufferers and that's guidelines are now once again lifelong diet!"*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Of the 108 responses, only 15 patients/carers responded that they're satisfied to an extent with the current treatment option available through NHS. The majority (70 responders) agree that there's a lack of options available in UK. While 12 of the responders who are satisfied with what is available have strongly argued that they'd like to have the chance to at least try other options to see if they work. Treatment and Care for PKU patients available through the NHS vary greatly across the nation. A total of 73 patients and carers stated that they have bad experience with the treatment and care available through the NHS. A total of 39 responders stated they or the patients they care for are still suffering from healthcare issues due to

	elevated PHE levels or as side effects from the supplements. All have responded mentioning the various negative effects the dietary restrictions have on the quality of life and the whole family's lifestyle. There are difficulties accessing prescription food. A common theme identified was that patients and carers take it upon themselves to constantly follow up on deliveries of food supplements and/or prescriptions: time, quality and whether it's correct or not. They do not always find enough support needed, thus, create additional sources of stress they've to worry about. Additionally, mental health of both patient and carer is easily overlooked. *"I reiterate the NHS has served us very well, however science can offer PKU patients a more normal diet, why are we not offering this?"* *"The care is different for everyone. I still visit the GP, and if it isn't my regular doctor, they will always have to google PKU. Care is very fragmented across the UK. From prescription costs, to knowledge, or support events"* *"….as sticking to the diet is very expensive. I.e. A pint of cows milk is about 60p and a carton of coconut milk (low protein alternative) is £1.70."* *"…because at present only a low protein diet is the only available treatment in the UK. Even being on a very restricted diet, I'm unable to sustain phe levels within the normal range which affects me greatly such as low mood, brain fog, poor focus, memory problems and anxiety to name a few when my phe levels rise."*
8. Is there an unmet need for patients with this condition?	All 108 responses agreed that only one treatment option is available which is dietary control. A common theme picked up, through asking them whether they're satisfied with what is available, was that there is a sense of being forced to follow a singular treatment option that is dietary restriction. News about other treatment options available worldwide and their positive impact has been circulating among the community for long time and yet, they're not offered any as options. *"There is only one treatment available- the diet.It places so much strain on the whole family."* *"Options? There is only one option - a severely restricted diet and foul tasting amino acid supplement. The UK is behind the rest of the developed world."*

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients and carers have high hopes that Sapropterin could be life changing for those who respond to it. Patients can adhere to a more normal diet and thus relieve a lot of the downsides of the dietary restrictions and it's burden as stated in questions 7 and 8. It's generally thought to not only improve the quality of life for the patients but their families as well. Also, it is thought to help with a lot of the hidden costs of PKU for both the patients and the NHS. PKU patients and carers feel like they're ignored, and this is thought to -hopefully- be the first major positive change towards a better treatment option to take place in decades. "*A significant increase in the amount of protein they can tolerate. Better health from being able to eat a more varied diet. Fewer gastro issues from not needing to consume so much artificial protein. Greater social access. Fewer mental. Health issues for teenagers who come off diet.*" "*I think we all should have a chance to trial it. Those that respond will have a higher allowance of protein a day and I see it meaning we need less of the expensive prescription foods that GPs moan about us costing too much money.*" "*…Parents would be in a better mental state therefore needing less support from our NHS.*" "*…At last, patients and their families would feel listened to and like they had the back-up of drug option that might help support the diet which is universally acknowledged to be extremely difficult to follow."*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients and carers shared various opinions. There were 55 responses mentioning that they don't think Sapropterin has any disadvantages, while 15 people said they were not sure what the negative impacts of Sapropterin could be. Only 4 stated their fear of not knowing the side effects clearly. Only 16 responses think that it may be a bit costly for the NHS and it is thought that that is the main reason the drug is yet to be available through NHS. Also, 25 responses stated that they understand that Sapropterin may not work for everyone and patients should be educated appropriately before trying it. Other concerns raised included the long-term continuity of the drug in the market, the need of close monitoring by hospitals and clinics, and that not everyone eligible will be able to easily receive it due to local authorities and/or its budget.

	Examples of the responses received: "*None. Those for whom it doesn't work or who suffer side effects always have the diet regime to fall back on. I believe the costs would come down significantly but even with an increased cost compared to diet there are other advantages that outweigh the cost in what is a relatively small number of patients.*" "*It doesn't work for everyone and it is expensive. But so is a lot of other treatment for conditions that are available for them to use so why can't we have Kuvan?"*
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Yes, only PKU patients who respond well to Sapropterin will benefit from the use of this drug. Appropriate education and raising awareness among the patients and their carers before they try Sapropterin is vital.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	As the nature of the available treatment option (dietary restriction) for PKU patients is dependent on caregiver's administration, two forms of inequalities should be considered: A) Patients who face difficulties in accessing healthcare services for various inequality reasons. B) Patients or carers with low socio-economic status might find it harder to prepare and maintain the appropriate diet. Also, the fact that some people can afford to obtain Sapropterin for themselves or their children with Sapropterin because they can financially afford it while others cannot should be an important issue to be considered.

	"*Many families up and down the country who live with PKU get declined when they try to order items such as bread, cereal or biscuits through their doctors. How is it possible that in 2018 in the UK we have people who are being held hostage to their diet and medical condition simply because the doctors cannot afford to uphold the prescription*." *"My husband and I work full time and pay our taxes. We claim no benefits and feel that our son deserves the same treatment choices as the rest of the world. Also, the fact that he will have to pay for his prescriptions in the future is very upsetting."* *"We have taken on the financial burden of funding Kuvan for my son having had him gene tested and discovering we had one responsive gene. He has responded so well and doubled his exchanges on half the dose I believe is required. I understand he would be on more exchanges if we increased to dose but sadly we can't afford it."*
Other issues	
13. Are there any other issues that you would like the committee to consider?	Adult patients showed concerns in their responses that Sapropterin may not be available for them and that the priority will be given to children. "*As an adult, an alternative treatment that eases the restrictions of the diet would be life changing. Please do not just write off a generation of PKU patients. We have families to support, lives to live too*." Patients from Northern Ireland and Scotland are also concerned about being overlooked by the process. *"I feel that because there is no government in Northern Ireland that we will be left behind when the rest of the UK will be able to receive Kuvan"*
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • **Freedom of Choice:** PKU patients and carers strongly agree that they're not given the freedom of choice between options that might work for them or their children. They're all forced to adhere to a single treatment option which is a strict dietary restriction. • **Options:** Patients and carers are aware of various treatment options available overseas. They have high expectations from NICE and NHS to make some of them available if they treatment option works for the patient. They want to be at least able to try for themselves.	

- **Hidden cost of the burden of the Disease:** Knowledge among healthcare professionals on how to manage PKU vary greatly from across UK. Accordingly, access to prescription food is not equally easy. Purchasing food and preparing meals take a lot of time and can be costly. Many carers are not able to maintain a full-time job.
  Patients and carers feel that the hidden cost of the disease should be accordingly assessed.
- **Mental Health** of the patients and carers should be made priority in light of the burden caused by the disease. Patients who have siblings who do not have PKU have their own share of stress as well and that is easily overlooked.
- **Quality of Life** of the whole family becomes affected not only the patients. Other than feeling of isolation and restriction on activities that can be done, families' have to change their entire lifestyle.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Sapropterin for treating phenylketonuria [ID1475]

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- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	National Society for Phenylketonuria UK Limited (NSPKU)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	NSPKU is the national charity to support people living with PKU and was founded in 1973. It has 665 funded members (including "family memberships"). Thousands of people affected by PKU engage with NSPKU through social media, our website, annual conference and regional events. NSPKU is managed by a Council of Management, all of whom have PKU or have children with PKU. NSPKU is funded by its members. NSPKU does not accept funding from the pharmaceutical industry. Some of NSPKU's activities are sponsored by manufacturers of specialist dietary foods and supplements.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	The NSPKU ran an online survey which asked patients and carers questions about their experience of PKU. The questions were a mixture of multiple choice and open-ended questions inviting "free-text" responses. The survey ran from 9th November 2017 to 31st January 2018 and we received 631 responses. This is referred to as the "NSPKU survey". The results of the survey were published in two peer reviewed articles "Living with Phenylketonuria: Lessons for the PKU community" Ford, et al Molecular Genetics and Metabolism Reports, Volume 17, December 2018, pages 57-63 and "Reproductive experience of women living with phenylketonuria" Ford et al, Volume 17, Molecular Genetics and Metabolism Reports, December 2018, pages 64-68.

	In addition, the NSPKU sought information from patients or caregivers in the UK that have experience of using Kuvan for 6 months or more. These patients had access to Kuvan through clinical trials, individual funding or personal funding.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Please refer to the journal articles "Living with Phenylketonuria: Lessons from the PKU community" and "Reproductive experience of women living with phenylketonuria" (ibid) which provides a full description from the 631 responses from the survey conducted by NSPKU. PKU is characterised by the inability to metabolise phenylalanine within protein. Too much phenylalanine is toxic to the brain, causing permanent brain damage in children. In adults, high phenylalanine levels can impair cognitive and neuropsychological functioning. The current treatment is to remove virtually all protein from the diet and the consume prescribed low phenylalanine foods and protein supplements. The severe restrictions of the diet place a great burden on patients and carers. Patients or carers need to check the phenylalanine content of all foods, weigh and measure food according to their levels of phenylalanine and prepare special prescribed foods. Adults responding to the survey reported the following issues: difficulty with focus (54%), depression or anxiety (52%), disordered eating (40%), digestive problems (34%), frequent headaches (32%), low mood and sadness (54%), and feeling tired all the time (53%). Many described the impact that high phenylalanine levels have on them, describing "brain fog", feelings of irritability, with a verbatim extract from the survey "I have mood swings, extremely tired and want to sleep all the time and feels like this is a grey cloud hanging over my head, but not depression." The existing treatment is the low phenylalanine diet has low levels of adherence. The NSPKU surveyed carers of children 18 and under who reported the following issues: difficulty with focus (48%), depression or anxiety (29%), disordered eating (15%), digestive problems (34%), frequent headaches (18%), low mood and sadness (24%), and feeling tired all the time (23%). A young patient described that "*I find it hard because I get headaches, I am currently sitting GCSEs and I get foggy brain and I find it very hard to concentrate*."

	Having a child with PKU considerably impacts on the life of carers and the wider family. In the NSPKU survey, the mother was the main carer in 84% of cases and care was shared jointly with parents in 11% of respondents. PKU causes considerably worry and strain which affects the wellbeing of 75% of parents and caregivers according to the NSPKU survey. They describe the constant pressure of dealing with dietary management and how this is a daily struggle in their lives. In free text comments, many respondents described the overwhelming impact of PKU and all-consuming responsibility for caregivers. One caregiver stated that "*When you can cause irreversible brain damage to your child, it causes a lot of worry, stress and even panic."* The burden of care lasts many years, with parents of teenagers also describing time-consuming work and emotional strain, with one respondent stating that *"What is tough is seeing your child struggle and knowing how much effort is required to ensure the dietary regime is adhered to. We are still up doing bread at 6 am…At 17 our daughter finds it tough…She is perpetually tired and in bed by half nine most nights."* 59% of caregivers stopped working, changed job or working pattern to take care of a person with PKU. 77% find it difficult to organise any childcare due to the challenges in others understanding of PKU management. 37% of caregivers said that taking care of their child had affected their ability to give attention to other children in the family. Women with PKU can have unmet sexual and reproductive health needs which are addressed in the article "Reproductive experience of women living with phenylketonuria" which was written from data gathered in the NSPKU survey. This showed that fear of Maternal PKU could impact women's sexual and reproductive choices. Further, mothers with PKU describe being unable to cope with the pressures of strict dietary management whilst caring for their child. And experiencing anxiety, depression and inability to focus.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The low phenylalanine diet involves removing almost all natural protein from the diet. It is common for PKU patients to eat only tiny amounts of natural protein each day – equivalent to the protein in 1 or 2 slices of bread. Even foods such as cauliflower and potato need to be restricted. The abnormal diet places a great burden on individuals, parents and carers who need to devote extraordinary levels of time and skill to the task of managing the diet. Patients typically prepare special replacement meals from

	prescribed low phenylalanine ingredients. They need to learn the phenylalanine content of different foods, be able to read labels and calculate and weigh out the exact amount of different foods that may be eaten. Patients or carers need good cooking and organisation skills and access to storage and cooking facilities. 73% of respondents – both adults and caregivers of children said they found dietary management difficult. PKU patients rely upon prescription foods and protein substitutes to avoid malnourishment. However, many patients find them unpalatable and even disgusting. 39% of adults and 11% of children either did not take protein supplements or took less than the prescribed amounts. Families often have a daily battle to get their children to drink the protein substitute. One family reported that "*our greatest struggle is to get our son to take his supplements. He refuses to take it and it can take up to 45 minutes for him to finish one with a lot of upsets. We repeat 3 times a day…*" Many adult patients fail to take any, or the full recommended dose of protein supplement, whilst maintaining a restricted diet, and risk malnourishment. Many patients associate their protein substitute with nausea and stomach ache. The PKU diet requires constant vigilance in the patient or carer with regard to the phenylalanine content of foods. This is a very drastic modification of normal eating patterns. Many adults reported an abnormal relationship with food. 55% of adults reported difficulty controlling their weight, 14% suffer with eating disorders or disordered eating patterns and 4% had received therapy for eating disorders. In children, 15% reported their children had disordered eating. The diet is restricted and socially abnormal. This can inhibit participation in ordinary social activities. Stigmatisation, misconceptions and the feeling of social exclusion were common issues in both children and adults, and eating away from the home was a huge barrier to adherence. Some respondents described bullying, with abuse occurring at mealtimes. Many patients describe social withdrawal as a means of coping. In children, the diet can prevent participation in normal activities, like school trips or parties, or alternatively, participation in such events is a source of anxiety. In adults, treatment adherence is low. 79% of adults fail to control their blood phenylalanine levels within target range. Some patients describe moving in and out of dietary treatment, but struggling to recommence dietary treatment. Some adult respondents described themselves as going into a "downward spiral" if they disrupted dietary management and that this was hard to climb out of. One respondent said "*I am finding it extremely difficult to get back on diet and stick to it. It is extremely time*

	consuming, tiring and confusing. I feel that if I could get back on diet properly then it would all become easier, but it is so complicated. When I have a high or a low protein day I am affected for days following, this knock-on effect wears me out…At worst, struggling with the diet is upsetting and exhausting, having both physical and mental effects on me." Many patients with high phenylalanine levels suffer poor concentration, motivation and mood which can inhibit the ability to cope with the complex low phenylalanine diet.
8. Is there an unmet need for patients with this condition?	Dietary management of PKU is very burdensome and affects the patient and wider family significantly. Although stringent blood phenylalanine control is recommended through life, it is well established that adherence deteriorates from adolescence. Poor metabolic control will affect children for life, but a variety of factors will affect treatment adherence. Only one in four adults with PKU control their phenylalanine levels within recommended levels with the PKU diet. The NSPKU survey discloses significant neurocognitive, mental health and general health issues within the population with PKU.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	This section is derived from the Kuvan users survey which include 15 children and 4 adults. Of these 9 of the children are participating in post marketing clinical trials of Kuvan and 2 are taking Kuvan as a result of individual NHS funding or private funding. The adults were all participants in a pre-licensing clinical trial. The parents of the children reported large increases in their natural protein intake whilst taking Kuvan. The children typically ate no prescription foods and consumed 50% of the usual protein supplements for their age group. Parents described their children having a far wider and more socially normally diet. All the parents reported that their children had greater social freedom to participate in normal activities as their diet normalised. Many parents of the children reported improvements in mood, energy, concentration and behaviour. "*Kuvan transformed my son's performance at school. He seemed slow in listening. He was also "zoning out" – glazing over and appearing sleepy. The Special Educational Needs Co-ordinator was planning to bring in an external behaviour consultant. After he started Kuvan his teacher noticed the difference. He was alert and less irritable. He paid attention*."

	Two of the children are on the autistic spectrum and both families report improvements in their children's ability to communicate and join in with activities at school. "*Kuvan has helped my daughter… better eye contact and speech, she is calmer, more confident, better socialisation and she has more life skills."* *A parent who has purchased a low dose of Kuvan for her son reported "I have witnessed a transformation in my son. Kuvan has allowed him to cope in mainstream education. His writing has improved so much and the school has noticed a big improvement in concentration*." The reduced volume of protein supplements was experienced as a benefit by children and caregivers. "*Pre Kuvan we spent all day trying to persuade her to take this large volume of protein substitute. Things are much easier now she is on a lower dose of protein substitute. The dose is not overwhelming anymore*." Health benefits were reported, increase in bodyweight and growth, improvements in gastro-intestinal symptoms and a lessening in mouth ulcers. Caregivers reported a significant easing of the burden of care. There was no need to prepare special prescribed low phenylalanine foods. Some parents were able to delegate childcare to others for the first time. Caregivers reported the ability to return to work or study, increase their working hours, spend more time with other children or other family responsibilities. The 4 adults who participated in our survey took part in a pre-licensing clinical trial. They all reported that Kuvan improved their day to day functioning, particularly concentration and mood. One woman took Kuvan for 3 years from the age of 21 "*I became happier, could concentrate, had more energy, felt more relaxed, was more organised, could think more clearly. In fact, I felt like superwoman. Whilst I was on Kuvan, I was able to resume my studies as a teacher and qualified*." An adult male respondent describes "*an overall positive effect on my health, concentration, sleep and mood*".
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	NSPKU supports the use of this technology for all patients who will respond to the treatment.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	PKU raises health inequality issues which should be considered. First, some individuals are likely to be unable to cope with conventional dietary management due to its complexity, the cooking and organisational skills required, the associated time burden and socio-economic factors. The following (non-exhaustive) issues may be considered to be risk factors which may affect the ability to adhere to the conventional treatment (which may be relevant to parental carers and/or the individual patient): Learning disabilities including poor literacy. Certain physical co-morbidities Mental health problems Living in poor or temporary housing Having additional caring obligations Certain ethnic groups, such as people from Gypsy or Traveller backgrounds. Individuals/families with English as a second language.

	The use of sapropterin in breastfeeding women with PKU should be considered (see page 37 of European Guidelines in which it is considered that it is not a contra-indication for breastfeeding). NSPKU survey work found that women with PKU with young children reported difficulties in managing their dietary treatment alongside their caring role. In addition, research conducted by NSPKU shows that the burden of care on PKU falls upon women, with 81% reporting that women do the majority of PKU care in the household. The care of children with PKU restricts earnings or earning potential and their quality of life. The failure to commission sapropterin to ease the burden of care will have a greater impact on women, due to the higher number of women who are primary carers.
Other issues	
13. Are there any other issues that you would like the committee to consider?	Many issues relevant to the QALY calculations are not researched in published materials or are smaller scale studies. This reflects the low prevalence of PKU and its low priority as an academic topic. Therefore, NICE should have regard to wider data, such as conference abstracts etc, to understand the impact and cost of this rare disease. STA is an in appropriate system for the appraisal of this treatment. Kuvan is already a standard treatment, widely available in almost every country in the EU.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • The use of this treatment would have substantial health related benefits, increasing treatment adherence and the reduction of poor outcomes. Health inequalities are reduced, as currently the outcome for patients is dependent on the ability of either the caregiver or the patient to manage a complex diet. • The treatment reduces the burden of treatment, both for the patient, the caregiver and the wider family.	

- The use of this treatment improves executive functioning and mental health, and the life chances of children and adults and functioning in daily life
- increase in natural protein improves nutrition, reduces physical side effects
- The use of this treatment would reduce need for other health services (eg psychology/psychiatry, primary health care) and other pharmacological interventions and reduce the reliance on social care or informal care.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Sapropterin for treating phenylketonuria [ID1475]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**RCPath**

3. Job title or position	**Consultant Medical Biochemist, [redacted]**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ✓ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation committed to promoting excellence in the practice of pathology. Its main function is the overseeing of postgraduate training, and its Fellowship Examination is recognised as the standard assessment of fitness to practise in this branch of medicine. Almost half the UK adult PKU population are seen by doctors who trained in Chemical Pathology with Metabolic medicine through the RCPath and JCRPTB.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Avoidance of brain damage (either through development stage till 12 or maintenance stage) requires a complex low protein diet with amino acid supplementation to keep phenylalanine levels low. The outlook depends on maintaining low phenylalanine levels throughout life. This treatment will allow a 20-25% to consistently achieve therapeutic goals and a far more relaxed diet with more natural protein intake. The dietary demands have a significant impact on the individual and family leading to increased stress. Failure to maintain levels results in memory impairment (educational achievement lowered), social issues

or prevent progression or disability.)	(more prone to anxiety, depression and impaired relationships) plus risk of long-term neurological impairment (e.g. tremor).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The general decision is a 30% reduction. Given performance of aminoacid analyser (CV~6% for plasma samples), I would wish to see on a low-protein diet, a reduction in phenylalanine over 200umol/l to under the age related range, or over 350umol/l if not achieving cut-off 600 umol/l. It is essential that the individual is on his normal diet before and throughout and that this reduction is maintained.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Different direct questioning reveals increased anxiety, depression, and failure to achieve therapeutic goals compounding feelings of inadequacy. This is a new approach to support the complex diet which is a major burden on the individual or family.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Phenylalanine free amino acid supplementation with a wide variety of low protein products (e.g. artificial milk, bread, pasta) are prescribable. It requires good cooking skills and time from patient/parent to prepare and deliver a suitable diet.
• Are any clinical guidelines used in the treatment of the	Key European guidelines for the diagnosis and management of patients with phenylketonuria Published: January 09, 2017 DOI: https://doi.org/10.1016/S2213-8587(16)30320-5

condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	My experience is from Scotland. The UK has discussed management goals at meetings organised by the British Inherited Metabolic Disease group and have endorsed the approach taken by the European guidelines. Our clinical practice in Scotland is similar – any difference being easier access to therapy without requiring individual CCG agreement.
• What impact would the technology have on the current pathway of care?	For a minority of patients who respond, it will allow a little more natural protein and for others it will allow the patients to achieve the phenylalanine therapeutic goals. The key will be deciding whether all are tested and offered the drug, just a specific age group is tested and supported, or whether only those currently struggling to meet the therapeutic goal are tested for response and offered therapy. Presentations from elsewhere, suggest clinical improvements to individuals wellbeing and impact on family dynamics.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This will support some with PKU but some form dietary management will still need to be undertaken while on Sapropterin.
• How does healthcare resource use differ between the technology and current care?	The drug cost is substantially more than the current amino acid supplement and low protein products. While some reduction in their use is anticipated, the resource will mainly be additional to current care.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	These individuals are seen by clinicians with experience in PKU management who have support from metabolic dieticians. It will be these specialist clinics which advise/prescribe the drug.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	I do not believe any specific needs other than having good access to outpatient facilities if plasma amino acid levels used, or ensure patients can submit blood samples – capillary or blood spots - at regular intervals during the four week response assessment period.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The treatment should help some feel less anxious and improve their memory and reduce long-term neurological impairment disability over years/decades. Higher phenylalanine is associated with poorer outcomes from a number of common medication problems such as epilepsy control, dermatitis, migraines.
• Do you expect the technology to increase length of life more than current care?	Unknown – no.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – as above.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are issues with selecting cohorts for treatment. While starting a single age group – e.g. children through higher education may be appropriate, what would be criteria for stopping? Major patient concern that if only given to those who as patients or parents are failing to achieve dietary control, then rewarding those who may not be struggling to deliver and maintain to the strict dietary regime.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	There should be limited additional issues for clinicians. The one issue may be that there is a need to monitor and assess more frequently. Currently some adults will go on the diet for a period, and then stop. It is likely that if they stop the diet, then we should reconsider Sapropterin prescriptions. Many adults are poor at submitting blood spots regularly. To be on the drug, they may be expected (or required) to submit regularly, and ongoing prescribing would then require review that achieved appropriate therapeutic goals. This requires agreed goals to be achieved and monitored. From the patient's perspective, while few relatively minor symptoms, most will find taking it straightforward – issue will be ensuring compliance with ongoing expensive oral therapy.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	These will be decided once it is agreed which patients would be offered therapy as previously discussed.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	QALY calculation should cover most issues but unclear how long term benefits such as more stable jobs, relationships which would be expected, can be demonstrated.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes – reducing the burden of diet and its impact on the family unit. May allow more social inclusiveness

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes for a minority with PKU
• Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Minimal side effects.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Social and neuropsychological functioning such as educational achievement and performance in the workplace - No
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. How do data on real-world experience compare with the trial data?	
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Who will be tested – and who will be offered. Those on diet but failing to achieve goals, while others struggle more and achieve therapeutic goal.
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Equity of access
- Long term social, educational and neuropsychiatric benefits
- Current diet is a major burden on the individual and their family
-
-

Thank you for your time.

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ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Sapropterin for treating phenylketonuria [ID1475]

Confidential until published

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Completed 6th October 2020

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Sapropterin dihydrochloride for treating phenylketonuria [ID1475]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Sarah Nevitt, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Rebecca Bresnahan, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Sophie Beale, Associate Senior Researcher, LR*i*G, University of Liverpool

Angela Boland, Director, LR*i*G, University of Liverpool

Tosin Lambe, Research Associate (Health Economics), LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Katherine Edwards, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Bernd Schwahn, Consultant Clinical Paediatrician in Inherited Metabolic Medicine, Royal Manchester Children's Hospital

Correspondence to: Dr Janette Greenhalgh, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

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Contributions of authors:

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervised the final report
James Mahon	Critical appraisal of the economic model
Sarah Nevitt	Critical appraisal of the statistical evidence
Rebecca Bresnahan	Critical appraisal of the clinical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Tosin Lambe	Summary of the economic evidence
Yenal Dundar	Critical appraisal of the clinical evidence, including search strategies
Katherine Edwards	Critical appraisal of the clinical evidence
Joanne McEntee	Critical appraisal of the company submission
Bernd Schwahn	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

AE	adverse event
BH4	tetrahydrobiopterin
CI	confidence intervals
CS	company submission
CSR	clinical study report
EMA	European Medicines Agency
EQ-5D	EuroQol–5 Dimensions
ERG	Evidence Review Group
FDA	US Food and Drug Administration
HPA	hyperphenylalaninaemia
HRQoL	health-related quality of life
HTA	Health Technology Assessment
IA10	10th interim analysis
ICER	incremental cost effectiveness ratio
ICIEM	International Congress of Inborn Errors of Metabolism
IQ	intelligence quotient
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
KAMPER	The Kuvan Adult Maternal Paediatric European Registry
KOGNITO	Kuvan's Effect on the Cognition of Children with Phenylketonuria
od	once daily
PAH	phenylalanine hydroxylase
PAS	patient access scheme
Phe	phenylalanine
Phenoptin™	a previous trade name for sapropterin dihydrochloride which is now superseded by Kuvan®
PKU	phenylketonuria
PKUDOS	The Phenylketonuria Demographics Outcomes and Safety Registry
PKU-MOMS	PKU in the Maternal Phenylketonuria Observational Program
PPE	per protocol extension
PRD	phenylalanine-restricted diet/protein-restricted diet
PSS	personal social services
RCT	randomised controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SPARK	Safety Paediatric efficAcy phaRmacokinetic with Kuvan
TRAE	treatment-related adverse event
TTO	time-trade off

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of the company's key model outcomes and the modelling assumptions that have the greatest effect on the ICER per quality adjusted life year (QALY) gained. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report (Section 2 to Section 6).

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

Table 1 Summary of key issues

ID1475	Summary of issue	Report sections
1	Long-term clinical effectiveness data are only available from two company sponsored non-comparative registry studies	Section 1.3 Section 2.6.1 Section 3.2.1 to Section 3.4
2	Data for some of the health outcomes specified in the final scope issued by NICE are not fully addressed by the company	Section 1.3 Section 2.6.5, Section 3.3.1, Section 3.3.2
3	Blood Phe concentration level as a measure of efficacy	Section 1.3 Section 2.6.5
4	RCTs that compare treatment with sapropterin+PRD versus PRD are short-term	Section 1.4 Section 2.6.1
5	Unrealistic company model pathway	Section 1.5 Section 5.2.1
6	Implausible time and age invariant health state transition probabilities	Section 1.5 Section 5.2.1
7	Methods used to calculate transition probabilities are not robust	Section 1.5 Section 5.2.2
8	Annual attrition rate used in the company model may not be generalisable to patients who stop taking sapropterin	Section 1.5 Section 5.2.2
9	Utility values used in the company model are highly unlikely to reflect the experience of NHS patients with PKU	Section 1.5 Section 5.2.3
10	Effect of sapropterin on PRD is uncertain	Section 1.5 Section 5.2.4

PKU=phenylketonuria; PRD=protein restricted diet; RCT=randomised controlled trial

1.2 Overview of company's key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life (QALY). An ICER per QALY gained is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled by the company to increase QALYs by:

- 0.84 QALYs (all years)
- reducing the need for PRD (protein supplements and low protein foods)

Overall, the technology is modelled by the company to reduce costs by:

- £4,802

The company's modelling assumptions that have the greatest effect on the ICERs per QALY gained are:

- Unit cost and dose of sapropterin (0-12 year olds)
- Cost of protein supplements (0-4 year olds)
- Reduction in PRD (controlled PKU)
- Cost of PRD (4-18 year olds).

1.2.1 ERG's alternative approach to estimating cost effectiveness of sapropterin+PRD versus PRD

The ERG considers that the company model generated unreliable results and has therefore produced alternative results. The costs and benefits associated with treatment with sapropterin generally only occur whilst a patient takes sapropterin and cease when a patient stops taking sapropterin. Therefore, a complex model is not required. The ERG considers that an estimation of the cost effectiveness of sapropterin+PRD versus PRD can be best made through a simple calculation of the costs and benefits. The results of the ERG's alternative approach to assessing cost effectiveness are presented in the ERG report (Section 5.4).

1.3 The decision problem: summary of the ERG's key issues

Issue 1 Limited relevance of the registry data to the decision problem

Report section	Section 2.6.1, Section 3.2.1 to Section 3.4
Description of issue and why the ERG has identified it as important	Long-term clinical effectiveness data are available from two company sponsored registry studies. The registry studies are of good methodological quality; however, they were not designed to enable a comparison of treatment with sapropterin+PRD versus PRD (the comparison specified in the final scope issued by NICE). The data collected in the two registry studies are relevant only to patients who have a history of treatment with sapropterin+PRD. There are no data for patients who have never been treated with PRD only (the main comparator in the final scope issued by NICE)
What alternative approach has the ERG suggested?	The ERG acknowledges that there are no alternative real-world datasets available that can be used to address the decision problem
What is the expected effect on the cost effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	A long-term RCT that compares the effectiveness of treatment with sapropterin+PRD versus PRD would provide the optimal data for decision-making; there are no comparative trials available of this kind and there are no known plans to conduct such a trial. Effectiveness data from the currently available RCTs are limited by their short durations and small numbers of included patients

ERG=Evidence Review Group; PRD=protein restricted diet; RCT=randomised controlled trial

Issue 2 Outcomes not addressed in the company submission

Report section	Section 2.6.5, Section 3.3.1, Section 3.3.2
Description of issue and why the ERG has identified it as important	Data in the CS for the outcomes of neuropsychological function, biochemical indicators of poor nutrition (specified in the final scope issued by NICE) are limited and not quantifiable. None of the published studies discussed in the CS reported HRQoL data and no HRQoL data collected directly from patients with PKU are presented in the CS
What alternative approach has the ERG suggested?	The ERG cannot suggest any alternative sources of HRQoL data
What is the expected effect on the cost effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	A long-term RCT that compares treatment with sapropterin+PRD versus PRD would provide the optimal data for decision-making; there are no comparative trials available of this kind and there are no known plans to conduct such a trial.

CS=company submission; HRQoL=health-related quality of life; PRD=Phe-restricted diet; RCT=randomised controlled trial

Issue 3 Blood Phe concentration level as a measure of efficacy

Report section	Section 2.6.5
Description of issue and why the ERG has identified it as important	Clinical advice to the ERG is that blood Phe concentration level is a poor efficacy outcome and should only be considered in conjunction with dietary Phe intake; this is especially important in young children whose blood Phe concentration levels tend to fluctuate according to season, growth rate and age
What alternative approach has the ERG suggested?	Clinical advice to the ERG is that blood Phe concentration levels should only be considered in conjunction with dietary Phe intake. The currently available evidence does not include a composite outcome (i.e., blood Phe concentration level and dietary Phe intake)
What is the expected effect on the cost effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	A long-term RCT that compares treatment with sapropterin+PRD versus PRD using a composite outcome would provide valuable information to clinicians

HRQoL=health-related quality of life; Phe=phenylalanine; PRD=Phe-restricted diet; RCT=randomised controlled trial

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 4 Limited randomised controlled trial data available

Report section	Section 2.6.1
Description of issue and why the ERG has identified it as important	The value of the evidence from the three RCTs that are relevant to this appraisal is limited due to the short duration of the trials (10-13 weeks)
What alternative approach has the ERG suggested?	The ERG acknowledges that there are no alternative datasets available that can be used to address the decision problem
What is the expected effect on the cost-effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	A long-term RCT that compares treatment with sapropterin+PRD versus PRD would provide the optimal data for decision-making; there are no comparative trials available of this kind and there are no known plans to conduct such a trial. Effectiveness data from the currently available RCTs are limited by their short durations

ERG=Evidence Review Group; PRD=Phe-restricted diet; RCT=randomised controlled trial

1.5 The cost effectiveness evidence: summary of the ERG's key issues

Issue 5 Unrealistic company model pathway

Report section	Section 5.2.1
Description of issue and why the ERG has identified it as important	In clinical practice, within a given year, a patient may switch from having controlled to uncontrolled blood Phe concentration levels. However, within the company model, the cycle length is 1 year and, therefore, a patient whose blood Phe levels are (un)controlled at the beginning of a year is modelled to have (un)controlled blood Phe concentration levels for the whole of that year Furthermore, once patients have discontinued treatment with sapropterin they are only permitted to receive PRD for the remainder of the model time horizon
What alternative approach has the ERG suggested?	The ERG has undertaken an alternative approach to modelling cost effectiveness that relates only to the period when patients are taking sapropterin. This negates the need to model a complex pathway
What is the expected effect on the cost effectiveness estimates?	The ERG considers that the company model pathway does not reflect the experience of patients with PKU and, therefore, company cost effectiveness results should not be used to inform decision making
What additional evidence or analyses might help to resolve this key issue?	The likelihood of relevant effectiveness data becoming available from long-term real-world studies is low

ERG=Evidence Review Group; Phe=phenylalanine; PKU=phenylketonuria; PRD=Phe-restricted diet

Issue 6 Implausible time and age invariant health state transition probabilities

Report section	Section 5.2.1
Description of issue and why the ERG has identified it as important	The Markov model health states have no 'memory' and, for the majority of a patient's life, the transition probabilities do not change. This means that a patient's prior ability or inability to maintain control of their blood Phe concentration levels does not affect the likelihood of them being in a controlled or uncontrolled health state. Clinical advice to the ERG is that patients' incentives to control their blood Phe levels differ between individuals and may change over time for each individual
What alternative approach has the ERG suggested?	The ERG has undertaken an alternative approach to modelling cost effectiveness that relies less heavily on the transition probabilities used in the company model
What is the expected effect on the cost effectiveness estimates?	The ERG considers that the use of implausible time and age invariant health state utilities means that company cost effectiveness results are unreliable and should not be used to inform decision-making
What additional evidence or analyses might help to resolve this key issue?	The likelihood of relevant effectiveness data becoming available from long-term real-world studies is low

ERG=Evidence Review Group; Phe=phenylalanine

Issue 7 Methods used to calculate transition probabilities

Report section	Section 5.2.2
Description of issue and why the ERG has identified it as important	The company used data from the PKUDOS registry study to calculate health state transition probabilities. The ERG has the following concerns about the reliability of these estimates: • it is unclear whether all patients in the PKUDOS registry were responsive to sapropterin • sample sizes from which probabilities were calculated were very small (probabilities between years may be correlated and the company made no attempt to address for bias) • it is unclear whether individual patients were moving between controlled and uncontrolled health states
What alternative approach has the ERG suggested?	The ERG has undertaken an alternative approach to modelling cost effectiveness that relates only to the period when patients are taking sapropterin and, therefore, relies less heavily on the transition probabilities used in the company model
What is the expected effect on the cost effectiveness estimates?	The ERG considers that the company transition probabilities are unreliable and are of limited use to inform decision-making
What additional evidence or analyses might help to resolve this key issue?	The likelihood of relevant effectiveness data becoming available from long-term real-world studies is low

ERG=Evidence Review Group

Issue 8 Annual rate that patients stop taking sapropterin (attrition rate)

Report section	Section 5.2.2
Description of issue and why the ERG has identified it as important	The ERG is concerned that the attrition rate used in the company model is not generalisable to the UK population. The value was derived from an interim analysis of KAMPER registry study data: • it is unclear from the CS whether the rate used in the model is an annual rate or the rate calculated for the period for which data for the interim analysis were available • over four-fifths of the patients who provided data for the analysis were children and therefore the attrition rate may not reflect the experience of adults • the company used the KAMPER registry study discontinuation rate; this rate included data from patients who were lost to follow up or dead. The ERG considers that this discontinuation rate is not the same as the attrition rate that would be seen if sapropterin were used in routine commissioning
What alternative approach has the ERG suggested?	The ERG's alternative cost effectiveness results only consider the time period during which patients take sapropterin and, therefore, these analyses do not rely on a robust attrition rate
What is the expected effect on the cost effectiveness estimates?	The ERG considers that the company's attrition rate is unreliable and should not be used to inform decision-making
What additional evidence or analyses might help to resolve this key issue?	The likelihood of relevant effectiveness data becoming available from long-term real-world studies is low

CS=company submission; ERG=Evidence Review Group

Issue 9 Utility values used in the model are highly unlikely to reflect the experience of NHS patients with PKU

Report section	Section 5.2.3
Description of issue and why the ERG has identified it as important	The ERG has the following concerns: • the methods used by the company to elicit health state values are not in line with the NICE Reference Case • there is a mismatch between the health state descriptions valued by the company in the TTO study and the health states used in the company model • the utility values for patients with uncontrolled blood Phe concentration levels are unrealistically low • the method used to map health state utility values from the company TTO study to the company model health states is overly simplistic
What alternative approach has the ERG suggested?	Given the absence of data available directly from patients with PKU and the uncertainty around the disutility from following a PRD, the ERG considers that the company's TTO study is the best available source of utility values
What is the expected effect on the cost effectiveness estimates?	Due to unreliable company utility values, the company and the ERG's cost effectiveness results are uncertain
What additional evidence or analyses might help to resolve this key issue?	A long-term RCT that compares treatment with sapropterin+PRD versus PRD and collects EQ-5D data would provide the optimal data for decision making

ERG=Evidence Review Group; EQ-5D=EuroQol-5 dimensions; Phe=phenylalanine; PKU=phenylketonuria; PRD=Phe-restricted diet; RCT=randomised controlled trial; TTO=time-trade off

Issue 10 Effect of sapropterin on PRD

Report section	Section 5.2.4
Description of issue and why the ERG has identified it as important	The extent to which taking sapropterin reduces the need for low protein foods and for dietary protein supplements (PRD) is unclear. In their base case, the company has assumed that taking sapropterin leads to a 71.2% reduction in PRD (PKUDOS data); however, clinical advice to the ERG is that this may be an overestimate and there may be no reduction in PRD
What alternative approach has the ERG suggested?	The ERG has generated cost effectiveness results assuming that taking sapropterin leads to a 71.2% or a 0% reduction in PRD
What is the expected effect on the cost effectiveness estimates?	Overestimating the effectiveness of sapropterin is likely to overestimate the cost effectiveness of sapropterin+PRD (versus PRD)
What additional evidence or analyses might help to resolve this key issue?	The likelihood of relevant effectiveness data becoming available from long-term real-world studies is low

Evidence Review Group; PRD=Phe-restricted diet; RCT=randomised controlled trial

1.6 Other key issues: summary of the ERG's view

Not applicable

1.7 Summary of ERG's preferred assumptions and resulting ICER

Table 2 Cost effectiveness results (PAS price of sapropterin)

Scenario	Incremental cost	Incremental QALYs	ICER per QALY gained (change from company base case)
Company approach			
Company base case: all years (with PAS)	[redacted]	0.840	[redacted]
Company approach: adults (with PAS)	[redacted]	0.470	[redacted]
Company approach: 0-17 years (with PAS)	[redacted]	0.660	[redacted]
ERG alternative approach: adults, 12.5mg/kg, 0% reduction in PRD			
Symptomatic PKU results in mild symptoms	[redacted]	0.013	[redacted]
Symptomatic PKU results in moderate symptoms	[redacted]	0.020	[redacted]
Symptomatic PKU results in severe symptoms	[redacted]	0.052	[redacted]
ERG alternative approach: adults, 12.5mg/kg, 71.2% reduction in PRD			
Symptomatic PKU results in mild symptoms	[redacted]	0.141	[redacted]
Symptomatic PKU results in moderate symptoms	[redacted]	0.148	[redacted]
Symptomatic PKU results in severe symptoms	[redacted]	0.180	[redacted]
ERG alternative approach: 0-17 years, 10mg/kg, 0% reduction in PRD			
Symptomatic PKU results in mild symptoms	[redacted]	0.004	[redacted]
Symptomatic PKU results in moderate symptoms	[redacted]	0.007	[redacted]
Symptomatic PKU results in severe symptoms	[redacted]	0.018	[redacted]
ERG alternative approach: 0-17 years, 10mg/kg, 71.2% reduction in PRD			
Symptomatic PKU results in mild symptoms	[redacted]	0.130	[redacted]
Symptomatic PKU results in moderate symptoms	[redacted]	0.134	[redacted]
Symptomatic PKU results in severe symptoms	[redacted]	0.145	[redacted]

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PKU=phenylketonuria; PRD=Phe-restricted diet; QALY=quality adjusted life year

The ERG's critique of the company model is described in Section 5.2 of the ERG report. Details of the ERG's alternative approach to assessing cost effectiveness of sapropterin+PRD versus PRD is presented in Section 5.3 of the ERG report.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The focus of this appraisal is on the use of sapropterin dihydrochloride (sapropterin) to treat children and adults with phenylketonuria (PKU) whose hyperphenylalaninaemia (HPA) has been shown to be responsive to sapropterin. Within this Evidence Review Group (ERG) report, references to the company submission (CS) are to the company's document B, which is the company's full evidence submission.

2.2 Phenylketonuria

Phenylketonuria (PKU), also known as phenylalanine hydroxylase (PAH) deficiency, is a rare, inherited disorder which is present from birth. The PAH enzyme metabolises phenylalanine (Phe), an amino acid found in protein-rich foods, to tyrosine.[1] By 10th November 2019, 1184 gene variants of PAH had been identified.[2] Mutations of the PAH gene result in decreased activity to complete inactivation of the PAH enzyme.[3] The reduced activity of PAH means that patients with PKU are unable to break down Phe, resulting in increased levels of Phe in the blood.[4] High levels of Phe are harmful to the central nervous system, leading to neurological complications, such as cognitive impairment, intellectual disability and psychiatric symptoms.[4,5] Clinical advice to the ERG is that PKU does not affect life expectancy or mortality.

Tyrosine, the product of Phe metabolism, is a precursor to the neurotransmitters dopamine, noradrenaline and serotonin which are important for mood, anxiety and cognition.[6] Reduced production of dopamine, noradrenaline and serotonin may be associated with symptoms of inattention, hyperactivity, depression and anxiety.[7]

In the NHS, babies are routinely screened for PKU within 5 days of birth through the newborn blood spot screening programme.[8] Approximately 1 in 10,000 babies in the UK are diagnosed with PKU.[8] Treatment for PKU begins immediately after diagnosis.

Current clinical management of patients with PKU comprises a Phe-restricted diet (PRD) which aims to reduce Phe intake and therefore reduce blood Phe concentration levels. A PRD consists of restricted natural protein intake (according to individual Phe-tolerance), supplemented with prescribed low-protein and Phe-free medical foods to help reduce dietary Phe intake and prescribed Phe-free amino acid supplements to improve nutrition.[4,8] When following a PRD, patients with PKU must avoid all high protein foods that are rich in Phe (for example, meat, fish, dairy products and soya), tightly control their intake of foods that contain less natural protein (for example, fruit, vegetables, cereals and flour), avoid food and drinks

containing aspartame (which is converted to Phe) and alcoholic beverages containing protein (for example, beer and stout).[9]

Phe is required for protein synthesis and is an essential amino acid (i.e., it cannot be synthesised in the body).[10] Blood Phe concentration levels in patients with PKU are regularly monitored and are considered a surrogate marker for Phe concentrations levels in the brain.[4] Phe must be acquired directly from food so patients with PKU need to consume some Phe.[10] Clinical advice to the ERG is that by monitoring blood Phe concentration levels, dietitians can help advise patients how to adjust their PRD to best manage their PKU. Clinical advice to the ERG is that monitoring of blood Phe concentration levels and review of PRD is done on a weekly to fortnightly basis and patients are contacted by telephone.

NHS England estimates that approximately 2000 patients with PKU are under regular NHS review.[11] Clinical advice to the ERG is that UK metabolic centres follow the European PKU guidelines[4] that recommend that patients aged 0 to 1 years should attend six outpatient clinic visits per year and that patients aged >1 year should attend two to three outpatient clinic visits per year.

Treatment recommendations, including target blood Phe concentration levels for subpopulations of patients with PKU are provided in the European PKU guidelines[4] and summarised in Table 1. It is unclear whether patients with PKU aged >12 years with untreated blood Phe concentrations levels between 360µmol/L to 600µmol/L should be treated.[4]

Table 1 Target blood Phe concentration levels for patients with PKU

Subpopulation	Untreated blood Phe concentration level requiring treatment (µmol/L)	Duration of treatment	Target blood Phe concentration levels (range, µmol/L)
Patients with PKU aged ≤12 years	360 to 600	Up to age of 12 years	120 to 360
Patients with PKU aged ≤12 years	>600	Up to age of 18 years	120 to 600
Patients with PKU aged >12 years	>600	Life-long	120 to 600
Treated pregnant women with PKU	>360	Preconception onwards	120 to 360

Phe=phenylalanine; PKU=phenylketonuria
Source: Adapted from CS, Table 3

2.2.1 Elevated Phe in patients with PKU

High blood Phe concentration levels can result in neurological damage, some of which may be irreversible.[3] The most critical time period for irreversible neurological damage is in the early years of brain development.[11] Neurological damage during early brain development can lead to severe intellectual disability, microcephaly, seizures and tremors, stunted growth, delayed speech and impaired executive function.[12,13] Early dietary intervention to limit Phe intake and control blood Phe concentration levels is effective at preventing irreversible neurological damage.[14] If blood Phe concentration levels are well-controlled during early childhood, patients with PKU can have similar cognitive function to the general population.[14]

High blood Phe concentration levels can cause reversible neurological damage in adults.[4] Symptoms include impaired executive function (including attention deficits, reduced response inhibition and increased response time related to slower cognitive processing),[7,15] neuropsychiatric symptoms (including depression, anxiety and inattention)[7,16] and psychosocial impairments (including reduced autonomy, impaired social maturity and difficulty forming relationships).[14,17] These symptoms can be improved or completely reversed in adults by returning to a PRD.[4] However, the company reports (CS, p13) that impaired executive function can affect PRD adherence and compliance and if a patient is unable to maintain and adhere to a PRD then this can lead to further increases in blood Phe concentration levels.

2.2.2 Elevated Phe in pregnancy

Maternal PKU syndrome relates to women with PKU who have high blood Phe concentration levels during pregnancy.[4] High blood Phe concentration levels during pregnancy can have teratogenic effects on the developing foetus and can lead to the unborn child having impaired growth, impaired intellectual ability and birth defects (for example, congenital heart defects).[18]

There is evidence that children whose mothers have well-controlled blood Phe concentration levels before conception have better cognition than children whose mothers either begin or re-start a PRD after conception.[18]

It is recommended in the European guidelines[4] that women with PKU should maintain their blood Phe concentration levels between 120µmol/L and 360µmol/L before and during pregnancy, and should avoid unplanned pregnancies.

2.2.3 Comorbidities

Retrospective studies have shown that adults with PKU have higher rates of comorbidities than the general population.[19,20] The comorbidities reported to be more prevalent in patients with PKU are: chronic ischaemic disease, urticaria, oesophageal disorders, gastroesophageal reflux disease, gastritis, anaemia, obesity, asthma, renal insufficiency, eczema, alopecia, osteoporosis, rhinitis, gall bladder disease and kidney calculus.[19,21] It has been suggested that high blood Phe concentration levels in patients with PKU could initiate biological mechanisms that are linked to increased risk of chronic diseases.[22] Additionally, it has been suggested that PRD, the use of medical food and related dietary deficiencies may also contribute to the increased risk of chronic diseases.[23-25]

2.3 Sapropterin

Sapropterin dihydrochloride (sapropterin) is a synthetic formulation of tetrahydrobiopterin (BH4), which is a cofactor for the enzyme, PAH.[11] BH4, increases the metabolic activity of PAH and, therefore, increases the amount of Phe that is metabolised into tyrosine.[11] By mimicking the action of BH4, sapropterin can increase the activity of some of the mutated forms of PAH identified in patients with PKU.[11] By increasing the activity of PAH, sapropterin simultaneously decreases blood Phe concentration levels[11] while increasing the availability of neurotransmitters, such as dopamine, noradrenaline and serotonin.[26] Sapropterin can help patients with PKU to control and maintain their blood Phe concentration levels within, or closer to, the blood concentration levels recommended in the European PKU guidelines[4] (see Table 1). Sapropterin can also allow some patients to increase their daily natural protein intake and reduce their need to take low-protein and Phe-free medical foods, which can be unpalatable.[11]

Sapropterin is dispensed as 100mg sapropterin dihydrochloride soluble tablets.[27] The sapropterin tablets are dissolved in water and taken orally.[27] The starting dose for patients with PKU (adults and children) is 10mg/kg/day.[27] Healthcare professionals may then adjust the dose, usually to between 5 to 20 mg/kg/day to achieve and maintain blood Phe concentration levels within the recommended range.[27]

Since June 2015,[28] sapropterin has held a marketing authorisation from the European Medicines Agency (EMA) for the treatment of HPA in adults and children with PKU who are responsive to sapropterin. It is specified in the EMA licence for sapropterin that active management of dietary Phe intake and overall protein intake are required while taking sapropterin.[28]

According to the SmPC,[27] the criteria for responsiveness to sapropterin are either a ≥30 percent reduction in blood phenylalanine concentration levels or attainment of the therapeutic

blood phenylalanine concentration level recommended for an individual patient by the treating physician. Patients who fail to achieve this level of response within a one month test period should be considered non-responsive and should not receive treatment with Kuvan.[27]

In the European PKU guidelines,[4] it is recommended that responsiveness is determined via a loading test, i.e., blood Phe concentration levels are measured before and after a single dose of 20mg/kg sapropterin administered on two consecutive days.[4] The NHS England clinical commissioning policy guidance[29] is that responsiveness to sapropterin should be determined by relaxing dietary Phe intake for 2 weeks (to achieve moderately increased blood Phe concentration levels) and then by introducing a 4-week trial of a therapeutic dose of sapropterin in conjunction with weekly monitoring of blood Phe concentration levels.

Sapropterin also has an orphan drug designation from the EMA, due to expire in December 2020.[30] Sapropterin is currently commissioned by NHS England for pregnant women with PKU who are unable to establish adequate dietary control and achieve the target non-teratogenic range of Phe (100µmol/L to 300µmol/L).[29]

2.4 Company's overview of current service provision

2.4.1 Treatment pathway

The company describes the current service provision for patients with PKU in the NHS (CS, p15) and summarises information from the 2017 European guidelines[4] for diagnosis and management (CS, pp17-18).

The primary aim of clinical management is to prevent neurological damage by keeping patients' blood Phe concentration levels within the ranges recommended in the European guidelines[4] (and summarised in Table 1). Current clinical management for patients with PKU is a PRD that consists of restricted natural protein intake (according to individual Phe-tolerance), supplemented with prescribed low-protein and Phe-free medical foods and Phe-free amino acid supplements.[4]

Clinical advice to the ERG is that adhering to a PRD can be time- and resource-consuming and burdensome for patients with PKU and their caregivers. A PRD also requires significant input from healthcare professionals. Monitoring involves routinely taking blood samples at home and sending them to a central laboratory. Patients then receive their blood Phe concentration level result via telephone from a healthcare professional who, if necessary, will provide advice to the patient about how to adjust their diet to manage their blood Phe concentration level. Clinical advice to the ERG is that a multidisciplinary team is involved in the clinical management of patients with PKU, including consultants, psychologists, specialist

nurses and dieticians. Specifically, clinical advice to the ERG is that patients with PKU are followed up in specialist metabolic centres. Clinical advice to the ERG agrees with the company (CS, p20) that adherence to PRD can be especially problematic for older children due to increasing independence and peer pressure.

2.4.2 Number of patients eligible for treatment with sapropterin

In the company's document A (Company evidence submission summary for committee), the company estimates that, if recommended by NICE, 391 patients in England and Wales will be eligible for treatment with sapropterin next year. In terms of eligible patients, the company estimates (company budget impact assessment report) that current prevalence is 366 patients, and there is an annual incidence rate of 25 patients per year. The ERG's clinical expert and the company agree that the PKU incidence rate is stable over time and that the estimate is reasonable.

2.5 History of the appraisal of sapropterin

In 2019, the company requested that sapropterin be appraised under the NICE Highly Specialised Technology appraisals programme.[31] The company considers (CS, p34) that the STA process does not account for the rarity of the disease or make allowance for the fact that only limited data are available to support the appraisal.

2.6 Critique of company's definition of decision problem

A summary of the decision problem outlined in the final scope[32] issued by NICE and addressed by the company is presented in Table 2. Each parameter is discussed in more detail in the text following Table 2 (Section 2.6.1 to Section 2.6.8).

Table 2 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	ERG comment
Population	Patients with PKU whose hyperphenylalaninaemia has been shown to be responsive to sapropterin therapy	As per scope	As per scope
Intervention	Sapropterin in combination with a protein-restricted diet	As per scope	As per scope
Comparator(s)	Established clinical management without sapropterin	As per scope	As per scope
Outcomes	The outcome measures to be considered include: • Phe concentration in the blood • neuropsychological function • natural protein intake • biochemical and clinical indicators of poor nutrition • adverse effects of treatment • cognitive and mood symptoms • health-related quality of life.	As per scope	The company has presented data for Phe concentration in the blood, protein intake and AEs. The ERG has identified evidence (from references provided by the company) for most of the remaining outcomes. No health-related quality of life data are available from the published studies discussed in the CS. HRQoL data were derived from the general public in the Swedish TTO study. No HRQoL data collected directly from patients with PKU are presented in the CS.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	ERG comment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The use of sapropterin is conditional on responsiveness to this treatment. The economic modelling should include the costs associated with establishing sapropterin responsiveness in patients with PKU who would not otherwise have had a therapeutic trial	No company comment	The economic model only considers patients who are responsive to sapropterin (as per scope)
Subgroups	If evidence allows, consideration may be given to subgroups based on: • Patients with childbearing potential • Age • Adherence to diet If consideration is given to these subgroups, the committee will consider any equalities implications of its considerations. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	No company comment	As per scope

Phe=phenylalanine
Source: Final scope[32] issued by NICE and CS, Table 1

2.6.1 Source of clinical effectiveness data

The company has presented clinical effectiveness evidence (CS, Section B.2.6) from:

- four RCTs (PKU-003,[33] PKU-006,[34] PKU-016[35] and SPARK[36])
- three follow-up single-arm studies (PKU-004,[37] PKU-008,[38] SPARK extension study[39])
- three single-arm studies (PKU-015,[40] ENDURE[41] and KOGNITO[42])
- one single-arm screening study (PKU-001[43])
- and two registry studies (PKUDOS[44] [including the PKU-MOMS subregistry[45]] and KAMPER[46]).

The company has also described three meta-analyses[47-49] that compared the effectiveness of sapropterin+PRD versus PRD using data from subsets of the four RCTs[33-36] (CS, Section B.2.8).

The company originally listed Burton et al[50] as an included study (CS, Table 6). However, in response to question A2 of the clarification letter, the company confirmed that Burton et al[50] was not considered a relevant study. The ERG agrees that as the Burton et al[50] study is a retrospective study it does not meet the company's inclusion criteria. In response to question A2 of the clarification letter, the company also confirmed that PKU-015[40] was considered a relevant study and that it should have been included in Table 5 of the CS. The company included eight[12,51-57] non-comparative studies in the systematic literature review; these studies are only documented in the appendices (D or E) to the CS. For completeness, details of the eight[12,51-57] studies are summarised in Table 40 (Appendix 1).

The company only used effectiveness data from the PKUDOS registry study and the KAMPER registry study to populate the economic model (see Section 3.2.1 of this ERG report). The ERG has summarised the characteristics of the RCTs,[33-36] single-arm studies,[37,38,40-42] extension study[39] and screening study[43] in Appendix 1. A summary of the study design and characteristics of the registry studies (PKUDOS and KAMPER) are presented in Section 3.2.2 and results from the most recent interim analyses of data from these registries are presented in Section 3.3.

2.6.2 Population

The population considered by the company is patients with PKU whose Phe blood concentration levels have been shown to be responsive to sapropterin. This is consistent with the final scope[32] issued by NICE. The ERG does not consider that the characteristics of the patients included in the PKUDOS and the KAMPER registry studies are different to the characteristics of patients with PKU who are likely to be treated with sapropterin in the NHS, except for age (which differs between the two studies)

2.6.3 Intervention

The company has presented clinical effectiveness evidence for treatment with sapropterin in combination with PRD (See Section 3.2). Within this ERG report, sapropterin in combination with PRD is referred to as sapropterin+PRD.

2.6.4 Comparators

The company has provided evidence for the effectiveness of established clinical management without sapropterin, i.e., PRD (described in detail in Section 2.2). Only three of the four RCTs (PKU-006,[34] PKU016[35] and SPARK[36]) provide data for the effectiveness of sapropterin+PRD versus PRD (at 10 weeks, 13 weeks and 13 weeks, respectively). Neither the PKUDOS registry study nor the KAMPER registry study include data describing current clinical management without previous exposure to sapropterin and therefore do not provide evidence for a comparison of sapropterin+PRD versus PRD. However, some data from these registries were used to populate the company model.

2.6.5 Outcomes

Clinical advice to the ERG is that the outcomes listed in the final scope[32] issued by NICE are the most relevant outcomes for patients with PKU and that health-related quality of life (HRQoL) is an important outcome but is difficult to measure in patients with PKU. Clinical advice to the ERG is that blood Phe concentration level is a poor measure of efficacy and should only be considered in conjunction with dietary Phe intake; this is especially important in young children whose blood Phe concentration levels tend to fluctuate according to season, growth rate and age.

The company has presented short-term data from clinical trials[33,35-37,39,43] (CS, Section 2.6.1 and Section 2.6.2 and Table 21) and longer-term data from registry studies (CS, Section 2.6.3 and Table 21) for some of the outcomes listed in the final scope[32] issued by NICE (Table 3). However, short-term data from clinical trials[33-43] (Appendix 1) and longer-term data from the registry studies[44,46] (Section 3.3) are available for most of the outcomes (Table 3). None of the published studies discussed in the CS reported HRQoL data (Table 3).

Table 3 Summary of the outcomes reported in the company submission and in study publications

Outcome	Short-term data		Long-term data	
	Reported in CS	Reported in study publications[33-44,46]	Reported in CS	Reported in study publications[33-44,46]
Phe concentration in the blood	Yes	Yes	Yes	Yes
Neuropsychological function	No	Yes	No	Yes
Natural protein intake	Yes	Yes	Yes	Yes
Biochemical and clinical indicators of poor nutrition	No	Yes	No	Yes
AEs of treatment	Yes	Yes	Yes	Yes
Cognitive and mood symptoms	No	Yes	No	Yes
HRQoL	No	No	No	No

AEs=adverse events; CS=company submission; HRQoL=health-related quality of life; Phe=phenylalanine
Source: Adapted and extracted from CS, Section 2.6.1 to 2.6.3; study publications[33-44,46]

2.6.6 Economic analysis

The cost effectiveness of sapropterin+PRD versus PRD was expressed in terms of incremental cost per quality adjusted life year (QALY) gained and the results were generated using the patient access scheme (PAS) price for sapropterin. Outcomes were assessed over a lifetime horizon and costs were considered from an NHS and Personal Social Services (PSS) perspective.

2.6.7 Subgroups

The company has presented (CS, Appendix E) clinical effectiveness data for blood Phe concentration levels and data for adherence to PRD for the subgroups shown in Table 4.

Table 4 Summary of the subgroups presented by the company

	Subgroups	Outcome	
		Blood Phe concentration	Adherence to PRD
Defined in the final scope issued by NICE	Patients with childbearing potential	Yes	Yes
	Age	Yes	Yes
	Adherence to PRD	No	
Additional to the final scope issued by NICE	Patients with ADHD	Yes	No
	Severity of PKU	Yes	Yes

ADHD=attention deficit hyperactivity disorder; Phe=phenylalanine; PKU=phenylketonuria; PRD=Phe-restricted diet
Source: Extracted and adapted from CS, Appendix E

2.6.8 Other considerations

As noted in Section 2.3, sapropterin is currently commissioned by NHS England for pregnant women with PKU who are unable to establish adequate dietary control and achieve the target non-teratogenic range of Phe (100µmol/L to 300µmol/L).[29]

The company identified equality issues for adults with PKU. The company considers (CS, pp34-5) that appraising sapropterin via the STA process could potentially disadvantage certain subpopulations of patients with PKU. The company has expressed special concern for adults with PKU who have cognitive impairments as this group of patients may have difficulty communicating their HRQoL and may also experience difficulties adhering to a PRD (CS, p35). The company reports that these patients are disadvantaged by current clinical management and should be considered for treatment with sapropterin to avoid disability discrimination.

The company has (appropriately) not put forward a case for treatment with sapropterin+PRD to be considered under NICE's End of Life[58] criteria.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The full details of the process used by the company to conduct a systematic search and the methods used by the company to identify evidence demonstrating the clinical effectiveness and safety of sapropterin for treating PKU are presented in the CS (Appendix D.1.1). The ERG has identified a minor issue with the company systematic review methods (described in Table 5) but, overall, the ERG considers the methods were appropriate and that the company has identified all relevant evidence.

Table 5 ERG appraisal of the company's systematic review methods

Review process	ERG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix D.1.1
Were appropriate sources searched?	Yes	See CS, Appendix D1.1, Table 5
Was the timespan of the searches appropriate?	Yes	Databases were searched from inception to the 13 July 2020. In response to clarification question C1, the company confirmed that conference proceedings from SSIEM 2018 and 2019, ICIEM 2017 and the international, European, Asia Pacific and Latin American ISPOR congresses published up to 3 years before the search date were hand searched
Were appropriate search terms used?	Yes	No additional ERG comments
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Appendix D.1.1, Table 7
Was study selection applied by two or more reviewers independently?	Yes	No additional ERG comments
Were data extracted by two or more reviewers independently?	Yes	No additional ERG comments
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Partially	The company quality assessed the included RCTs using the minimum assessment criteria recommended by NICE[59] and quality assessed single-arm studies using the Institute of Health Economics (IHE) Quality Assessment Checklist form for case-series studies (as adapted by Guo et al)[60] The company did not assess the quality of the included registry studies
Was the quality assessment conducted by two or more reviewers independently?	Yes	No additional ERG comments
Were attempts to synthesise evidence appropriate?	N/A	The company (appropriately) did not carry out any data syntheses; however, they did identify three published meta-analyses[47-49] that compared the effectiveness of sapropterin+PRD versus PRD (CS, Section B2.8)

ICIEM=International Congress of Inborn Errors of Metabolism; ISPOR=International Society for Pharmacoeconomics and Outcomes Research; PRD=Phe-restricted diet; SSIEM=Society for the Study of Inborn Errors of Metabolism
Source: LR*i*G in-house checklist

3.2 ERG summary and critique of the clinical effectiveness evidence

3.2.1 Included trials

The company identified 13 studies[33-46] (See Section 2.6.1) that provided evidence for the effectiveness of sapropterin for patients with PKU whose HPA had been shown to be responsive to sapropterin, namely:

- four RCTs (PKU-003,[33] PKU-006,[34] PKU-016[35] and SPARK[36])
- three single-arm follow-up studies (PKU-004,[37] PKU-008,[38] SPARK extension study[39])
- three single-arm studies (PKU-015,[40] ENDURE[41] and KOGNITO[42])
- one single-arm screening study (PKU-001[43])
- two registry studies (PKUDOS [including PKU-MOMS[45] sub-registry] and KAMPER).

The studies[33-46] identified by the company are described in detail in the CS (Sections 2.2 to 2.6) and are summarised in Table 38 and Table 39 in (Appendix 1) of this ERG report. The ERG notes that the four identified RCTs[33-36] are of short duration (between 6 weeks[33] and 13 weeks[35,36]) and include patient populations with different age ranges (≥8 years,[33] 4 to 12 years,[34] <4 years[36]). Only three[34-36] of the RCTs compared the effectiveness of sapropterin+PRD versus PRD (PKU-003[33] compared sapropterin+relaxed or abandoned diet with placebo+ relaxed or abandoned diet). The remaining non-RCTs are single-arm studies[37-43] and registry studies.[44-46]

The company considered (CS, p42) that the RCTs[33-36] and non-RCTs[37-43] were not appropriate sources of data to inform the economic model and instead used data from the PKUDOS and KAMPER registry studies. The company states that the identified RCTs[33-36] and non-RCTs[37-43] are 'largely historical' and that the PKUDOS and KAMPER registry studies provide longer-term data that are more representative of clinical practice than the data collected during clinical trials.

Data presented in Section 3.2.2 and Section 3.2.3 were extracted from the most recent interim registry study reports: PKUDOS-01 interim report (2018)[44] and the 10th Interim Report of the KAMPER Registry (2020).[46]

3.2.2 Characteristics of the PKUDOS and the KAMPER registry studies

Phenylketonuria Demographics Outcomes and Safety Registry (PKUDOS)

PKUDOS is an ongoing, phase IV, multi-centre, prospective, observational registry study being conducted in the USA. It was established by the company in fulfilment of a post-marking commitment to the United States Food and Drug Administration (FDA).[44] The purpose of the PKUDOS registry study is to assess the long-term safety and efficacy of sapropterin for

patients with PKU. Clinical advice to the ERG is that current clinical management of PKU in the USA is comparable to current clinical management of PKU in the UK. The PKUDOS registry study, at the time of the most recent interim analysis (7th December 2018), included 1922 patients who had previously received or were currently receiving sapropterin.[44] The PKU Maternal Observation Program (PKU-MOMS[45]) is a sub-registry of the PKUDOS registry. It was set up to allow the investigation of the safety and efficacy of sapropterin during and after pregnancy for pregnant and lactating women.

Kuvan Adult Maternal Paediatric European Registry (KAMPER)

KAMPER is an ongoing, phase IV, multi-centre, prospective, European observational registry study designed to assess the long-term safety of sapropterin for patients with PKU. It was established by the company in fulfilment of a post-marketing commitment to the EMA.[46] The study is being carried out in nine European countries (Table 6). Clinical advice to the ERG is that current clinical management of PKU in these countries is comparable to current clinical management of PKU in the UK. At the time of the most recent interim analysis (31 January 2020) 627 patients had been enrolled in this registry. However, 49 of these patients have HPA due to BH4-deficiency and two patients do not meet eligibility criteria for responsiveness to BH4. Therefore, 576 patients (91.9%) from the registry study match the population described in the final scope[32] issued by NICE.

The key characteristics of the PKUDOS and KAMPER registry studies are summarised in Table 6.

Table 6 Key characteristics of the PKUDOS and KAMPER registry studies

Trial parameters	PKUDOS[44]	KAMPER[46]
Design	• Ongoing, phase IV, single country, multi-centre, prospective, observational registry study • Includes the PKU-MOMS sub-registry • 68 sites in US • Planned study duration is up to 15 years	• Ongoing, phase IV, multiple countries, multi-centre, prospective, observational registry study • 69 sites in Europe (Austria, France, Germany, Italy, the Netherlands, Portugal, Slovakia, Spain and Sweden) • 63 active sites by the IA10 data cut • Planned study duration is approximately 15 years
Patient population	• Patients with confirmed diagnosis of PKU with HPA (blood Phe concentration >360µmol/L) • Previously received sapropterin, are currently receiving sapropterin, or intend to receive sapropterin within 90 days of enrolment • Patient must not be participating in a BioMarin-sponsored clinical study of sapropterin	• Patients with HPA due to PKU or BH4 deficiency (no age restrictions) • Responsive to BH4 or sapropterin • Receiving treatment with sapropterin at an included site • No known hypersensitivity to sapropterin • Not breastfeeding
Treatment	• Continuous, uninterrupted treatment with sapropterin+PRD • Previous, short-term treatment with sapropterin	• Sapropterin+PRD
Efficacy measures	• Blood Phe concentration • Dietary Phe tolerance • Blood tyrosine concentration	• Blood Phe concentration • Dietary Phe tolerance • Blood tyrosine concentration
Other measures	• Neurological assessment • Neurocognitive assessment • Behavioural assessment • Somatic growth • PAH genotyping • Bone density • Electrocardiogram assessment	• Neurological assessment • Neurocognitive assessment • Behavioural assessment • Somatic growth • PAH genotyping • Bone density • Electrocardiogram assessment
Safety measures	• AEs and SAEs • Physical examination findings, vital signs and laboratory tests	• AEs and SAEs • Physical examination findings, vital signs and laboratory tests
Report period for the most recent interim analysis	• 24th September 2008 to 7th December 2018	• 8 December 2009 to 31 January 2020
ERG comment	The registries provide long-term data that are more representative of usual clinical practice than trial data. The ERG agrees that the registries are the most appropriate data sources to inform conclusions relating to long-term efficacy and safety outcomes	

AEs=adverse events; BH4=tetrahydrobiopterin; HPA=hyperphenylalaninemia; IA=interim analysis; PAH=phenylalanine hydroxylase; Phe=phenylalanine; PKU=phenylketonuria; SAEs=serious adverse events
Source: Adapted from CS, Table 7; PKUDOS-01 Interim Report: 24 September 2008 to 7 December 2018, report date 16 April 2020;[44] CSR of the 10th Interim Report of the KAMPER Registry: 08 December 2009 through 31 January 2020, report date 29 June 2020[46]

3.2.3 Characteristics of patients in the PKUDOS and KAMPER registry studies

The company did not provide any details of the characteristics of the PKUDOS and KAMPER registry study patients in the main body of the CS. However, the ERG has summarised details of baseline safety analysis population characteristics extracted from the PKUDOS and KAMPER registry study reports (Table 7).

The majority of patients in the PKUDOS and KAMPER registry studies were classified as white (87.1% and 95.5%, respectively). In the PKUDOS study, patients were evenly distributed between the age subgroups. Specifically, 49.6% of patients were aged 4 years to 18 years and 40.8% were aged ≥18 years. In the KAMPER registry study, a large proportion of patients were aged 4 years to 18 years (81.6%) and only a small proportion of patients were aged ≥18 years (16.5%).

The ERG does not consider that the characteristics of the patients included in the PKUDOS and the KAMPER registry studies are different to the characteristics of patients with PKU who are likely to be treated with sapropterin in the NHS, except for age (which varies between the two registry studies).

Table 7 PKUDOS and KAMPER registry study patient characteristics (safety analysis population)

Baseline characteristic	PKUDOS[44] (n=1922)	KAMPER[46] (n=576)
Age, years		
<4, n (%)	[redacted]	[redacted]
4 to <18 years, n (%)	[redacted]	[redacted]
≥18 years, n (%)	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Sex, n (%)		
Female	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Intellectual disability, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Unknown	[redacted]	[redacted]

NR=not reported; SD=standard deviation
[a] Calculated from a total of 1921 patients. Data were missing for one patient
[b] Calculated from a total of 621 patients. Data were missing for four patients
Source: Extracted from PKUDOS-01 Interim Report: 24 September 2008 to 7 December 2018, report date 16 April 2020;[44] CSR of the 10th Interim Report of the KAMPER Registry: 08 December 2009 through 31 January 2020, report date 29 June 2020[46]

3.2.4 PKUDOS and KAMPER registry studies: quality assessment and critique of the statistical approach

The company did not complete a quality assessment of the PKUDOS or KAMPER registry studies. The ERG, therefore, carried out a quality assessment of the PKUDOS and KAMPER registry studies using the National Heart Lung and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies,[61] with the addition of an item regarding the source of funding. Quality assessments were carried out independently by two ERG reviewers, and consensus reached by discussion.

Periodic interim analyses of data from the PKUDOS and KAMPER registry studies were conducted. The ERG's quality and statistical approach assessments were carried out using the information available from the most recent interim analysis report for each registry study (PKUDOS-01 Interim Report: 24 September 2008 to 7 December 2018, report date 16 April 2020;[44] CSR of the 10th Interim Report of the KAMPER Registry: 08 December 2009 through 31 January 2020, report date 29 June 2020[46]), the statistical analysis plans (SAPs) for the

most recent interim analyses,[62,63] and the registry study protocols.[64,65] ERG quality assessments are presented in Table 8 and Table 9 for the PKUDOS and KAMPER registry studies respectively, and the ERG critiques of the pre-planned statistical approaches for the latest interim analyses of data from both registries are provided in Table 10.

Table 8 ERG quality assessment of the PKUDOS registry study

Assessment criteria	ERG assessment	ERG comment
Was the research question or objective clearly stated?	Yes	The objective of the PKUDOS registry study is clearly stated (SAP, Section 3.1; Protocol, Section 8.1)
Was the study population clearly specified and defined?	Yes	Inclusion and exclusion criteria of the population of interest are mostly clearly specified (SAP, Section 3.3; Protocol, Section 2). However, it is unclear whether responsiveness to sapropterin was an eligibility criterion. The ERG notes that the PKUDOS-01 interim report (Section 9) includes results for "responders" and "non-responders" to sapropterin
Was the participation rate of eligible persons at least 50%?	CD	The number of eligible patients who were invited to join the registry study but declined is not reported and, therefore, the participation rate cannot be calculated
Were all the participants selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	The population from which patients were recruited for the 15-year period of the registry study was pre-specified (Protocol, Section 10.1) Inclusion and exclusion criteria were prespecified (SAP, Section 3.3.1; Protocol, Section 2). The ERG considers that it is likely that these eligibility criteria have been applied uniformly, but notes that the number of patients screened who were deemed ineligible is not stated
Was a sample size justification, power description, or variance and effect estimates provided?	NA	The sample size of the registry study was not based on statistical power considerations; rather all eligible patients were invited to enrol in the registry study (SAP, Section 3.5)
For the analyses were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	All patients for whom outcome data are reported had received, or were currently receiving, sapropterin when their outcome data were collected (PKUDOS-01 interim report, Section 6)
Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	At the time of the latest interim analysis, the mean duration of exposure to sapropterin was 4.58 years, range 0.01 to 10.27 years (PKUDOS-01 interim report, Section 6.3) Given that the EMA licence for sapropterin stipulates a test period of 1 month to achieve a response,[27] the ERG considers that, for the majority of patients within the registry study, the timeframe was sufficient
For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	No	Patients who had previously received, or were currently receiving, sapropterin were eligible for inclusion in the registry study but separate results were not provided by previous or current sapropterin treatment (PKUDOS-01 interim report) Mean sapropterin dose (mg/kg/day), and a summary of dose adjustments made across the registry study patients were summarised (PKUDOS-01 interim report, Section 6.3). Dose of sapropterin was not examined as a categorical or continuous variable related to outcomes
Were the exposure measures (independent	Yes	The only exposure variable is receipt of sapropterin treatment, recorded at each routine clinic visit for each

variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		patient (Protocol, Section 2.1). Treatment exposure is summarised (PKUDOS-01 interim report, Section 6.3). The ERG has not identified any reason to suspect that treatment exposure has not been measured reliably and consistently across patients within the registry study
Was the exposure(s) assessed more than once over time?	Yes	Sapropterin treatment exposure is recorded at each routine clinic visit for each patient (Protocol, Section 2.1) and summarised in Section 6.3 of the PKUDOS-01 interim report
Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Efficacy evaluations (i.e., outcome measures) and the measurements required to inform these outcomes are predefined (SAP, Section 5.11 and Table 3.2.1, Protocol, Section 10.3). The ERG considers that outcomes are clearly defined and it is likely that outcome measures have been measured reliably and consistently across patients
Were the outcome assessors blinded to the exposure status of participants?	NA	Exposure status (i.e., current or previous treatment with sapropterin) is an inclusion criterion for enrolment into the registry study (SAP, Section 3.3.1; Protocol, Section 2) and, therefore, blinding of exposure status was not possible
Was loss to follow-up after baseline 20% or less?	No	Loss to follow-up of all patients was 20.5% between 24 September 2008 and 7 December 2018 (PKUDOS-01 interim report, Table 3)
Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	No confounding variables were identified
Was the funding source for the study stated?	Yes	BioMarin Pharmaceutical Inc are the sponsors of the PKUDOS registry study (PKUDOS-01 interim report, title page)

PKUDOS-01 Interim Report;[62] protocol of the PKUDOS registry study[64]
CD=cannot determine; CSR=clinical study report; EMA=European Medicines Agency; ERG=Evidence Review Group; NA=not applicable; SAP=statistical analysis plan
Source: National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies;[61] PKUDOS-01 Interim Report: 24 September 2008 to 7 December 2018, report date 16 April 2020;[44] SAP of the PKUDOS-01 Interim Report;[44] protocol of the PKUDOS registry study[64]

Table 9 ERG quality assessment of the KAMPER registry study

Assessment criteria	ERG assessment	ERG comment
Was the research question or objective clearly stated?	Yes	The objective of the KAMPER registry study is clearly stated (SAP, Section 6, Protocol, Section 4)
Was the study population clearly specified and defined?	Yes	Inclusion and exclusion criteria of the population of interest are clearly specified (SAP, Section 6, Protocol, Section 5.3)
Was the participation rate of eligible persons at least 50%?	CD	The number of eligible patients who were invited to join the registry study but declined is not reported and, therefore, the participation rate cannot be calculated
Were all the participants selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	The population from which patients are recruited for the follow-up period of at least 15 years was pre-specified (Protocol, Section 5.3). Measures taken to minimise recruitment selection bias are described (CSR, Section 9.6) Inclusion and exclusion criteria are pre-specified (SAP, Section 6, Protocol, Section 5.3). The ERG considers that it is likely that these eligibility criteria have been applied uniformly, but notes that seven included patients did not meet eligibility criteria (CSR, Section 10.1.1)
Was a sample size justification, power description, or variance and effect estimates provided?	Yes	The sample size was not based on statistical power considerations; rather an 'evaluable population' of 500 patients by the end of the study was proposed (estimated to represent 20% of patients responding to sapropterin among an initial population of 2500 patients with HPA) (SAP, Section 7, Protocol Section 8.1)
For the analyses were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	All eligible patients were receiving sapropterin when they were enrolled into the study and when their outcome data were collected (Protocol, Section 5.3; CSR, Section 10)
Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	From the latest interim analysis, the median duration within the registry study was 2265 days, range 14 days to 3510 days (CSR, Section 10.1.2) Given that the EMA licence for sapropterin stipulates a test period of 1 month to achieve a response,[27] the ERG considers that, for the majority of patients within the registry study, the timeframe was sufficient
For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	No	Mean sapropterin dose (mg/kg/day), and a summary of dose adjustments made across the registry study patients are summarised (CSR, Section 10.6.1). Dose of sapropterin was not examined as a categorical or continuous variable related to outcomes
Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently	Yes	The only exposure variable is receipt of sapropterin treatment, recorded at each routine clinic visit for each patient (Protocol, Section 6.9, Appendix I). Treatment exposure is summarised (CSR, Section 10.6.1). The ERG considers that it is likely that treatment exposure

across all study participants?		has been measured reliably and consistently across patients within the registry study
Was the exposure(s) assessed more than once over time?	Yes	Sapropterin treatment exposure is recorded at each routine clinic visit for each patient (Protocol, Section 6.9, Appendix I) and summarised in Section 10.6.1 of the CSR
Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Efficacy and safety endpoints and the measurements required to inform these outcomes are predefined (Protocol, Section 8, Appendix I; SAP, Section 16). The ERG considers that outcomes have been clearly defined and it is likely that outcome measures have been measured reliably and consistently across patients
Were the outcome assessors blinded to the exposure status of participants?	NA	Exposure status (i.e., current treatment with sapropterin) is an inclusion criterion for enrolment into the registry study (Protocol, Section 5.3) and, therefore, blinding of exposure status was not possible
Was loss to follow-up after baseline 20% or less?	Yes	Twenty-seven patients (4% of the Safety Analysis Set) were lost to follow-up between 08 December 2009 and 31 January 2020 (CSR, Figure 10-2)
Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	No confounding variables identified
Was the funding source for the study stated?	Yes	BioMarin Pharmaceutical Inc. are the sponsors of the KAMPER registry study (CSR, Section 4.1)

CD=cannot determine; CSR=clinical study report; EMA=European Medicines Agency; ERG=Evidence Review Group; HPA= hyperphenylalaninemia; NA=not applicable; SAP=statistical analysis plan
Source: NIH National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies;[61] CSR of the 10th Interim Report of the KAMPER Registry study: 08 December 2009 through 31 January 2020, report date 29 June 2020;[46] SAP of the 10th interim analysis of the KAMPER registry study;[62] protocol of the KAMPER registry study[65]

Table 10 ERG assessment of statistical approaches used in the PKUDOS and KAMPER registry studies

Item	ERG assessment	Statistical approach with ERG comments
Were all analysis populations clearly defined and pre-specified?	Yes	The analysis populations of the latest interim analyses of the PKUDOS registry study are the safety analysis set and the strict adherence set. These populations were prespecified in the SAP (Section 4.1) The analysis population of the latest interim analysis of the KAMPER registry study was the safety analysis set, which was prespecified in the SAP (Section 10.1)
Were all protocol amendments clearly described and made prior to analysis?	Yes	Protocol amendments are listed in Section 5 and Section 8 of the latest interim analysis reports of the PKUDOS and KAMPER registry studies, respectively The ERG considers that all protocol amendments are appropriate. They mainly relate to minor clarification of inclusion criteria, outcome definitions and data collection procedures. All protocol amendments were made prior to the most recent interim analyses. The ERG considers that it is unlikely that protocol amendments would have had an impact on previous interim analyses as these analyses were mostly descriptive with no formal hypothesis testing
Were all efficacy and safety outcomes pre-defined and analysed appropriately?	Yes	Definitions and analysis approaches for efficacy and safety outcomes are described in Section 5.11 and Section 5.12 respectively of the SAP for the latest interim analysis of the PKUDOS registry study and in Section 16.1 and Section 16.2 respectively of the SAP for the latest interim analysis of KAMPER registry study data The ERG is satisfied that all efficacy and safety outcomes were pre-specified and that descriptive analysis approaches are appropriate
Was a suitable approach employed for handling missing data?	Yes (but bias due to missing data is possible)	No imputation of missing assessment or outcome data imputation is conducted within either registry study, except for conservative imputation of partial dates for the PKUDOS registry study (Section 4.7 and Section 11.4 of the SAPs of the latest interim analyses of the PKUDOS and KAMPER registry studies respectively) The ERG agrees that it is appropriate not to conduct any data imputation and to present data as recorded. However, the ERG notes that a large amount of missing data is likely due to the observational nature of the registry study studies, and that potential biases resulting from missing data should be considered when drawing conclusions from the interim analysis results
Were all subgroup and sensitivity analyses pre-specified?	Yes (subgroup analyses) NA (sensitivity analyses)	All analyses of the latest interim analysis of the PKUDOS registry study data are summarised by age subgroups, predefined in the SAP (Section 4.2). Age subgroups and BH4-deficiency diagnosis subgroups (not relevant to the subgroup of patients with PKU) were pre-defined in the SAP for the latest interim analysis of the KAMPER registry study (Section 10.5) No sensitivity analyses were pre-specified in the SAPs or presented in the latest interim analysis reports for either registry study

BH-4=tetrahydrobiopterin; NA=not applicable; PKU=phenylketonuria; SAP=statistical analysis plan
Source: CSR of the 10th Interim Report of the KAMPER Registry study: 08 December 2009 through 31 January 2020, report date 29 June 2020[46]; SAP of the 10th interim analysis of the KAMPER registry study;[62] protocol of the KAMPER registry study;[65] PKUDOS-01 Interim Report: 24 September 2008 to 7 December 2018, report date 16 April 2020;[44] SAP of the PKUDOS-01 Interim Report;[44] protocol of the PKUDOS registry study[64]

Summary of ERG quality assessment and critique of statistical approaches

The ERG considers that the strengths of the PKUDOS and KAMPER registry studies are that they were well-designed and that interim analyses were well-conducted and transparently reported according to pre-specified protocols and SAPs. Specifically, the pre-defined research objectives, eligibility criteria and recruitment methods, outcome measures and data collection processes were clearly defined and appropriate. Sapropterin treatment exposure and all pre-defined efficacy and safety outcomes were well-described in detailed interim analysis reports. The ERG also notes that the statistical analysis approaches adopted for the latest interim analyses of the PKUDOS and KAMPER data are mostly descriptive, without any formal hypothesis testing and considers that this was appropriate given the objectives of the registry studies.

However, despite these strengths, the ERG notes that the objectives of these registry studies were to provide long-term efficacy and safety data for patients currently treated with (or previously treated with in the PKUDOS registry study) sapropterin; rather than to provide a comparison between sapropterin+PRD and PRD, as described in the decision problem outlined in the final scope[32] issued by NICE.

The ERG also notes several areas of uncertainty related to the PKUDOS and KAMPER registry studies. The number of eligible patients who declined to enrol is not provided for either registry, therefore participation rates are unknown. The ERG also notes that over 20% of the patients enrolled in the PKUDOS registry study had been lost to follow-up at the time of the most recent interim analysis and missing data were highlighted as a limitation of the latest interim analysis of the KAMPER registry study (CSR, Section 13). While the ERG considers that it was appropriate for both studies to describe data as recorded, without any imputation of missing assessment or outcome data, there is a potential for attrition bias, which should be considered when drawing conclusions from the interim analysis results of the registry studies.

Furthermore, the ERG notes no potential confounding variables (i.e., factors which may confound the relationship between sapropterin treatment and clinical outcomes) were identified in the interim analyses. Clinical advice to the ERG is that a known confounder of sapropterin treatment on clinical outcomes is dietary adherence and also that intercurrent illness, seasonal changes and age (particularly for children of primary school age) may lead to temporary fluctuations in blood Phe concentration levels, which may confound the relationship between sapropterin treatment and clinical outcomes.

Patients who had previously received, or were currently receiving, sapropterin were eligible for inclusion in the PKUDOS registry study. However, it was unclear whether responsiveness to sapropterin was an eligibility criterion for this study. The ERG notes that the PKUDOS-01 interim report (Section 9) includes results for "responders" and "non-responders" to sapropterin and that separate results were not provided by previous or current sapropterin treatment, nor according to whether a patient was responsive to sapropterin (PKUDOS-01 interim report).

Quality assessment of RCTs and single-arm studies of sapropterin

The company completed quality assessments of the four included RCTs (PKU-003,[33] PKU-006,[34] PKU-016[35] and SPARK[36]) using the minimum assessment criteria recommended by NICE.[58] For three included single-arm studies (PKU-001,[43] PKU-004[37] and PKU-008[38]), the company used the Institute of Health Economics (IHE) Quality Assessment Checklist form for case-series studies, as adapted by Guo et al.[60] The ERG agrees with the company quality assessments of the RCTs and single-arm studies, provided in the CS (Appendix D.1.3). The ERG comments on the RCTs and single-arm studies can be found in Appendix 1.

Statistical approaches adopted in RCTs and single-arm studies of sapropterin

The company summarised the statistical approaches of the four included RCTs (PKU-003,[33] PKU-006,[34] PKU-016[35] and SPARK[36]) and three included single-arm studies (PKU-001,[43] PKU-004[37] and PKU-008[38]) (CS, Table 20). Additionally, the statistical approach for the PKU-006[34] study is presented in the CS (Appendix F). Hypotheses relating to the trial objective, sample size calculations and statistical analysis method that was used were described for the RCTs (PKU-003,[33] PKU-006,[34] PKU-016[35] and SPARK[36]). The ERG notes that for three single-arm studies (PKU-001,[43] PKU-004[37] and PKU-008[38]), the statistical analysis approaches were mainly descriptive. The ERG considers that the statistical approaches employed to analyse data from the RCTs and non-RCTs of sapropterin were appropriate.

3.3 Efficacy results from the PKUDOS and KAMPER registry studies

In this section, the ERG summarises the efficacy results for the clinical outcomes listed in the final scope[32] issued by NICE from the latest interim analyses of the PKUDOS and KAMPER registry data. Neither of the registry studies recorded mood, symptoms or HRQoL as outcomes.

At the time of the latest interim analyses,[44,46] data had been collected and reported for up to 9 years from both registries. However, for some outcomes, data that had been contributed at later time points were very limited as only a small proportion of patients had been followed-up for this length of time and because not all assessments had been performed routinely for all

patients at each time point. Therefore, the ERG has summarised the results, extracted from the reports of the latest interim analyses,[44,46] at baseline, 1 year, 2 years and 5 years and presented results at 9 years of follow-up only when sufficient data were available (Section 3.3.1 and Section 3.3.2).

Published results from earlier interim analyses of the PKUDOS registry study data can be found in the Longo et al 2015 journal article[66] and in the Lilienstein et al 2017 poster presentation.[67] Results from earlier interim analyses of KAMPER registry study data can be found in the Trefz et al 2015 journal article[68] and in the Muntau et al 2017[69] poster presentation.

3.3.1 Efficacy results from the PKUDOS registry study

Results are summarised for the safety analysis set, defined as 1922 patients enrolled in the registry who were currently receiving sapropterin or had received sapropterin between 24 September 2008 and 7 December 2018. Results by age subgroups at baseline, <4 years (n=183), <12 years (n=805), <18 years (n=1137) and ≥18 years (n=784) are also presented (age missing for one patient). Sapropterin treatment exposure of patients enrolled in the PKUDOS registry up to 7 December 2018 is summarised in Table 11.

Table 11 Sapropterin treatment exposure: latest interim analysis of the PKUDOS registry study

	<4 years [redacted]	<12 years [redacted]	<18 years [redacted]	≥18 years [redacted]	All patients [redacted][a]
Years exposed to sapropterin during the PKUDOS registry study					
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sapropterin dose (mg/kg/day)					
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a.] Age at baseline missing for one patient, therefore subgroups <18 years and ≥18 years add up to 1921 patients
Source: Extracted and adapted from PKUDOS-01 interim report,[44] Table 10

Blood Phe concentration levels

Blood Phe concentration levels over time for all patients, and by age subgroup, are summarised in Table 12. The ERG notes that the number of patients contributing longer-term blood Phe concentration level data to the PKUDOS registry study is small; for example, [redacted] contribute blood Phe concentration level results at 2 years, [redacted] contribute results at 5 years and only [redacted] contribute results at the latest follow-up time of 9 years.

At baseline (i.e., enrolment into the registry study), the mean blood Phe concentration level among all patients was [redacted]; mean blood Phe concentration level at baseline was higher in older age groups. At baseline, [redacted] had blood Phe concentration levels in the target range of [redacted] and [redacted] had blood Phe concentration levels in the target range of [redacted].

In the age subgroups <18 years, an increase in mean blood Phe concentration level was observed over time and within each age subgroup, but the proportion of patients with blood Phe concentration levels in the target range of 120 to 360µmol/L (or 120 to 600µmol/L for patients ≥12 years, although results were not presented specifically for this subgroup) were relatively similar over time. The proportions of patients ≥18 years with blood Phe concentration levels in the target range of 120 to 600µmol/L was also relatively similar over time. Over time, higher proportions of patients achieved blood Phe concentration levels within target ranges in the younger age subgroups (<4 years and <12 years) than the older age group (≥18 years). Clinical advice to the ERG is that blood Phe concentration level alone is a poor measure of efficacy and should only be considered in conjunction with dietary Phe intake.

Table 12 Blood Phe levels over time: latest interim analysis of the PKUDOS registry study

Visit	Phe level (µmol/L)	<4 years [redacted]	<12 years [redacted]	<18 years [redacted]	≥18 years [redacted]	All patients [redacted][a]
Baseline	n (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Phe level 120 to 360µmol/L, n (%)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Phe level 120 to 600µmol/L, n (%)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 year	n (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Phe level 120 to 360µmol/L, n (%)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Phe level 120 to 600µmol/L, n (%)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	n (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Phe level 120 to 360µmol/L, n (%)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Phe level 120 to 600µmol/L, n (%)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	n (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Phe level 120 to 360µmol/L, n (%)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Phe level 120 to 600µmol/L, n (%)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9 years	n (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Phe level 120 to 360µmol/L, n (%)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Phe level 120 to 600µmol/L, n (%)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Age at baseline missing for one patient, therefore subgroups <18 years and ≥18 years add up to 1921 patients
[b] Percentage calculated based on total n within the age subgroup or all patients within the registry study
[c] Percentage calculated based on n within the subgroup or within the registry study contributing data at the time point
L=litre; Phe=phenylalanine; SD=standard deviation
Source: Extracted and adapted from PKUDOS-01 interim report,[44] Table 14.2.01.01

Actual (natural) protein intake

Many measures of dietary protein intake were reported in Section 6.4.3 of the PKUDOS-01 interim report.[44] Clinical advice to the ERG is that actual Phe intake is the most precise and relevant measure of natural protein intake. Therefore, actual Phe intake (milligrams [mg] per day) over time for all patients and by age subgroup are summarised in Table 13.

The ERG notes that the number of patients who contributed data on their dietary protein intake is small, particularly at later time points. At baseline, [redacted] patients [redacted] contributed data and [redacted] and [redacted] contributed data at 1 year, 2 years and 5 years respectively. At the latest follow-up time of 9 years, [redacted] patients provided actual Phe intake data.

At baseline, the mean actual Phe intake among all patients was [redacted], with higher mean actual Phe intake reported by older age groups. Increases in mean actual Phe intake over time were observed in the subgroups <18 years old. For patients ≥18 years mean actual Phe intake was similar over time.

Table 13 Actual Phe intake over time: latest interim analysis of the PKUDOS registry study

Visit	Actual Phe intake (mg / day)	<4 years [redacted]	<12 years [redacted]	<18 years [redacted]	≥18 years [redacted]	All patients [redacted][a]
Baseline	n (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 year	n (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	n (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	n (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Age missing for one patient, therefore subgroups <18 years and ≥18 years add up to 1921 patients
[b] Percentage calculated based on total n within the age subgroup or all patients within the registry study
mg=milligrams; Phe=phenylalanine; SD=standard deviation
Source: Extracted and adapted from PKUDOS-01 interim report,[44] Table 14.2.04.13

Neuropsychological function, cognitive outcomes and nutritional biochemistry

Very limited data were available for psychological disorders, behavioural and neurological disorders, developmental assessments and Intelligence Quotient (IQ) assessments and outcomes related to nutrition such as cholesterol, serum B12, serum zinc and vitamin D at baseline or during follow-up. These assessments were not routinely conducted at the centres recruiting patients to the PKUDOS registry study (PKUDOS-01 interim report[44]).

The majority of patients did not exhibit any psychological, behavioural or neurological disorders at baseline. Very few patients showed any changes in psychological, behavioural or neurological disorders during follow-up assessments, and very few new cases of psychological, behavioural or neurological disorders were reported during follow-up. Only very small changes from baseline were observed for developmental and nutritional measures.

No conclusions about the effects of sapropterin on psychological, behavioural or neurological disorders (Section 6.4.4, Section 6.4.5, Section 6.4.6), development and IQ (Section 6.4.7, Section 6.4.8, Section 6.4.9) or nutritional outcomes (Section 6.5.4) could be reached using results from the latest Interim Report of the PKUDOS registry.

3.3.2 Efficacy results from the KAMPER registry study

Results are summarised for the 576 patients with PKU in the safety analysis set, defined as all enrolled patients who met all eligibility criteria between 08 December 2009 and 31 January 2020. Results are presented according to age subgroups at baseline <4 years (n=11), 4 to <18 years (n=470) and ≥18 years (n=95). As the majority of the patients enrolled in the KAMPER registry study are between the ages of 4 to 18 years, results for patients < 4 years and ≥18 years of age are limited.

Sapropterin doses received by patients in each age subgroup enrolled in the KAMPER registry up to 31 January 2020 are summarised in Table 14. At the latest follow-up time of 9 years, only five patients contributed data on their sapropterin doses.

Table 14 Sapropterin doses: latest interim analysis of the KAMPER registry study

Visit	Sapropterin dose (mg/kg/day)	<4 years [redacted]	4 to <18 years [redacted]	≥18 years [redacted]
Baseline	n (%)	[redacted]	[redacted]	[redacted]
	Mean (range)	[redacted]	[redacted]	[redacted]
1 year	n (%)	[redacted]	[redacted]	[redacted]
	Mean (range)	[redacted]	[redacted]	[redacted]
2 years	n (%)	[redacted]	[redacted]	[redacted]
	Mean (range)	[redacted]	[redacted]	[redacted]
5 years	n (%)	[redacted]	[redacted]	[redacted]
	Mean (range)	[redacted]	[redacted]	[redacted]

kg=kilogram; mg=milligram; NA=not applicable
Source: Extracted and adapted from CSR of the 10th Interim Report of the KAMPER registry study,[46] Table 10-26

Blood Phe concentration

Blood Phe concentration levels over time for all patients and by age subgroup are summarised in Table 15. The number of patients contributing longer-term blood Phe concentration level data to the KAMPER registry is small. From baseline up to 5 years, between [redacted] and [redacted] of patients across subgroups contribute blood Phe concentration level results but at 9 years, [redacted] patients contributed blood Phe concentration level results, [redacted] were <4 years of age. At baseline, mean blood Phe concentration level was [redacted] in [redacted] and [redacted] in [redacted]. Increases in mean blood Phe concentration levels were observed over time in all age subgroups.

Table 15 Blood Phe levels over time: latest interim analysis of the KAMPER registry

Visit	Phe level (µmol/L)	<4 years [redacted]	4 to <18 years [redacted]	≥18 years [redacted]
Baseline	n (%)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
1 year	n (%)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
2 years	n (%)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
5 years	n (%)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
9 years	n (%)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]

L=litre; NA=not applicable; Phe=phenylalanine; SD=standard deviation
Source: Extracted and adapted from CSR of the 10th Interim Report of the KAMPER registry,[46] Table 10-11

Data describing target blood Phe concentration levels were limited for all of the age subgroups (CSR for the 10th Interim Report of the KAMPER registry;[46] Section 10.4.1.8.1). At baseline, [redacted] of patients [redacted] had blood Phe levels in the range of [redacted]. Median blood Phe concentration levels, up to 5 years, in this age group were [redacted] (median ranging from [redacted] to [redacted]). In the largest subgroup of patients ([redacted]), up to 7 years of follow-up, between [redacted] and [redacted] of patients had blood Phe concentrations [redacted]. For patients [redacted], median blood Phe concentration levels, up to 7 years, were [redacted] (ranging from [redacted] to [redacted]). Clinical advice to the ERG is that blood Phe concentration level alone is a poor efficacy outcome and should only be considered in conjunction with dietary Phe intake.

Actual (natural) protein intake

Actual Phe intake (mg per day) over time by age subgroups are summarised in Table 16. The number of patients who contributed data on their actual Phe intake was small. From baseline up to 5 years, between [redacted] and [redacted] of patients across subgroups contributed actual Phe intake data and at 9 years [redacted] patients in the [redacted] subgroup contributed actual Phe intake data. At each time point, mean actual Phe intake was highest in patients [redacted]. Increases in mean actual Phe intake over time were observed in the subgroups [redacted]. For patients [redacted] mean actual Phe intake was [redacted] over time.

Table 16 Actual Phe intake over time: latest interim analysis of the KAMPER registry study

Visit	Actual Phe intake (mg / day)	<4 years (n=11)	4 to <18 years (n=470)	≥18 years (n=95)
Baseline	n (%)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
1 year	n (%)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
2 years	n (%)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
5 years	n (%)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]

mg=milligram; NA=not applicable; Phe=phenylalanine; SD=standard deviation
Source: Extracted and adapted from CSR of the 10th Interim Report of the KAMPER registry study,[46] Table 10-8

Neuropsychological function, cognitive outcomes and nutritional biochemistry

Very limited data were available for psychological disorders, behavioural and neurological disorders, developmental and performance assessments and outcomes related to nutrition such as vitamin D at baseline or during follow-up as these assessments were not routinely conducted at the centres recruiting patients to the KAMPER registry study (CSR of the 10th Interim Report of the KAMPER registry study[46]).

The majority of patients did not exhibit any psychological, behavioural or neurological disorders at baseline. Very few patients showed any changes in psychological, behavioural or neurological disorders during follow-up assessments, very few new cases of psychological, behavioural or neurological disorders were reported during follow-up. Only very small changes from baseline were observed for developmental and nutritional measures.

No conclusions about the effects of sapropterin on psychological, behavioural or neurological disorders (Section 10.4.2.3, Section 10.4.2.4, Section 10.4.2.5), development and IQ (Section 10.4.2.6, Section 10.4.2.7) or nutritional outcomes (Section 10.4.2.1.1) could be made using results from the latest interim analysis of the KAMPER registry study.

3.4 Safety and tolerability results from the sapropterin trials

Safety and tolerability data are presented in the CS (Section B.2.10). The AE data from the PKUDOS registry were extracted from the publication by Longo et al 2015[66] with additional data taken from a 2017 poster presentation.[67] The AE data from the KAMPER registry were extracted from the 8th interim analysis (2018[70]).

Other sources of AE data reported in the CS are listed in Table 17. The company states (CS, p124) that PKU-008,[38] a single-arm follow-up study, is the only study where safety was the primary endpoint; the study assessed the long-term safety (2.6 years) of sapropterin treatment in patients with PKU who participated in either PKU-004[37] or PKU-006.[34]

Table 17 Sources of adverse event data reported in the company submission

Study design	Study ID	Location in the CS
Registry	PKUDOS[44]	Page 136 and Table 35
Registry	KAMPER[46]	Table 36
RCT	PKU-003[33]	Table 29
RCT	PKU-016[35]	Table 31
RCT	SPARK[36]	Table 32
Single-arm extension study	SPARK extension[39]	Page 137
RCT	PKU-006[34]	Appendix F (p10)
Single-arm screening study	PKU-001[43]	Table 28
Single-arm extension study	PKU-004[37]	Table 30
Single-arm safety study	PKU-008[38]	Table 33 and Table 34
Single-arm cohort study	PKU-015[40]	Table 38
PKUDOS sub-registry	PKUMOMS[45]	Appendix F (Table 4)
Single-arm cohort study	ENDURE[41]	Appendix F (Table 5)

RCT=randomised controlled trial

3.4.1 Adverse events

Registry studies

PKUDOS. The company reports (CS, p137) that in the overall patient population of the PKUDOS registry study (n=1189), most treatment-related AEs (TRAE) were non-serious and were related to the gastrointestinal, respiratory and nervous systems. There were 113 recorded TEAEs, 12% resulted in permanent treatment discontinuation, 10% in temporary treatment discontinuation and 4% in dose reductions. Ten serious AEs (SAE) related to treatment were recorded.

Data for the most common TRAEs (taken from the 2017 poster presentation[67]) are provided in Table 35 of the CS. These data were, i) reported by patients who were previously treated with sapropterin or ii) data from patients who were continuously treated with sapropterin.

KAMPER. The company reports (CS, p138) that in the overall patient population ([redacted]) of the KAMPER[70] registry study, [redacted] patients experienced 58 events [redacted]. The types of TRAEs were not reported in the CS. One SAE (headache) was considered to be related to treatment. One death was reported; however, this was not related to treatment with sapropterin.

Other adverse event data reported in the CS

The PKU-008[38] study was designed to assess the safety of treatment with sapropterin and the outcomes for 111 patients are reported. Patients (age range 4 years to 50 years) were monitored every 3 months for AEs and SAEs. The mean duration of treatment with sapropterin

was almost 2 years (CS, p133). No TRAEs occurred at a frequency >5%. One severe TRAE was reported, and three patients discontinued the study due to a TRAE. The most common TRAEs were viral gastroenteritis, vomiting, and headache.

Given the heterogeneity between the studies reported in the CS (e.g., different study designs, different lengths of follow-up and different patient populations) the AE data cannot be meaningfully summarised. In the Summary of Product Characteristics[28] for sapropterin, the EMA states that the most common AEs in patients aged ≥4 years are headache and rhinorrhoea and the most commonly reported AEs in children <4 years are hypophenylalaninaemia, vomiting and rhinitis.

The company states (CS, p124) that treatment with sapropterin is 'well tolerated and demonstrates a favourable risk-benefit profile for treatment in children and adults'. The company also states that most of the AEs observed in the studies were considered to be mild or moderate and did not result in patients discontinuing treatment with sapropterin. Clinical advice to the ERG is that treatment with sapropterin is well-tolerated and there are no safety concerns.

3.5 Conclusions of the clinical effectiveness section

- Evidence from the three RCTs[34-36] that are relevant to this appraisal and compare treatment with sapropterin+PRD versus PRD are limited due to the short duration of the trials (10 weeks[34] to 13 weeks[35,36]). The effectiveness data from the RCTs are not used to populate the company's model.

- Results from the RCTs show that most patients treated with sapropterin+PRD achieve and maintain target blood Phe concentration levels[34-36] and increase or maintain their intake of dietary Phe[34,36] compared to patients treated with PRD.

- Longer-term effectiveness data (up to 9 years duration) are available from the company-sponsored PKUDOS and KAMPER registries and show that most patients treated with sapropterin+PRD achieve and maintain target blood Phe concentration levels and increase or maintain their intake of actual (natural) protein.

- Data from the PKUDOS and KAMPER registry studies for the remaining outcomes listed in the final scope[32] issued by NICE (neuropsychological function, biochemical and clinical indicators of poor nutrition, cognitive and mood symptoms) are sparse.

- No HRQoL evidence has been provided for the comparison of sapropterin+PRD versus PRD.

- The ERG acknowledges that blood Phe concentration level is a widely used measure of efficacy. However, clinical advice to the ERG is that, in clinical practice, blood Phe concentration level, as a measure of treatment efficacy, is dependent on and is best used in conjunction with dietary Phe intake. Blood Phe concentration levels should, therefore, only be considered in conjunction with dietary information, particularly in the long term.

- The PKUDOS and KAMPER registry studies are well-designed and well-reported and are of good methodological quality. However, the objectives of the PKUDOS and KAMPER studies are to provide long-term efficacy and safety data for patients treated with sapropterin+PRD, rather than to provide a comparison between sapropterin+PRD and PRD, as specified in the final scope[32] issued by NICE.

- The results reported from the PKUDOS and KAMPER studies do not (and are unable to) take account of confounding factors, for example, dietary adherence, intercurrent illness, seasonal change and age (of children) which may lead to temporary fluctuations in blood Phe levels.

- The population of the PKUDOS registry study included patients who had previously received, or were currently receiving, sapropterin. It also included patients who were responsive to sapropterin and those who were not responsive to sapropterin. However, separate results are not provided by previous or current sapropterin treatment, nor according to whether a patient was responsive to sapropterin.

- The available AE data from the registry studies and the company's clinical studies show that treatment with sapropterin is well-tolerated and there are no safety concerns.

4 COST EFFECTIVENESS EVIDENCE

This section provides a structured critique of the economic evidence submitted by the company in support of the use of sapropterin for treating HPA in patients with PKU. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of its economic model, which was developed in Microsoft Excel.

4.1 ERG summary and critique of the company review of cost effectiveness studies

Full details of the methods used by the company to identify and select cost effectiveness evidence are presented in the CS, Appendix G.

4.1.1 Objective of the company's literature searches

The company undertook systematic and targeted searches to identify cost utility analyses relating to European populations with PKU that could be used to inform the company's cost effectiveness modelling to support this appraisal of sapropterin.

4.1.2 Search strategy

The searches were initially carried out on 1 October 2018 and were updated on 13 July 2020. Relevant electronic databases (MEDLINE, Embase, NHS Economic Evaluation Database [NHS EED], Cost Effectiveness Analysis [CEA] registry, EconPapers, and the Health Technology Assessment [HTA] database) were searched. The search terms used included combinations of keywords and medical subject headings.

Websites of key conferences, including those held by the International Congress of Inborn Errors of Metabolism (ICIEM), Medical Decision Making (MDM) and the International Society for PharmocoEconomics and Outcomes Research (ISPOR), were searched to identify relevant published abstracts. Also, the websites of international HTA agencies were searched to identify appraisals or assessments of relevant therapies for PKU.

4.1.3 Inclusion and exclusion criteria

The inclusion and exclusion criteria used by the company are provided in the CS (Appendix G, Table 5). These criteria were designed to identify cost utility analyses undertaken from a payer perspective over a lifetime horizon. There were no date limits, but studies had to relate to Europe or Turkey. Foreign language papers were included at first pass if sufficient information was included in the English abstract to suggest the eligibility criteria had been met.

4.1.4 Study selection

Two researchers independently screened all publications according to their title and abstract content. Any discrepancies in terms of inclusion/exclusion decisions between the researchers were resolved through discussion with or without a third reviewer. The same process was repeated for the full-length articles selected during the title and abstract screening process.

4.1.5 Findings from the company's cost effectiveness review

The company's selection strategy identified five publications[71-75] reporting the cost effectiveness results from four models. The first model evaluated the cost effectiveness of reimbursed PRD (and not sapropterin).[71,72] The three other models evaluated the cost effectiveness of sapropterin+PRD as part of the company's (BioMarin) submissions to Swedish,[73] Irish[74] and Scottish[75] HTA agencies, but none of the populations in the models matched the population specified in the final scope[32] issued by NICE (Table 18). The company has provided a detailed description of these models in Appendix G and presented summary details in the main body of the CS (Section B.3.1).

Table 18 Summary list of published cost effectiveness studies

Study	Summary of model	Patient population
Mlcoch 2016[71,72]	Payer perspective, lifetime CUA Markov model, 1-year cycle length, costs and outcomes discounted at 3%, 3 health states (on diet, non-compliance to diet [mental retardation], death)	Patients with PKU requiring lifetime PRD
TLV 2017[73] HTA evaluation summary	Payer perspective (no indirect costs), lifetime horizon, landmark model, 1-year cycle length, 5 health states (controlled, partially controlled, uncontrolled, asymptomatic, death)	Children and adults with HPA due to PKU with genetic conditions responding to sapropterin who do not achieve an adequate response to dietary treatment alone
NCPE 2017[74] HTA evaluation summary	Payer perspective, 100-year time horizon, decision analytic model, cohort-based Markov-type model, after BH4 response test responders move to recursive Markov part of model, 1-year cycle length, 5 health states (controlled, partially controlled, uncontrolled, asymptomatic, and death), half cycle correction applied	Patients with HPA due to PKU, uncontrolled or partially controlled
SMC 2018[75] HTA evaluation	Payer perspective, 100-year time horizon, decision analytic model (during 4-week period of testing responsiveness) and, for responders, Markov model, 1-year cycle length, 5 health states (controlled, partially controlled, uncontrolled, asymptomatic, and death)	Patients aged 0 to 18 years with HPA due to PKU, uncontrolled (elevated Phe, with symptoms) & partially controlled (Phe in target, with symptoms), sapropterin-responsive, & maternal PKU females

BH4=tetrahydrobiopterin; CUA=cost utility analysis; HPA=hyperphenylalaninaemia; HTA=Health Technology Assessment; NCPE=National Centre for Pharmacoeconomics (Ireland); Phe=phenylalanine; PKU=phenylketonuria; SMC=Scottish Medicines Consortium
Source: CS, Table 40

4.1.6 ERG comments

The ERG is satisfied with the company's cost effectiveness literature search and study selection methods (see Table 19). The model reported by Mlcoch[71,72] did not include sapropterin as a comparator. The three other models[73-75] have similar structures to the model currently submitted by the company; however, as the Irish and Scottish HTA agencies[74,75] have already criticised these models for not reflecting the natural course of PKU in patients, the ERG considers that these model structures are not relevant to this appraisal.

Table 19 ERG appraisal of systematic review methods

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	Yes
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Yes
Were attempts to synthesise evidence appropriate?	Yes

Source: LRiG in-house checklist

The searches used by the company to identify cost effectiveness models were also used to identify HRQoL, resource and cost information that could be used to populate the company's economic model. The study selection process used by the company to identify these types of data differed, but only slightly, from the criteria used to identify cost utility studies.

4.2 ERG summary of the company's submitted economic evaluation

The company developed a de novo economic model to compare the cost effectiveness of sapropterin+PRD versus PRD for the treatment of HPA in patients with PKU that is responsive to treatment with sapropterin. The primary outcomes from the company model are incremental cost effectiveness ratios (ICERs) per QALY gained.

4.2.1 NICE Reference Case checklist and Drummond checklist

Table 20 NICE Reference Case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	No. Health effects (i.e., transition probabilities) were obtained from the company's analyses of data from two registries (PKUDOS and KAMPER[76])
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No. No measurements of HRQoL were taken but rather hypothetical vignettes were created
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No. TTO for hypothetical vignettes were valued by adults living in Sweden and used to represent utilities for adults in the UK. The Swedish adult utility values were modified (based on clinical advice) for UK children
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

EQ-5D=EuroQol-5 dimensions; HRQoL=health-related quality of life; NHS=National Health Service; PSS=Personal Social Service; QALY=quality adjusted life year; TTO=time-trade off
Source of checklist: NICE Guide to the Methods of Technology Appraisal[58]

Table 21 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	No	There are no long-term randomised head-to-head trials of sapropterin+PRD versus PRD, nor are there sufficient reliable data to allow an ITC to be undertaken Estimates of the relative treatment effectiveness of sapropterin+PRD versus PRD were obtained from the company's analyses of registry data
Were all the important and relevant costs and consequences for each alternative identified?	Partly	The cost and health impact of AEs could not be considered because robust data were not available
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Partly	Detailed information on how the cost of PRD was calculated was not presented HRQoL values used in the model were derived from the general public and not from patients with PKU
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

HRQoL=health-related quality of life; ITC=indirect treatment comparison; PRD=Phe-restricted diet; PKU=phenylketonuria; Source of checklist: Drummond and Jefferson (1996)[77]

4.2.2 Population

The population described in the final scope[32] issued by NICE is patients with PKU whose HPA has been shown to be responsive to sapropterin. It is also stated that, if evidence allows, consideration may be given to the following subgroups: patients with childbearing potential, age and adherence to diet.

The population considered in the company base case is patients who have been shown to be responsive to sapropterin treatment during a 4-week testing period. It is assumed that treatment commences at 4 weeks of age and continues for a lifetime. The company has also generated cost effectiveness results for the following subgroups: 0 to 4 year olds, 0 to 12 year olds, 0 to 17 year olds, 5 to 12 year olds, 13 to 17 year olds, 18 years or older, and women of

childbearing age (defined as aged between 18 and 40 year olds). In the company model, for the age-related subgroups, the lower bound age is the age at which treatment with sapropterin commences and the upper bound age is the age at which treatment with sapropterin is discontinued. For women of childbearing age, treatment is assumed to start at age 18 years and continue for 1 year.

4.2.3 Interventions and comparators

The intervention is treatment with sapropterin, an oral preparation, along with PRD (i.e., sapropterin+PRD). A PRD consists of restricted natural protein intake supplemented with prescribed low-protein and Phe-free food and Phe-free amino acid supplements.

Average sapropterin doses of 10mg/kg once-daily for children (<18 years) and 12.5mg/kg once-daily dose for adults (18 years or older) were modelled. The company states that these doses were informed by the doses used in their clinical trial programme[78] and align with the values presented by NHS England in their Integrated Impact Assessment Report[78] on sapropterin in PKU.

The comparator treatment is PRD alone. This is standard of care in the UK.[79]

4.2.4 Model structure

The company's model structure (a decision analytic Markov cohort model) comprises five mutually exclusive health states: four disease health states and dead. The disease health states are treatment with sapropterin+PRD (SPRD) with, and without, controlled Phe levels (i.e., controlled-SPRD and uncontrolled-SPRD health states), and treatment with PRD alone with and without controlled Phe levels (i.e., controlled-PRD and uncontrolled-PRD health states). Controlled PKU is defined as Phe levels that are within the target ranges set out in the European PKU guidelines.[80]

Patients in the intervention arm enter the model in the controlled-SPRD health state and those in the comparator arm start in the controlled-PRD health state. At the end of each yearly cycle, patients can either remain in their current health state or move to a permitted health state. Patients whose disease remains uncontrolled after receiving sapropterin+PRD for a year discontinue sapropterin and progress to one of the two PRD health states (controlled-PRD or uncontrolled-PRD). The company has assumed that patients cannot be re-challenged with sapropterin once treatment has been discontinued. Dead is an absorbing health state from which transitions to other health states are not permitted. The permitted pathways between health states are shown in Figure 1.

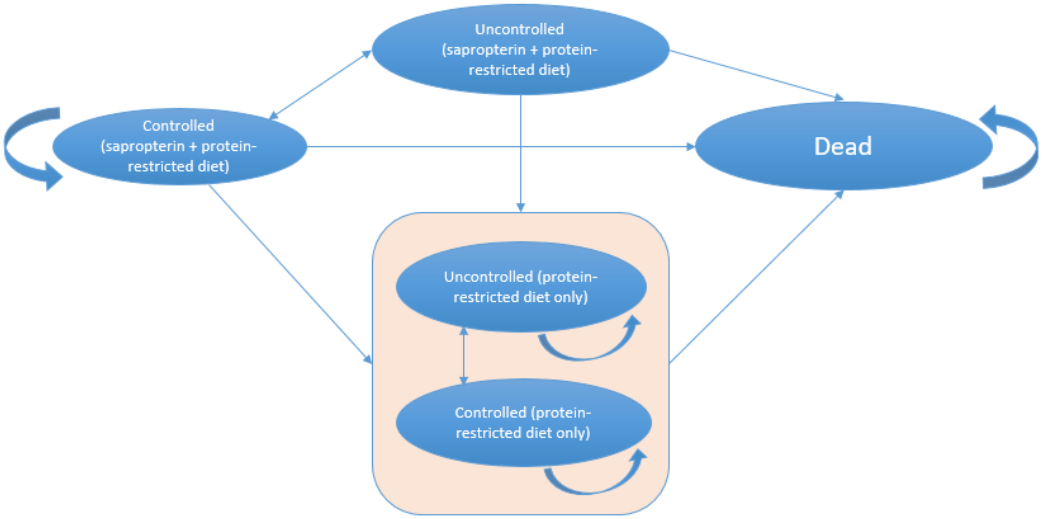

Figure 1 Structure of the company model

Source: CS, Figure 36

4.2.5 Perspective, time horizon and discounting

The company states that costs are considered from the perspective of the NHS and Personal Social Services (PSS). The model cycle length is 1 year, and in the base case the time horizon is a lifetime, which the company considers is long enough to reflect important differences between treatment arms. Relevant costs and outcomes are discounted at 3.5% per annum.

4.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness for sapropterin+PRD and PRD are modelled using the health state transition probability matrix developed by the company. This transition probability matrix was populated with results from the company's analyses of PKUDOS and KAMPER[76] registry data.

The PKUDOS registry is an ongoing prospective observational dataset that holds information on about 2000 patients with PKU. At the time of the data cut off, a total of 1867 patients had been followed up for at least 10 years: 557 had previously received sapropterin, 1069 were currently receiving sapropterin, 221 intended to start receiving sapropterin (within 90 days of enrolment) and 20 had missing treatment information. The company used data from a cohort of PKUDOS registry patients who intended to start sapropterin and for whom a baseline blood Phe concentration level and sapropterin treatment dose were available (i.e., 191 of the initial 221 patients). Data from patients who had previously received sapropterin before enrolling in PKUDOS or discontinued sapropterin whilst in the registry (n=160) were used to model the experience of patients in the PRD arm of the model.

Transition probabilities were estimated using the first 6 years of PKUDOS registry data. For each year, and for each treatment (sapropterin+PRD and PRD), the company estimated probabilities from the number of patients with controlled disease who later developed uncontrolled disease, and vice versa. The average (weighted by the number of patients each year) transition probabilities over the 6 years were used to populate the transition probability matrix (Table 22). A full description of the PKUDOS registry is presented in Appendix M to the CS and in the company's response to question B3 of the clarification letter.

Table 22 Annual transition matrices used in base case analysis (≥19 years)

	Controlled-SPRD	Uncontrolled-SPRD	Controlled-PRD	Uncontrolled-PRD
Controlled-SPRD	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled-SPRD	[redacted]	[redacted]	[redacted]	[redacted]
Controlled-PRD	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled-PRD	[redacted]	[redacted]	[redacted]	[redacted]

*=values were obtained from the analysis summarised in Appendix M (Table 5 or Table 6) to the company submission, but values reported in Table 5 and Table 6 of Appendix M to the company submission do not match values presented in Table 45 of the company submission and economic model; NA=not applicable; PRD=Phe-restricted diet; SPRD=sapropterin in conjunction with protein-restricted diet
Source: CS, Table 45

The data from the KAMPER registry,[76] a multinational prospective observational registry (Section 3.3.2), showed that over a 1-year follow-up period, [redacted] of patients discontinued treatment with sapropterin. The company, therefore, adjusted their initial transition probability matrix so that, each year, [redacted] of the [redacted] of patients in the controlled-SPRD health state discontinued treatment with sapropterin and moved to either the controlled-PRD health state (7.0%) or to the uncontrolled-PRD health state (2%).

The company also assumed that all patients whose disease remained uncontrolled with sapropterin at the end of each cycle (uncontrolled-SPRD health state) would migrate to one of the PRD health states (controlled-PRD and uncontrolled-PRD health states). The final transition probability matrix used in the economic model is shown in Table 23.

As the impact of PKU on risk of mortality is unclear, risk was modelled using all-cause mortality life tables for England and Wales.[81] Rates were stratified by age and gender; PKU is gender agnostic.

Table 23 Annual transition matrix used in the model after the inclusion of attrition rates (≥19 years)

	Controlled-SPRD	Uncontrolled-SPRD	Controlled-PRD	Uncontrolled-PRD
Controlled-SPRD	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled-SPRD	[redacted]	[redacted]	[redacted]	[redacted]
Controlled-PRD	redacted	redacted	redacted	redacted
Uncontrolled-PRD	[redacted]	[redacted]	[redacted]	[redacted]

PRD=Phe-restricted diet; SPRD=sapropterin in conjunction with protein-restricted diet
Source: Company model

4.2.7 Health-related quality of life

None of the sapropterin clinical trials[33-46] collected preference based HRQoL data. In the base case, the company used health state utility values obtained from a time-trade off (TTO) study[82] carried out in Sweden to elicit general population preferences for a range of hypothetical vignettes representing PKU health states. This study was commissioned by the company.

As the Swedish data only relate to adults, the company held expert panel meetings and carried out clinician surveys to elicit UK clinician views on how utility values for children with PKU might differ from the (Swedish) adult values. Full details about this elicitation exercise are provided in the CS (Appendix H). The utility values used in the company model are presented in Table 24.

Table 24 Baseline utility value and utility decrements used in the company model

Health state	Children	Adults
Baseline	[redacted]▲	[redacted]◆
Decrement		
Controlled-SPRD Controlled-PRD	[redacted]*	[redacted]#
Uncontrolled-SPRD Uncontrolled-PRD	[redacted]*	[redacted]#

▲=age-dependent parameter, reported value was applied to 0-year olds; ◆=age-dependent parameter, reported value was applied to 18-year olds; *=valued applied to 0-4-year olds, 4-12-year olds, 13-17-year olds; #=value applied to adults and women of childbearing age; PRD=Phe-restricted diet; SPRD=sapropterin in conjunction with Phe-restricted diet
Source: CS, Table 52 and company model

4.2.8 Adverse events

Neither the cost nor the HRQoL impact of AEs were included in the company model.

4.2.9 Resources and costs

Three categories of costs were included in the company base case (Section B.3.5):

- drug acquisition costs
- PRD costs
- health state costs.

Drug acquisition and administration cost

The modelled cost of sapropterin is based on the cost of soluble tablets rather than powder as cost data are only available for tablets (£597.22 for 30 100mg tablets).[83] Sapropterin was implemented at a dose of 10mg/kg once daily (od) for children and 12.5mg/kg od for adults. The company used standard weight by age tables (no reference supplied) to estimate tablet numbers by age (0 to 100 years).

No wastage or administration costs were included in the company model. Sapropterin is available to the NHS at a confidential discounted PAS price. This discounted PAS price was used to generate the company's cost effectiveness results.

Phe-restricted diet cost

The cost of PRD comprises the cost of medical foods (low-protein foods and Phe-free foods) and Phe-free amino acid supplements. The company estimated these costs by eliciting expert advice and averaging the cost of three brands.

The cost of protein supplementation for children up to the age of 4 years old was based on an assumed need for 40g of supplementary protein daily, whilst children aged between 4 to 18 years were assumed to need 50g of supplementary protein. The cost of protein supplementation for adults was estimated based on a requirement of 70g of supplementary protein daily. The annual costs of protein supplementation are provided in

Table 25.

The costs of low protein food were estimated based on weekly dietary requirements for a 3 year old weighing 14kg, a 7 year old weighing 22kg and an adult. The total costs of PRD used in the model, by age group, are shown in

Table 25.

Table 25 Cost of Phe-restricted diet used in the model

Resource use	0 to 3 year olds		4 to 17 year olds		18 years and older	
	Weekly requirement	Annual cost	Weekly requirement	Annual cost	Weekly requirement	Annual cost
Phe-restricted diet						
Protein substitute	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low protein food						
- Bread	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- Flour	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- Milk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- Pasta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- Pizza base	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- Sausage/burger mix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]		[redacted]		[redacted]

Phe=phenylalanine
Source: CS, Table 55 to Table 59

Resource use by health state

The company asked clinical experts (n=5) to estimate the resources used by patients. The estimates varied depending on whether Phe levels were controlled (SPRD-controlled and PRD-uncontrolled health states) or uncontrolled (SPRD-uncontrolled and PRD-uncontrolled health states) and by age (adults versus children). Health state costs were obtained by applying unit costs to the mean resource use estimates provided by clinical experts (Table 26).

Table 26 Mean number of healthcare visits and associated unit cost, by age and by model health state

Resource use	Unit cost	Source	0 to 17 year olds		18 year olds and older	
			Controlled	Uncontrolled	Controlled	Uncontrolled
GP consultation	£39.23	PSSRU (2019)[84]	4.3	4.0	5.3	6.0
Specialist outpatient appointment (consultant led)	£144.39	NHS RC (2018/19)[85]	2.7	3.3	1.6	2.3
Outpatient appointment (non-consultant led)	£83.72	NHS RC (2018/19)[85]	1.3	4.0	0.6	0.9

GP=general practitioner; NHS RC=National Health Service Reference Cost; PSSRU=Personal Social Services Research Unit
Source: Extracted from CS, Table 61 to Table 63

4.3 Base case analysis

The company base case ICER per QALY gained results show that treatment with sapropterin+PRD [redacted] treatment with PRD by [redacted] [redacted] and delivering more QALYs (Table 27). This analysis considers patients aged 4 months until death.

Table 27 Base cost effectiveness results for patients with PKU (discounted PAS price for sapropterin)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY gained
				Cost	LYG	QALYs	
Sapropterin+ PRD	[redacted]	[redacted]	[redacted]				
PRD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG=life years gained; PAS=Patient Access Scheme; PRD=protein-restricted diet; QALY=quality adjusted life years
Source: CS, Table 72

4.3.1 Subgroups

The company explored the cost effectiveness of sapropterin+PRD in women of childbearing age (18 years to 40 years) and in other age-related subgroups. Results from these subgroup analyses are presented in Table 28.

Table 28 Summary base case cost effectiveness results for subgroups of patients with phenylketonuria (discounted PAS price for sapropterin)

Subgroup	Incremental		Incremental cost per QALY gained
	Cost	QALYs	
0-4 years	[redacted]	[redacted]	[redacted]
0-12 years	[redacted]	[redacted]	
0-17 years	[redacted]	[redacted]	
5-12 years	[redacted]	[redacted]	[redacted]
13-17 years	[redacted]	[redacted]	[redacted]
All adults	[redacted]	[redacted]	[redacted]
Women of childbearing age	[redacted]	[redacted]	[redacted]

LYG=life years gained; PAS=Patient Access Scheme; PRD=protein-restricted diet; QALY=quality adjusted life years
Source: CS, Table 73

4.4 Probabilistic sensitivity analysis

The company undertook a probabilistic sensitivity analysis (PSA) to derive mean costs, QALYs and life years gained. Model parameters were randomly sampled from distributions that the company fitted around the mean parameter values and the model was run 1,000 times. The results from the company's PSA (Table 29) are similar to the company's base case deterministic analysis results. The scatter plot is provided in Figure 2. The cost effectiveness acceptability curve in Figure 3 shows that the probability of sapropterin+PRD being cost effective at a willingness-to-pay threshold of £20,000 per QALY gained is [redacted].

Table 29 Average results based on the probabilistic sensitivity analysis (discounted PAS price for sapropterin)

Treatment	Total cost	Total QALYs	Incremental		Incremental cost per QALY gained
			Cost	QALYs	
Sapropterin+PRD	[redacted]	[redacted]			
PRD	£394,533	11.54	[redacted]	[redacted]	[redacted]

PAS=Patient Access Scheme; PRD=protein-restricted diet; QALY=quality adjusted life years
Source: CS, Table 76

[redacted]

Figure 2 Probabilistic sensitivity analysis scatterplot for the comparison on sapropterin+PRD versus PRD – with discounted PAS price for sapropterin

PAS=Patient Access Scheme; PRD=protein-restricted diet; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year
Source: CS, Figure 37

[redacted]

Figure 3 Cost effectiveness acceptability curve for the comparison of sapropterin+PRD versus PRD – with discounted PAS price for sapropterin

PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: Company model

4.5 Deterministic sensitivity analysis

The company has presented the results from analyses varying the 10 parameters that had the largest impact on base case cost effectiveness results (CS, Figure 38). The most influential parameters were the unit cost and dose of sapropterin for 0 to 12 year olds, the cost of protein supplementation for 0 to 4 year olds and the reduction in food usage, as shown in Figure 4.

Figure 4 Tornado diagram showing OWSA results for the comparison of treatment with sapropterin+PRD versus PRD – with PAS discounted prices for sapropterin

OWSA=one-way sensitivity analysis; PAS=Patient Access Scheme
Source: CS, Figure 38

4.6 Scenario analyses

The company explored several alternative scenarios for the comparison of treatment with sapropterin+PRD versus PRD (CS, Section B.3.8). Table 30 shows results relating to scenarios where treatment with sapropterin+PRD did not dominate treatment with PRD.

Table 30 Company scenario analysis results where sapropterin+PRD is not dominant (PAS discounted price for sapropterin)

Scenario	Incremental		ICER (£/QALY)
	Costs	QALYs	
Base case	[redacted]	[redacted]	[redacted]
Treatment with sapropterin attrition rate (BC=[redacted])			
Without attrition	[redacted]	[redacted]	[redacted]
Treatment duration-women of childbearing age (BC=1 year)			
2 years on treatment	[redacted]	[redacted]	[redacted]
3 years on treatment	[redacted]	[redacted]	[redacted]
Sapropterin dose (BC: children=10mg/kg; adult=12.5mg/kg)			
14.4 mg/kg (all years)	[redacted]	[redacted]	[redacted]
18.7 mg/kg (all years)	[redacted]	[redacted]	[redacted]
20 mg/kg (all years)	[redacted]	[redacted]	[redacted]

BC=base case; PAS=Patient Access Scheme; PRD=protein-restricted diet; ICER=incremental cost effectiveness ratio; SPRD=sapropterin in conjunction with protein-restricted diet
Source: CS, Table 82 (p199), Table 83 (p200) and Table 84 (p200)

4.7 Model validation and face validity check

The company stated (CS, Section B.3.10) that an internal validation exercise was conducted whereby the model was assessed for coding errors and stress-tested using a model verification checklist.

5 ERG CRITIQUE OF COMPANY ECONOMIC MODEL

5.1 Introduction

The ERG considers that the company model structure and parameterisation are both too simplistic for the complexity of the condition being modelled. However, the ERG considers that the model is too complex for the decision problem that needs to be addressed. Generally, the costs and benefits associated with treatment with sapropterin only occur whilst a patient is taking sapropterin; furthermore, treatment with sapropterin does not deliver any long-term benefits, nor is treatment waning an issue. The ERG has, therefore, constructed a simple decision tree to generate estimates of the cost effectiveness of sapropterin+PRD versus PRD.

Summary details of the ERG's critique of the main aspects of the company model are provided in Table 31.

Table 31 Summary of ERG company model critique

Aspect considered	ERG comment	Section of ERG report (if appropriate)
Patient pathway	• The 1-year model cycle is too long to reflect all the important events that patients experience • The modelling of an implausible pathway whereby patients that discontinued treatment with sapropterin are not permitted to receive sapropterin at a later time	5.2.1
Transition probabilities	• The transition probabilities are unreliable and have limited use for decision making • The transition probabilities are also applied in the model such that they do not vary over time, which the ERG considers to be clinically implausible • The attrition rate (i.e., the annual rate at which patients stop receiving sapropterin) may not be generalisable to the UK population and the incorporation of that rate into the company model is problematic	5.2.2
Utility values	• The methods used by the company to elicit health state values are not in line with the NICE Reference Case • Health state descriptions valued by the company in the TTO study do not match the health states used in the company model. • The utility values for patients with uncontrolled blood Phe concentration levels are too low • The method used to map health state utility values from the company TTO study to the company model health states is overly simplistic	5.2.3
Drug costs	• The evidence base for sapropterin doses is not robust; modelled doses may be underestimates of real-world values	5.3.1
Resource use	• It is assumed in the company base case that taking sapropterin leads to a 71.2% reduction in PRD requirement; however, clinical advice to the ERG is that this may be an overestimation of the cost saving associated with sapropterin	5.2.4
AE costs	• AE costs were not considered in the company model	NA

AE=adverse event; ERG=Evidence Review Group; HRQoL=health-related quality of life; NA=not applicable; Phe=phenylalanine; PRD=protein restricted diet; QALY=quality adjusted life year; TTO=time trade off
Source: LR*i*G in-house checklist

5.2 Model issues identified by the ERG

5.2.1 Model structure

The company has provided a model that simulates the experience of patients with PKU whose HPA has been shown to be responsive to sapropterin. The maximum time horizon modelled by the company is from birth to death. The company has also considered the cost effectiveness of treatment with sapropterin for several subgroups (by age at baseline and for women of childbearing age). The ERG considers that the model structure is too simplistic to reflect the complexities of the lives of patients with PKU due to the 1-year cycle length and the implausibility of time and age invariant health state transition probabilities.

Cycle length

Clinical advice to the ERG is that PKU symptoms may signal a lack of control of dietary protein, leading patients to alter their diet. For example, a patient who has increased the natural protein content of their diet may begin to feel sick or have headaches and this may incentivise them to control their dietary intake of protein. Within any given year, a patient may switch between having controlled and uncontrolled blood Phe concentration levels. However, the cycle length of the company model is 1 year and, therefore, patients whose blood Phe concentration levels are controlled at the beginning of the cycle are modelled to have controlled blood Phe concentration levels for the whole of that year. The converse is true for patients whose blood Phe concentration levels are uncontrolled at the start of the year. The ERG considers that a 1-year model cycle is too long to reflect the true experience of patients with PKU.

Implausible time and age invariant transition probabilities

In the company model, the transition probabilities that determine the proportions of patients who move between the different model health states do not vary over time, rather the baseline level (which varies depending on baseline patient age) is used every year for the whole model time horizon. As is the case in Markov models, there is no 'memory' in the health states which means that a patient's prior ability or inability to maintain control of their blood Phe concentration level does not affect their probability of being controlled or uncontrolled in subsequent model cycles. In addition, once patients have discontinued treatment with sapropterin they are only permitted to receive PRD for the remainder of the model time horizon, they cannot resume treatment with sapropterin at a later date.

Clinical advice to the ERG is that, in practice, patients' incentives to control their blood Phe concentration levels differ between individuals and also that incentives may change over time for each individual. For example, an adult who has struggled for years to control their Phe levels through diet, and who has experienced significant side effects but then finds that they can gain control of their blood Phe concentration levels if they take sapropterin, may be less likely to stop taking sapropterin than a teenager with limited experience of the impact of uncontrolled blood Phe levels on their HRQoL. Or, a woman may discontinue treatment during teenage years due to peer pressure but resume treatment during childbearing age.

The time invariant transition probabilities, lack of health state memory and zero probability of resuming treatment with sapropterin mean that the company model produces implausible results. In the company base case patients start taking sapropterin at 4 months of age, by the time this cohort of patients is 18 years old, only 2.6% will still be taking sapropterin, with 97.4% never taking sapropterin again at any point in their life (despite it being effective). At this age,

age, 70.9% of this cohort will be in the uncontrolled PRD health state. Clinical advice to the ERG is that such a scenario is implausible.

5.2.2 Methods used to calculate transition probabilities

The company used data from the PKUDOS registry study to calculate the likelihood that patients would move from a controlled to an uncontrolled state and vice versa each year for 6 years. A weighted average, taken across 6 years, was used every year in the model. The ERG has the following concerns about the reliability of these estimates:

- as the company noted (CS, Appendix M), the sample sizes from which the underlying annual probabilities were calculated were very small for both patients taking sapropterin+PRD and those taking PRD
- it was unclear whether, as time went on, the same patients were moving between controlled and uncontrolled states
- the company made no attempt to address the potential bias arising from falling patient numbers between year zero and year six (for example, in the PRD arm, for patients aged 0-12, there were 40 patients in years 0-1 but only 14 patients in years 5-6)
- the sapropterin response status of patients in the PKUDOS registry study is unclear.

Due to these concerns, the ERG considers that the company transition probabilities are unreliable and have limited use for decision making.

Attrition rate

The ERG considers that the attrition rate in the model (i.e., the annual rate at which patients stop receiving sapropterin) is unreliable and, furthermore, the methods used to incorporate the attrition rate into the model is inappropriate.

In the company model, [redacted] of patients in the sapropterin+PRD arm whose blood Phe concentration levels are controlled, discontinue treatment each year. This proportion is in addition to the patients in this arm who move to the sapropterin+PRD uncontrolled health state or die each year. As the attrition rate is time invariant, the ERG has similar concerns to those described previously about transition probabilities in the model. Further, the ERG is concerned that the [redacted] rate is not generalisable to the UK population of patients with PKU:

- First, this value was derived from an interim analysis of KAMPER data and it is unclear whether this is an annual rate or the total number of patients who discontinued treatment over the period for which data were available at the time of the interim analysis. The company provided information during the clarification process that provided details about the reasons for discontinuation. The reasons provided by the 59 patients who provided data for the analysis included lost to follow up or withdrawn consent (n=15), inappropriate enrolment (n=4) and death (n=1). There were no reported instances of patients stopping treatment through choice. In reality, these figures are likely to relate to the reasons patients were no longer followed up in the KAMPER registry study, rather than the patient or clinician's choice to stop treatment.
- Second, at the time of analysis, over four-fifths (83.8%) of patients who provided data for the interim analysis of KAMPER data were children and, therefore, the attrition rate used in the company model may not reflect the experience of adults.
- Finally, clinical advice to the ERG is that, in the UK, if a child's blood Phe concentration level remains persistently uncontrolled because parents/carers are unable or unwilling to maintain a child's PKU treatment plan, safe-guarding procedures would be initiated, including further escalation to a child protection plan or removal from carers if required. Therefore, parents of children whose condition responds to sapropterin have a strong incentive to continue to give sapropterin to their child.

5.2.3 Utility values

The ERG considers that the utility values used in the company model are unlikely to reflect the HRQoL of patients with PKU who are treated in the NHS. The ERG's four areas of concern are around the:

- methods used by the company to elicit health state utility values
- mismatch between Swedish health state descriptions and company model health states
- unrealistically low utility values associated with uncontrolled PKU
- method used to map Swedish health state utilities to company model health states.

Methods used by the company to elicit health state utility values

In the company's TTO study, hypothetical vignettes were valued by adults living in Sweden. These were used to represent the experience of UK adults and modified for UK children by UK clinicians. This is not in line with the NICE Reference Case[58] recommendation, which is to obtain health state descriptions from patients and then ask the general public to value these health state descriptions.

Mismatch between Swedish health state descriptions and company model health states

None of the descriptions of the seven Swedish health states accurately reflect any of the company model health states. To map the Swedish health states to model health states, the company assumed that three Swedish health states could be used to represent the model controlled PKU health states and a different three Swedish health states could be used to represent the model uncontrolled PKU health states (Table 32).

Table 32 Swedish health state descriptions and associated utility values used to estimate utility values for company model health states

Company model health states	Swedish health states	
	Description	Adult utility values*
Controlled PKU with PRD and with/without sapropterin	• No symptoms, partially restricted diet without medical food	[redacted]
	• No symptoms, partially restricted diet with medical food	[redacted]
	• No symptoms, restricted diet with medical food	[redacted]
Uncontrolled PKU with PRD and with/without sapropterin	• Mild symptoms, restricted diet with medical food	[redacted]
	• Moderate symptoms, restricted diet with medical food	[redacted]
	• Severe symptoms, restricted diet with medical food	[redacted]

* The company undertook a combination of expert panel meetings and clinician surveys with UK experts to determine the extent to which the utility values for children would differ from those for adults (CS, Table 50)
Source: CS, Table 47

Three Swedish health states were used to represent the HRQoL of patients with controlled disease (defined as blood Phe concentration levels within optimum ranges) related to patients who were asymptomatic, and three other Swedish health states were used to represent HRQoL for patients with uncontrolled disease related to patients who were symptomatic. Clinical advice to the ERG is that many patients with PKU have blood Phe concentration levels outside of the optimum controlled ranges (i.e., are in an uncontrolled health state) yet are free from clinically relevant symptoms or perceive their symptoms to be sufficiently mild that they do not seek to improve their metabolic control.

Furthermore, the ERG highlights that all the Swedish health state descriptions also assume different levels of adherence to a PRD. The effect of this assumption is to alter utility by a difference of up to 0.129; however, dietary restriction is not a feature of the company model health states.

Unrealistically low utility values associated with uncontrolled PKU

The ERG considers that the disutilities applied for uncontrolled PKU in the company model lead to unrealistically low patient utilities. For example, in the model, a person aged 20 years old with uncontrolled PKU has a utility value of [redacted]. This is caused by the very low utility values in the Swedish TTO study, particularly for the utility value associated with severe symptoms ([redacted]), which is very close to the utility associated with death (0.0). Whilst severe PKU symptoms may lead to a substantial reduction in HRQoL, the ERG considers that there is a lack of validity in the model assumption that a patient with such a poor HRQoL would remain uncontrolled for many years, rather than modifying their diet and/or starting or returning to take sapropterin.

Method used to map Swedish health state utilities to company model health states

In the absence of information on the proportions of individuals in each of the six Swedish health states, the company used a simple average to 'map' Swedish health state utilities to represent model health state utilities. There is no evidence to demonstrate, or even suggest, that patients with PKU are evenly distributed between each set of three controlled and three uncontrolled Swedish health states. In assuming that a simple average can be applied across the three symptomatic health states from the Swedish TTO study, the company has implicitly assumed that not only will patients who maintain diet restrictions and have medical food have symptoms, but a third of such patients will have a utility that is close to death. Such a strong assumption would require supporting evidence; in the absence of this evidence the assumption is not credible and the utility values incorporated in the model cannot be considered reliable and, therefore, are not suitable to inform decision making.

5.2.4 Cost savings from reduction of protein supplements and low protein food for patients taking sapropterin

Protein supplements

Over 80% of the modelled cost of PRD is the cost of protein supplements. The company failed to provide a reference for the protein supplement costs used in their model, beyond stating that they had been calculated by Prof Anita Macdonald in December 2018 (CS, p170). The ERG reviewed the costs, listed in the British National Formulary,[83] of different protein supplements available for patients with PKU and concluded that these costs (which suggested a price of approximately £10 per 20g of protein) were in line with those used in the company model.

Low protein food

The costs of low protein food used in the company model are difficult to verify. The ERG does not consider the unit costs of the individual products unreasonable, and clinical advice to the ERG is that the volumes of the products consumed were also reasonable. In addition, the total annual costs of PRD (protein supplements plus low protein food) used in the company model are in line with those reported (but without details of data sources or calculation methods) in the NHS England Integrated Impact Assessment Report[78] on sapropterin in PKU. The ERG therefore considers the costs of PRD in the company model to be sufficiently robust for decision making.

In the company model, it is assumed that patients taking sapropterin who have controlled blood Phe concentration levels are able to relax their PRD through a 71.2% reduction in protein supplements and low protein food. This level of reduction is the value reported in a poster presented at a PKU conference in 2018.[86] The ERG was not able to verify that the methods employed to derive the value of 71.2% were robust.

The company highlighted that there is evidence to suggest that patients taking sapropterin were able to increase their intake of Phe from natural sources by 54%.[66] However, a 54% increase in Phe from natural sources is not the same as evidence that PRD is relaxed by 54%. The results from the PKUDOS analysis also showed that a 54% increase in natural Phe was only seen in the cohort of patients who had taken sapropterin for 6 years (n=5). For patients taking sapropterin continuously, dietary Phe increased by between 9% and 31%.[66] The ERG considers that the evidence from the PKUDOS registry study suggests that a 71.2% reduction in low protein food and protein supplements may be optimistic. Furthermore, clinical advice to the ERG is that it is likely that even if patients could reduce their intake of low protein foods, they would be advised to maintain their intake of protein supplements. It may, therefore, be

the case that use of sapropterin in the UK may lead to no reduction in patient intake of protein supplements.

5.3 ERG alternative approach to assessing cost effectiveness

The company has produced an overly simplistic model for a complex patient pathway. Even within the company's simplistic model, the evidence used to estimate transition probabilities is not robust. However, the ERG notes that there are no long-term benefits of treatment with sapropterin in terms of survival, and there is no evidence, or clinical reason, to consider that the effectiveness of sapropterin changes over time. Effectively, there are benefits to patients whilst they take sapropterin in terms of better control of blood Phe concentration levels and this reduces the requirement to adhere as closely to a PRD, with a potential increase in HRQoL for those who were previously unable to control their blood Phe concentration levels through PRD alone. In general, the costs and benefits associated with treatment with sapropterin only occur whilst a patient takes sapropterin and cease when a patient stops taking sapropterin. The ERG, therefore, considers that a complex model is not required and that an estimation of the cost effectiveness of sapropterin+PRD can be best made through a simple calculation of the costs and benefits to a patient whilst they take sapropterin+PRD. This focusses the discussion on the drivers of the cost effectiveness of sapropterin+PRD versus PRD, namely a reduction in the costs of PRD and a gain in HRQoL from not having to follow a PRD so rigidly and potentially a lower PKU symptom burden.

The ERG's cost effectiveness calculations include assumptions relating to the:

- cost of sapropterin
- costs of PRD
- reduction in the costs of PRD that can be expected with sapropterin
- utility gain whilst taking sapropterin.

5.3.1 The cost of sapropterin

The list price of sapropterin is £19.91 per 100mg tablet. The company has stated that the mean dose for children is 10mg/kg and the mean dose for adults is 12.5mg/kg. The evidence base for these doses is not robust. In the KAMPER registry study the average dose was 12.7mg/day and only 18% of patients were over the age of 18 in this study. This suggests that the values used in the company model may be underestimates of real-world dosages. Nevertheless, 10mg/kg for children and 12.5mg/kg for adults were the values used by NHS England in their Integrated Impact Assessment Report[78] on sapropterin in PKU; however, no details of the calculation methods used to reach these values were provided in the assessment report. The ERG has costed sapropterin based upon the dosages suggested by the company

and, in a separate analysis, a dosage of 12.7mg/kg for all patients as suggested by data from the KAMPER registry.

The company model includes estimates of average weight by age and the number of sapropterin tablets that would be required at different sapropterin dosages. The ERG, in line with the company, assumed that patients with PKU are evenly distributed by age, and used this information to estimate the average number of daily tablets required at dosages of 10mg/kg for children and 12.5mg/kg for adults with the number of tablets required rounded to the nearest whole tablet for each age. The ERG also ran an analysis using a dosage of 12.7mg/kg for all patients regardless of age. The estimated average daily cost of sapropterin (PAS price) is summarised in Table 33.

Table 33 Average daily cost of sapropterin tablets depending on age and dosage (PAS price)

Age	Dosage	Average daily cost of sapropterin per patient (PAS price)
0-3	10mg/kg	[redacted]
	12.7mg/kg	[redacted]
0-17	10mg/kg	[redacted]
	12.7mg/kg	[redacted]
18+	12.5mg/kg	[redacted]
	12.7mg/kg	[redacted]

Source: Company model and ERG calculations

5.3.2 Cost of PRD

As stated in Section 5.2.4, the ERG considers that the costs of PRD (protein supplements and low protein food) in the company model are reasonable and so has used the annual costs of PRD suggested by the company in the calculation ([redacted] for patients aged 0-3, [redacted] for children aged 4-17 and [redacted] for adults).

5.3.3 Reduction in the costs of PRD that can be expected with sapropterin

The ERG considers the evidence supporting the company assumption that patients taking sapropterin will reduce their PRD by 71.2% is not robust. Given the uncertainty around the extent to which PRD might be reduced, and clinical advice to the ERG that even if a patient responded well on sapropterin, they would still be encouraged to take protein supplements (with an unknown impact on low protein food), the ERG has produced results for two scenarios – no reduction in PRD, and a 71.2% reduction in PRD.

5.3.4 Utility gain with sapropterin

As described in Section 5.2.3, the ERG considers the utility values incorporated into the company model are flawed. Given the paucity of data available directly from patients with PKU and the uncertainty around the disutility from following a PRD, the ERG considers that the TTO study is the best available source of utility values for different modelled PKU states, with the caveat that 'best available' is not the same as 'robust' and that the values in the TTO study may not represent the true utility values of patients with PKU.

To incorporate utility values into the cost effectiveness calculations, the ERG assumed that utility decrements from PKU resulted from two independent elements: (i) from adhering to a PRD and (ii) due to PKU symptoms.

Adhering to a Phe-restricted diet

The disutility, from the company's TTO study, for those following a PRD who had no symptoms, was [redacted] for adults and [redacted] for children (CS, Table 47 and Table 50). The ERG assumed that the proportion of this disutility that was removed through taking sapropterin was either 0% or 71.2%, these values reflect reductions in PRD with sapropterin that are incorporated into the ERG calculations.

Phenylketonuria symptoms

The disutility from following a PRD and having symptoms of varying severity are available from the TTO study as shown in Table 34.

Table 34 Utility decrements due to PKU symptoms from company TTO study

Age	Level of PKU symptoms with PRD	Utility value of health state	Utility decrement with symptoms compared to no symptoms
0-17 years	No symptoms	[redacted]	
	Mild	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]
≥18 years	No symptoms	[redacted]	
	Mild	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]

PKU= phenylketonuria; PRD=Phe-restricted diet
Source: CS, Table 47 and Table 50

Whilst acknowledging that uncontrolled blood Phe concentration levels do not always mean that a patient is symptomatic, for the purposes of the calculations, the ERG has assumed that patients with controlled blood Phe concentration levels are symptom-free and patients with uncontrolled blood Phe concentration levels experience symptoms. Whilst recognising the

weaknesses in the PKUDOS registry study evidence, this is the only useful source of information about the long-term effectiveness of sapropterin+PRD versus PRD. The ERG has, therefore, estimated the increase in the proportion of patients who remain symptom free whilst taking sapropterin+PRD compared to the proportion of patients taking PRD using data from the CS (Table 43 and Table 45). This assumption may overestimate the QALYs gained for sapropterin+PRD versus PRD if some patients with uncontrolled blood Phe concentration levels are symptom-free.

In the company model, compared with PRD, sapropterin+PRD resulted in [redacted] more patients aged 0-17 years achieving control (assumed PKU symptom-free) each year and [redacted] more patients aged ≥18 years achieving control each year. As the proportions of patients experiencing mild, moderate and severe PKU symptoms are unknown, the ERG has produced three sets of results: assuming all symptoms are mild, all symptoms are moderate and all symptoms are severe. The utility gains, resulting from taking sapropterin+PRD leading to a reduction in PKU symptoms that are used in the ERG calculations are shown in Table 35.

Table 35 Utility gains from taking sapropterin+PRD leading to a reduction in PKU symptoms that are used in the ERG cost effectiveness calculations

Age	Level of PKU symptoms	Utility decrement from TTO[82] study	Increase in percentage of patients assumed to be symptom free with sapropterin	Utility gain resulting from a reduction in PKU symptoms
0-17 years	Mild	[redacted]	[redacted]	0.004
	Moderate	[redacted]		0.007
	Severe	[redacted]		0.018
≥18 years	Mild	[redacted]	[redacted]	0.013
	Moderate	[redacted]		0.020
	Severe	[redacted]		0.052

PKU=phenylketonuria; TTO=time-trade off
Source: Adapted from CS, Section B.3.3 and B.3.4

5.4 ERG alternative cost effectiveness results

The ERG has calculated potential ICERs per QALY gained under a range of cost and effectiveness assumptions. These results are shown in Table 36 and Table 37. The ERG has generated estimates for the following age groups: 0 to 3 years, 0 to 17 years and ≥ 18 years over a 12-month period; the ERG considers that costs and benefits are time invariant and extending the time horizon does not affect the size of the ICER per QALY gained. The ERG was unable to generate cost effectiveness results for the 'all years' population over a lifetime horizon considered in the company base case.

Table 36 No reduction in PRD with sapropterin (PAS price)

Age	Mean sapropterin dosage	Mean sapropterin cost per day	Reduction in daily PRD cost with sapropterin	Incremental daily cost with sapropterin	Annual incremental cost with sapropterin	Symptom severity	QALY incremental gain with sapropterin	ICER per QALY gained with sapropterin
0-3 years	10mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	0.004	[redacted]
						Moderate	0.007	
						Severe	0.018	
	12.7mg/kg					Mild	0.004	
						Moderate	0.007	
						Severe	0.018	
0-17 years	10mg/kg					Mild	0.004	
						Moderate	0.007	
						Severe	0.018	
	12.7mg/kg					Mild	0.004	
						Moderate	0.007	
						Severe	0.018	
≥18 years	12.5mg/kg					Mild	0.013	
						Moderate	0.020	
						Severe	0.052	
	12.7mg/kg					Mild	0.013	
						Moderate	0.020	
						Severe	0.052	

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PRD=Phe-restricted diet; QALY=quality adjusted life year

Table 37 Reduction (71.2%) in PRD with sapropterin (PAS price)

Age	Mean sapropterin dosage	Mean sapropterin cost per day	Reduction in daily PRD cost with sapropterin	Incremental daily cost with sapropterin	Annual incremental cost with sapropterin	Symptom severity	QALY incremental gain with sapropterin	ICER per QALY gained with sapropterin
0-3 years	10mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	0.130	[redacted]
						Moderate	0.134	
						Severe	0.145	
	12.7mg/kg					Mild	0.130	
						Moderate	0.134	
						Severe	0.145	
0-17 years	10mg/kg					Mild	0.130	
						Moderate	0.134	
						Severe	0.145	
	12.7mg/kg					Mild	0.130	
						Moderate	0.134	
						Severe	0.145	
≥18 years	12.5mg/kg					Mild	0.141	
						Moderate	0.148	
						Severe	0.180	
	12.7mg/kg					Mild	0.141	
						Moderate	0.148	
						Severe	0.180	

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PRD=Phe-restricted diet; QALY=quality adjusted life year

5.5 Discussion of ERG cost effectiveness results

The ERG has undertaken some simple calculations to estimate the cost effectiveness of sapropterin+PRD versus PRD for children and adults. At list price, the results from the calculations show that the cost effectiveness of sapropterin is driven by whether and by how much this treatment reduces the requirements for a PRD (specifically, protein supplements). Symptom reduction is not a major driver of cost effectiveness results.

Using the discounted PAS price for sapropterin, when treatment with sapropterin led to no reduction in PRD, the ERG's calculations showed that the ICERs per QALY gained for all age subgroups were higher than [redacted]. When treatment with sapropterin led to a reduction in PRD of 71.2% (as claimed in the CS), the ERG calculations showed that treatment with sapropterin+PRD [redacted] PRD for all scenarios for children 0 to 3 years of age, and for children 0 to 17 years of age the ICER ranged from [redacted] to [redacted] per QALY gained. For adults (i.e., those ≥18 years of age), the ICER was over [redacted] per QALY gained.

There are several factors not included in the ERG calculations that may mean the ERG calculations are underestimates of the cost effectiveness of sapropterin+PRD, namely:

- carer disutility for parents/carers of children with PKU
- the prevention of neurological damage to the unborn child
- the prevention of neurological damage in children from uncontrolled PKU
- additional healthcare costs from treating symptomatic PKU patients.

Inclusion of parent/carer disutilities could double the QALY gain resulting from taking sapropterin as the disutility from the company's TTO study for parents/carers of a child with PKU who is following a PRD and is suffering PKU symptoms is similar to that of the child in this health state. Inclusion of parent/carer disutility would, therefore, reduce the size of the ICER per QALY gained for children by approximately 50%. Similarly, the inclusion of prevention of neurological damage in children - if this could be evidenced - would significantly reduce the ICER per QALY gained. However, clinical advice to the ERG was that neurological damage arising from PKU in children is now exceptionally rare in the UK due to close clinical management to ensure blood Phe concentration levels remain controlled.

Pregnant women have not been included as a subgroup in the ERG calculations. The company did not treat pregnant women as a specific subgroup, but rather, they modelled the experience of a woman aged 18 years over a 12-month period, with no special consideration given to the reduction in neurological damage to the unborn child resulting from taking sapropterin. The company's analysis (and the ERG's analysis, if such an analysis were to be carried out) for women of childbearing age produced results that were very similar to the

results for all adults. The ERG highlights that the healthcare costs of treatment for a child with neurological impairment, and the potential lifetime QALY losses for that child, are both large. As such, if pregnant women or women trying to conceive took sapropterin and this led to a reduction in the number of children born with neurological damage (or reduced the extent of that damage), then the ICER per QALY gained for this subgroup may be substantially lower than the ICER per QALY gained for all adults.

The additional healthcare costs from treating symptomatic patients considered by the company are minimal (approximately £1 a day higher in the company model for being in the uncontrolled rather than in the controlled health state) and the inclusion of these costs in the ERG calculations would be unlikely to change any conclusions.

5.6 Conclusions of the cost effectiveness section

The ERG considers that the company model is overly complicated for the decision problem they are trying to model, has structural flaws and uses implausible parameterisation that mean the cost effectiveness results from the model are unsuitable for decision making. For the comparison of sapropterin+PRD versus PRD, using the PAS price of sapropterin and a 71.2% reduction in PRD for patients who have controlled blood Phe concentration levels, the cost effectiveness results generated by the ERG are only below the willingness to pay threshold normally considered by NICE for children aged 0 to 3 years of age.

6 END OF LIFE CRITERIA

The company has (appropriately) not put forward a case for treatment with sapropterin+PRD to be considered under NICE's End Of Life criteria.[58]

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8 APPENDIX

8.1 Appendix 1: Tables of studies of sapropterin identified in the CS

The company identified 22 studies for inclusion (CS, Appendix D). However, data were only presented for 14 of the identified studies in the CS. Data for the additional eight studies are presented in Table 40.

Table 38 Characteristics of the RCT and the RCT extension studies presented in the company submission

	RCTs				Single-arm follow-up/extension studies from RCTs		
Study reference	**Levy et al, 2007[33]**	**Trefz et al, 2009[34]**	**Burton et al, 2015[35]**	**Muntau et al, 2017[36]**	**Lee et al, 2008[37]**	**Burton et al, 2011[38]**	**Rutsch et al, 2018[39]**
Study name	**PKU-003**	**PKU-006**	**PKU-016/ ASCEND**	**SPARK**	**PKU-004 Follow-up of PKU-003**	**PKU-008 Follow-up of PKU-004/ PKU-006**	**SPARK extension**
Study purpose	To evaluate the efficacy and safety of SAP compared with PLA	To evaluate the efficacy and safety of SAP for children aged 4 years to 12 years with PKU who were following a PRD	To evaluate the efficacy of SAP for ADHD symptoms and global function for pts with PKU responsive to SAP compared with PLA	To evaluate the efficacy and safety of SAP+PRD compared with PRD for pts aged <4 years with PKU or mild HPA responsive to BH4	To evaluate the efficacy and safety of SAP for patients with PKU	To evaluate the safety of long-term treatment with SAP for patients with PKU who participated in previous phase 3 SAP trials	To evaluate the long-term safety and efficacy over an additional 36 months of treatment with SAP
Study design	Phase III, double-blind, PLA-controlled	Phase III, double-blind, PLA-controlled	Phase III, double-blind, PLA-controlled	Phase IIIb, open-label, parallel group	Phase III, open-label, single group extension study	Phase IIIb, open-label, single group, extension study	Phase IIIb, open-label, extension study
Study complete?	Yes	Yes	Yes	Yes	No (ongoing)	Yes	No (ongoing)
Number of patients	89	90	206	56	80	111	51
Study location	North America and Europe	USA and Europe	North America	Europe	North America and Europe	North America and Europe	Europe
Treatment duration	6-weeks	10-weeks	13 weeks	13 weeks(RCT) 13 weeks (open label)	22 weeks	3 years	3 years

	RCTs				Single-arm follow-up/extension studies from RCTs		
Study name	**PKU-003**	**PKU-006**	**PKU-016/ ASCEND**	**SPARK**	**PKU-004 Follow-up of PKU-003**	**PKU-008 Follow-up of PKU-004/ PKU-006**	**SPARK extension**
Population	• Aged ≥8 years • Responsive to SAP in PKU-001 • Blood Phe ≥450µmol/L • Not following strict PRD (pts had "relaxed" or "abandoned" a PRD)	• Aged 4 to 12 years • Blood Phe ≤480µmol/L at screening and ≥6 months prior to enrolment • PRD • Responsive to BH4 with PAH deficiency	• Aged ≥8 years • Responsive to SAP • Willing to continue PRD	• Aged <4 years • Blood Phe ≥400µmol/L • Responsive to BH4 • Good adherence to dietary treatment	• Aged ≥8 years. • All had participated in PKU-003	• Aged ≥4 years • All had participated in PKU-004 (PKU-001 /PKU-003) or PKU-006	• Aged <4 years (at start of SPARK RCT) • Responsive to BH4
Intervention and comparator	• SAP 10mg/kg/day (pts required to adhere to current diet but diet was not a component of treatment) vs • PLA	• SAP 20mg/kg/day +PRD vs • PLA + PRD	• SAP 20mg/kg/day +PRD vs • PLA+PRD	• SAP 10mg/kg/day +PRD vs • PRD	• SAP+PRD -Part 1: forced dose titration 5, 10 and 20 mg/kg/day for 2 weeks each consecutively. then 10mg/kg/day for 4 weeks -Part 2: fixed dose 5,10 or 20 mg/kg/day for 12 weeks	SAP (between 5 and 20 mg/kg/day) +PRD (local dietary recommendations)	• Continuous group SAP+PRD (previously on SAP+PRD in SPARK) vs Extension group SAP+PRD (previously on PRD only in SPARK))
Reported outcomes specified in the decision problem	• Blood Phe concentration • AEs	• Blood Phe concentration • Phe intake • AEs	• Blood Phe concentration • Neuropsychological function • AEs • Cognitive and mood symptoms	• Blood Phe concentration • Phe tolerance • Neuromotor development and physical growth parameters	• Blood Phe concentration • AEs	• Blood Phe concentration • AEs	• Blood Phe concentration (interpretation only) • Phe tolerance • AEs

	RCTs				Single-arm follow-up/extension studies from RCTs		
Study name	**PKU-003**	**PKU-006**	**PKU-016/ ASCEND**	**SPARK**	**PKU-004 Follow-up of PKU-003**	**PKU-008 Follow-up of PKU-004/ PKU-006**	**SPARK extension**
Study conclusions	• Significant mean decrease in blood Phe concentrations for SAP vs PLA (p=0.0002) • Mean blood Phe fell in the SAP group at week 1 and remained lower than the PLA group over time (p<0.0001)	• SAP lowered blood Phe levels (p<0.001) and allowed increased Phe intake (p<0.001), while maintaining adequate Phe control with PRD	• SAP treatment was associated with a significant improvement in ADHD inattentive symptoms that were maintained throughout the study for individuals with PKU and ADHD symptoms	• Dietary Phe tolerance was significantly increased with SAP+ PRD compared with PRD	• Change in blood Phe correlates with the dose of SAP	• SAP was well tolerated • AEs were mostly mild to moderate severity • Controlled blood Phe levels throughout the study show the durability of SAP response, regardless of dietary adherence	• Phe-tolerance increased significantly and was maintained throughout the 3 year study duration • Dietary Phe tolerance at 3 years increased by 38.74 mg/kg/day vs baseline p<0.0001)
Study data used in economic model? **Company rationale for non-inclusion**	No Short study duration	No No explanation given	No The study is focussed on neuropsychiatric symptoms	No Due to age limitations of study. The patient population is aged 0 years to 4 years	No Short study duration	No Phe intake was not monitored	No Due to age limitations of study. The patient population is aged 0 years to 4 years
ERG comment	This trial is of limited relevance to the scope. The pts had a 'relaxed' diet, so there is no comparison with PRD. Limited evidence due to short-treatment duration and small patient population.	This trial is of short treatment duration with SAP+PRD and has a small patient population. The results are relevant only to children aged between 8 and 12 years	This trial provides limited evidence due to the short-treatment duration	The trial included a small patient population. The results are relevant only to children aged between 0 and 4 years	This study is of limited relevance to the scope as it is a single-arm unblinded extension study with no comparison to PRD and has a small patient population	This study is of limited relevance to the scope as it was a single-arm extension study with no comparison to PRD	Limitations of this trial include the small sample size and no comparison to PRD

AE=adverse event; BH4=tetrahydrobiopterin; HPA=hyperphenylalaninaemia; PAH=phenylalanine hydroxylase; Phe=phenylalanine; PKU=phenylketonuria; PLA=placebo; PRD=Phe-restricted diet; SAP=sapropterin; vs=versus
Source: Extracted from CS, tables 4-9 and Section B.2.6

Table 39 Characteristics of non-RCT and registry studies

	Non-RCT studies				Registry studies		
Study reference	**Burton et al, 2007[43]**	**Longo et al, 2012[40]**	**Jorgensen et al, 2013[41]**	**ClinicalTrials.gov 2020[42]**	**Biomarin 2018[44]**	**Grange et al, 2014[45]**	**Biomarin 2020[46]**
Study name	**PKU-001**	**PKU-015**	**ENDURE**	**KOGNITO**	**PKUDOS**	**PKUMOMS**	**KAMPER**
Study purpose	A screening study to identify pts with PKU who are responsive to SAP, for enrolment into phase III trials	To evaluate the safety and efficacy of SAP for neuropsychological function, blood Phe and growth for pts with PKU aged 0 years to 6 years	To evaluate the proportion of responders (≥30% reduction in blood Phe concentration from baseline) for patients with PKU when taking SAP	To evaluate long-term neurocognitive outcomes in children aged 4 years to 5 years with PKU treated with SAP+PRD over af 7 year period	To evaluate long-term safety and efficacy for pts with PKU treated with SAP.	A subregistry from PKUDOS To evaluate SAP for pregnancy, lactation and infant outcomes at birth and at 1 month and 6-month follow-up	To evaluate the long-term safety of SAP for pts with PKU
Study design	Phase II, open-label, single-arm screening study	Phase IIIb open-label, single-arm study	Phase IV, open-label, single-arm study	Phase IV, open-label, single-arm study	Phase IV, prospective, observational registry study	A sub registry from the PKUDOS study for pregnancy outcomes	Phase IV, prospective, observational, registry study
Study complete?	Yes	No (ongoing)	Yes	No (ongoing)	No (ongoing)	No (ongoing)	No (ongoing)
Number of patients	489	55	59	33	1922	18 (21 pregnancies)	576 pts with PKU
Study location	North America and Europe	North America	Norway	Europe	USA	USA	Europe
Study duration	8 days	7 years	28 days	7 years	Up to 15 years	6 months post-partum	15 years

	Non-RCTs				Registry studies		
Study name	**PKU-001**	**PKU-015**	**ENDURE**	**KOGNITO**	**PKUDOS**	**PKUMOMS**	**KAMPER**
Population	• Aged ≥8 years • Blood Phe level ≥450 µmol/L at screening Not adhering to a strict PRD	• Aged 0 years to 6 years • PKU with HPA ≥360 µmol/L	• All PKU (blood Phe level ≥300µmol/L) • Aged >4 years • Adhere to their normal diet	• Aged 4 years to 5 years • Blood Phe level ≥400µmol/L • IQ≥70 • Adhering to PRD	• Patients with PKU previously, currently or planning to receive SAP within 90 days of enrolment • No age restrictions • Blood Phe level ≥360µmol/L	• Women participating in the PKUDOS registry • Enrolled within 10 weeks of last menstrual cycle • Adhere to CCM for maternal PKU	• Patients with HPA due to PKU or BH4-deficiency (no age restrictions) • Responsive to SAP or BH4 • Patients with BH4-deficiency (n=49) are not relevant to this appraisal
Intervention	• SAP 10mg/kg/day	• SAP 20mg/kg/day +PRD	• SAP 20mg/kg/day (unclear if diet also a component of treatment)	• SAP 5 to 20mg/kg/day +PRD	• SAP mean dose at baseline 18.71mg/kg/day +PRD	• SAP mean dose 15.2 mg/kg/day +PRD	• SAP median dose at baseline 14.4 mg/kg/day
Reported outcomes specified in the decision problem	• Blood Phe concentration • AEs	• Blood Phe concentration • Protein intake • AEs • Neuropsychological function	• Blood Phe concentration • AEs	• Dietary Phe tolerance • Neuropsychological outcomes • AEs • Cognitive outcomes	• Blood Phe concentration • Neuropsychological function • Protein intake • Biochemical and clinical indicators of poor nutrition • AEs • Mood and cognitive symptoms	• Blood Phe concentration • Phe intake • AEs	• Blood Phe concentration • Neuropsychological outcomes • Phe intake • AEs • Mood and cognitive symptoms

	Non-RCTs				Registry studies		
Study name	**PKU-001**	**PKU-015**	**ENDURE**	**KOGNITO**	**PKUDOS**	**PKUMOMS**	**KAMPER**
Study conclusions	• 20% of pts were responsive to SAP (reduction of >30% in blood Phe concentration) • AEs were mostly mild to moderate with minimal TE laboratory abnormalities	• SAP lowered blood Phe levels while allowing for increased prescribed dietary Phe	• 75% of pts were responsive to SAP. While most responders (86%) showed SAP response within 7 days, some did not. • A longer test period may be needed to identify all responders	• No results reported	• Strict adherence to sapropterin is associated with sustained lower blood Phe levels and improvements in dietary Phe intakes • Sapropterin has a tolerable safety profile	• The limited evidence for SAP for maternal PKU suggests that SAP is well-tolerated and reduces mean blood Phe during pregnancy	• Sapropterin has a favourable safety profile • Sapropterin allows for an increase in dietary Phe intake while maintaining blood Phe concentrations within the recommended range(s)
Study data used in economic model? **Company rationale for non-inclusion**	No Short follow up period, not a RCT, and pts were not on a PRD	No No reason provided	No No reason provided	No No reason provided	Yes. Data are used to inform transition probabilities between controlled and uncontrolled heath states	No	Yes. Data are used to inform rates of treatment attrition
ERG comment	This study is of limited relevance to the scope. It is a short (8 day) screening trial with no comparison with PRD	This study is of limited relevance to the scope. It is a single-group study, and with small sample size. There is no comparison with PRD	This study is of limited relevance to the scope. It is a single-arm study, with a small sample size and short duration. There is no comparison with PRD	This study is of limited relevance to the scope. The sample size is small and there is no comparison with PRD. In addition, there are also no published results yet available	A limitation of this study is the observational design. The number of eligible patients who were invited to join the registry study but declined is not reported, therefore the participation rate cannot be calculated. See Section 3.2.4 of this ERG report	Small numbers from this sub-study) may limit the generalisability of findings. There is no comparison with PRD	A limitation of this study is the observational design. The number of eligible patients who were invited to join the registry study but declined is not reported, therefore the participation rate cannot be calculated. See Section 3.2.4 of this ERG report

ADHD=attention deficit hyperactivity disorder; AE=adverse event; BH4=tetrahydrobiopterin; CCM=current clinical management; HPA=hyperphenylalaninaemia; NA=not applicable; Phe=phenylalanine; PKU=phenylketonuria; PLA=placebo; PRD=Phe-restricted diet; pts=patients; SAP=sapropterin; TE=treatment emergent
Source: Extracted from the CS, tables 4-9 and Section B.2.6, also the PKUDOS interim CSR (107), the KAMPER CSR (108) and study publications

Table 40 Characteristics of the included studies that were not presented in the company submission

Study reference	Bernstein et al 2009[51]	Christ et al 2013[12]	Cazzorla et al 2014[52]	Deschenes et al 2014[53]	Moseley et al 2009[54]	Scala et al 2015[55]	Senden et al 2015[56]	White et al 2013[57]
Study purpose	To evaluate the proportion of responders (≥30% reduction in blood Phe concentration from baseline) for patients with PKU when taking SAP	To evaluate the effects of SAP on brain function for patients with PKU	To evaluate quality of life in pts with PKU.	To evaluate the effect of SAP on executive function for patients with PKU	To evaluate the efficacy and safety of SAP for women with maternal PKU	To evaluate the long-term safety and efficacy of treatment with SAP and identify factors predicting responsiveness to BH4	To validate the significance of a positive response to SAP in pts with PKU	To evaluate the effects of treatment with SAP on white matter integrity and cognitive function
Study design	Expanded access program, prospective, observational study	Prospective, cohort study	Observational cohort study	Retrospective chart review	Case series study	Open-label, single group study	Cohort study	Open-label, single group study
Number of patients	34	12 (+12 without PKU)	43	29	2	46	14	32 (19 were responsive to SAP)
Study location	USA	USA	Italy	North America	USA	Italy	Sweden	USA
Study duration	Unclear	6 months	Treated with SAP for 1 years to 11 years (where applicable)	Duration of SAP treatment 22 days to 721 days	Unclear Women were followed during pregnancy and both infants underwent a follow-up evaluation	7 years	1 year	6 months

Study reference	Bernstein et al 2009[51]	Christ et al 2013[12]	Cazzorla et al 2014[52]	Deschenes et al 2014[53]	Moseley et al 2009[54]	Scala et al 2015[55]	Senden et al 2015[56]	White et al 2013[57]
Population	• Age unclear • Adhering to a PRD	• Blood Phe level ≥360µmol/L • PKU diagnosis at birth • Aged ≥6 years • Self-reported adherence to their normal diet	• Mild PKU responsive to BH4 and blood Phe level 600µmol/L to 1200µmol/L or classical PKU treated with PRD • PKU diagnosis at birth • Aged >4 years	• No inclusion criteria reported • Aged 4 years to 49 years • Blood Phe level 103µmol/L to 1678µmol/L	• Aged 37 years and 32 years • Blood Phe level before treatment 3636µmol/L and 2880µmol/L • Adhering to PRD	• Aged >4 year • PKU/HPA requiring PRD • Genotyping of PAH gene	• No inclusion criteria reported	• Aged 6 years to 35 years • Diagnosed and treated early by PRD ('early' was not defined)
Intervention	• SAP 20mg/kg/day +PRD	• SAP 20mg/kg/day +PRD	• SAP 10mg/kg/day +PRD (mild PKU) • PRD (classic PKU)	• SAP 10mg/kg.day to 20mg/kg/day (unclear if diet was a component of treatment)	• SAP+PRD	• SAP 20mg/kg/day +PRD	• Not reported	• SAP 20mg/kg/day +PRD
Reported outcomes specified in the decision problem	• Blood Phe concentration • Phe intake	• Blood Phe concentration • Neuropsychological function • Cognitive symptoms	• Blood Phe concentration • Mood symptoms • Health-related quality of life (PedsQL or WHOQOL-100)	• Neuropsychological function • Cognitive symptoms	• Blood Phe concentration • Protein intake • Biochemical and clinical indicators of poor nutrition • AEs	• Blood Phe concentration • Phe intake • AEs	• Blood Phe concentration • Phe intake	• Blood Phe concentration • Neuropsychological function • Cognitive symptoms

Study reference	Bernstein et al 2009[51]	Christ et al 2013[12]	Cazzorla et al 2014[52]	Deschenes et al 2014[53]	Moseley et al 2009[54]	Scala et al 2015[55]	Senden et al 2015[56]	White et al 2013[57]
Study conclusions	• 53% of pts were responsive to SAP (reduction of >30% in blood Phe concentration) • 38% of pts continue to take SAP • 9 pts have increased their Phe intake and decreased their intake of medical food	• Pts with PKU showed memory impairments and atypical brain activation compared to patients without PKU at baseline • At 4 weeks pts with PKU receiving SAP showed improved working memory and brain activation. • Improvement in working memory was maintained at 6 months	• Pts with mild PKU taking SAP had higher QoL scores compared to pts with classical PKU adhering to PRD	• Treatment with SAP for patients with PKU was associated with improved executive function	• SAP was well-tolerated with no AEs • Both infants developed normally and their birth measurements were within the normal range	• PAH genotype was the best predictor of responsiveness to BH4 • SAP was well-tolerated and efficacious for maintaining blood Phe and increasing Phe tolerance	• Pts with PKU who have a positive SAP loading test will have a positive response on Phe levels and an increase in protein intake with SAP	• SAP initially reduced blood Phe concentration by 51% • 37% reduction was maintained during the 6 months • SAP significantly improved white matter integrity at 6 months • There were no changes in executive function at 6 months
ERG comment	This study is of limited relevance to the scope. The duration of follow-up is unclear and there is no comparison with PRD	This study is of limited relevance to the scope. It is a small study that does not have a comparison with PRD	This study is of limited relevance to the scope. It has a small sample size. All patients treated with SAP had mild PKU so the comparator group (pts with classical PKU treated with PRD) may have biased the study in favour of SAP	This study is of limited relevance to the scope. It has a small sample size and does not have a comparison with PRD	This study is of limited relevance to the scope. It only includes two cases and does not have a comparison with PRD	This study is of limited relevance to the scope. It has a small sample size and does not have a comparison with PRD	This study is of limited relevance to the scope. It has a small sample size and does not have a comparison with PRD	This study is of limited relevance to the scope. It has a small sample size. The control group included patients without PKU so the study does not have a comparison with PRD

AE=adverse event; BH4=tetrahydrobiopterin; HPA=hyperphenylalaninaemia; PAH=phenylalanine hydroxylase; PedsQL=Pediatric Quality of Life Inventory; Phe=phenylalanine; PKU=phenylketonuria; PRD=Phe-restricted diet; pts=patients; QoL=quality of life; SAP=sapropterin; WHoQoL-100=World Health Organization Quality of Life assessment instrument
Source: Extracted and adapted from the CS, Appendix D and study publications

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Sapropterin for treating phenylketonuria [ID1475]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 16 October** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Summary

Thank you for the opportunity to comment on the Evidence Review Group (ERG) report. In reviewing the ERG report, the manufacturer found a number of inaccuracies with 4 key topics emerging throughout as a consistent theme. The manufacturer has sought to address each of these inaccuracies in turn, but these themes do flag some major concerns from the manufacturer perspective. These are:

1. **Clinical advice to the ERG is contrary to UK clinical expertise and contrary to published evidence**
   The manufacturer is concerned that the ERG has based their recommendations on what seems to be one clinician's opinion. This has led to recommendations that are contrary to current UK clinical opinion. The manufacturer undertook a series of expert meetings in July 2020 which involved three specialist adult metabolic physicians (collectively experienced in the care of approximately 50% of the UK adult PKU population), two-specialist paediatric metabolic physicians (collectively experienced in the care of approximately 20% of the UK paediatric PKU population),and an advanced practitioner in metabolic disease and experienced metabolic dietitian. This combined experience represents a significant portion of UK PKU clinical care and as such demonstrates the strength of the recommendations by the manufacturer.

2. **The challenges in obtaining quality of life data in PKU patients.**
   Capturing QoL data in PKU patients is extremely challenging due to the small patient population and range of disease states. The manufacturer has managed now to capture this data from a Swedish time trade-off (TTO) study in over 1000 members of the general population and PKU patients across a range of clinically validated disease states. Whilst this was undertaken in Sweden, UK clinical experts have confirmed that it is transferable to the UK.

   In order to fully appreciate the value this utility data offers, it is important to understand the significant challenges in trying to capture QoL data in this patient population. This has been captured in our response below, but it is important to understand the various attempts undertaken by the manufacturer to reach this stage and to find a solution.

3. **Rarity of disease has not been fully taken into account. This is reflected in the criticism of the data by the ERG.**
   The ERG should recognise that there is a PKUDOS dataset available with comparable data in a population of approximately 1922 patients with some patients' data available since 2008. This data has been published by Longo et al, 2015 (Molecular Genetics and

Metabolism 114 (2015) 557–563) and numerous posters all of which are referenced in the CS. PKU is a rare disease and as such it is difficult and impractical to collect long term data as an RCT from a small limited patient population. The ability to capture long-term evidence from the PKUDOS registry by the manufacturer (9 years in some cases) is testament to the commitment of the manufacturer to continue to expand the evidence base supporting PKU. As such, the use of this registry data should be welcomed and given due consideration in the assessment.

4. The ERG alternative model lacks credibility, is not validated and does not align to the clinical pathway for PKU.

The manufacturer is concerned with the approach taken by the ERG to develop a simple decision tree model. There are various issues with the approach taken but most notably that the ERG does not seem to have fully appreciated the complexity of PKU. This is illustrated by, for example, the ERG suggesting there are no benefits that treatment provides once the treatment is ceased. This level of understanding has thus informed the alternative model suggested by the ERG. Whilst the model has not been shared with the manufacturer, it is likely to struggle reaching clinical plausibility. From what has been described by the ERG, the model does not seem to have been validated by a group of clinical experts. From our understanding of the disease area and based on clinical experts' opinions in England, categorising patients into mild, moderate and severe presents significant challenges in clinical practice. The model health states based on mild, moderate and severe would, we assume, be based on blood Phe and the presence or absence of symptoms. The manufacturer is fully aware of the issues and limitations such a model presents.

The ERG model also contains extreme inputs which are not substantiated by evidence or clinical opinion. For example, a scenario that sapropterin treatment is associated with no reduction in PRD is both extreme and lacking evidence, and as such the manufacturer feels that this should not be presented as a main scenario of the model.

As the ERG acknowledge, clinical opinion confirmed adherence to PRD is burdensome for patients and their caregivers, but this is not incorporated into the ERG model. Its incorporation would lead to radically different QALY estimates, as the ERG also acknowledge, rendering the ERG model of limited value for decision making.

The manufacturers model is clinically validated, has a structure based on controlled/ uncontrolled and is underpinned by blood Phe. PKU patients with blood Phe levels above the threshold (as defined by EU PKU guidelines) are categorised as “uncontrolled”. These

states are clinically plausible and are a fair representation of the way PKU patients are managed in clinical practice. The model structure is fully validated by 5 clinical experts in England at two clinical advisory boards.

Taking these themes together, the manufacturer is concerned that the ERG has not fully appreciated the complexity of the disease or the challenges of collecting data in a rare disease. Inaccurate understandings may result from reliance on one clinician's opinion as opposed to the breadth of expertise from UK clinical experts across multiple disciplines, the spectrum of clinical evidence presented in the CS and the wealth of literature in the public domain. This is reflected in the modelling approach suggested by the ERG. It is clear the approach has not been clinically validated by a group of experts and thus lacks credibility and does not follow the disease course for PKU. The manufacturer is extremely concerned with the modelling approach adopted.

Issue 1 Phenylalanine is a relevant efficacy outcome measure for phenylketonuria (PKU)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It is stated on page 25, paragraph 3 that "clinical advice to the ERG is that blood Phe concentration level is a poor measure of efficacy and should only be considered in conjunction with dietary Phe intake". This also appears on: page 49, section 3.3.2; p53, section 3.5 The ERG states (See page 25, paragraph 3) that blood Phe is a poor efficacy outcome measure in PKU and should only be considered in conjunction with dietary Phe intake.	Blood Phe is the most widely used measure of efficacy, and is the dominant measure used in clinical practice. Hence the manufacturer recommends the ERG re-phrase the statement on page 25, paragraph 3 to "clinical advice, supported by a robust body of literature is that blood Phe concentration level is a validated measure of efficacy" Furthermore, on page 11, issue 3 this should be amended to "The ERG recognises that blood Phe is the most widely used and accepted outcome measure in PKU supported by a robust body of literature and clinical advice and that blood Phe concentration level is a validated measure of efficacy" A similar response Page 49, section 3.3.2	Blood Phenylalanine is the most widely used measure of efficacy in clinical practice. It is the dominant measure widely referenced across literally hundreds of publications and is referred to in national and international guidelines. It is used across the globe as a target measure to reach to demonstrate improvement in disease outcomes. For example, the European guidelines recommend target blood Phe levels between 120 and 600 µmol/l for patients older than 12 years – clearly an endorsement of the importance of blood Phe. The American College of Medical Genetics and Genomics (ACMG) guidelines in the US (Vockley et al, 2014) states a goal of maintaining blood phenylalanine in the range of 120–360 µmol/l, again recognition of the importance of using blood Phe as a measure to assess disease outcome. The body of literature is substantial in relation to the use of blood Phe and indeed, it's impact on other outcomes. For example, ten Hoedt et al, 2011 highlights the findings from a randomised double-blind placebo-controlled trial showing that "high plasma Phe levels have a direct negative effect	The ERG acknowledges that blood Phe concentration level is a widely reported outcome in the clinical literature. However, expert advice to the ERG is that blood Phe concentration level is a poor efficacy marker and best used in conjunction with dietary Phe intake. No change is required.

		on both sustained attention and on mood in adult patients with PKU." Waisbren et al, 2007 states in her systematic literature review and meta-analysis that "Blood phenylalanine (Phe) levels provide a practical and reliable method for the diagnosis and monitoring of metabolic status in patients with phenylketonuria (PKU)." They go on to highlight the relationship between blood Phe and IQ levels. This is further reinforced by Lindegren 2012 in her Comparative Effectiveness review 2012 which states "Increasing Phe is clearly associated with decreased IQ, with a probability of IQ less than 85 exceeding the population probability (approximately 15 percent) at blood Phe over 400 µmol/L and leveling off at about 80 percent at 2,000 µmol/L. This finding supports the typical target goal for blood Phe levels in individuals" The reliance on the use of blood Phe can be found in publications regarding co-morbidities (Bilder, Rutsch), cognition (Lindegren, Romani, Jahja) and neuropsychological deficit (Bik-Multanowski) to name just a few. This list is by no means exhaustive. The clinical papers are extensive and too numerous to list here. Whilst emphasising the criticality of blood Phe, we do also recognise the importance of Phe	

		intake which is why this was captured in our clinical trials (e.g. in the SPARK study) however they cannot be used as a composite endpoint as suggested by the ERG. There is no scientific or clinical basis to support this composite endpoint nor is there clinical support for such an approach. Furthermore, the outcome of poor nutrition results in elevated Phe, hence this reinforces the use of blood Phe as the dominant outcome measure. In addition, Phe intake influences blood Phe levels which therefore invalidates their use as a composite outcome measure (notwithstanding the lack of clinical rationale for such a measure). This was also recognised by the ERG which states on page 41 that “Clinical advice to the ERG is that a known confounder of sapropterin treatment on clinical outcomes is dietary adherence” The majority of UK clinical opinion is also aligned to the manufacturer position. Maintenance of blood Phe levels in, for example, paediatrics is very clear that blood Phe levels below 360 micromol/L is linked to good neuropsychological outcomes. The EU guidelines have a threshold of 600 micromol/L for patients over the age of 12 years and maintaining Phe levels below 600 micromol/L	

		will help prevent IQ loss, with implications on education, speed of processing and executive function. This will in turn also affect patients' quality of life, their ability to maintain relationships, engage in social interactions, operate effectively in a work environment etc.. The other huge advantage of Phe being the primary outcome measure is that it is readily measurable and consistent. All patients can measure it and can measure it frequently. Given the strength of use of blood Phe as an efficacy measure and the wealth of evidence underpinning its use as an efficacy measure, this does call into question the clinical opinion used by the ERG to justify this recommendation. **Hence in summary, the clinical advice to the ERG must be considered and weighed in conjunction with the robust body of literature and clinical opinions of experts consulted by the manufacturer (including three specialist adult metabolic physicians (collectively experienced in the care of approximately 50% of the UK adult PKU population), two-specialist paediatric metabolic physicians (collectively experienced in the care of approximately 20% of the UK paediatric PKU population),and an advanced practitioner in metabolic disease and experienced**	

		metabolic dietitian) which express a view that blood Phe concentration level is a validated measure of efficacy.	

The ERG states on p12, section 1.5 that "In clinical practice, within a given year, a patient may switch from having controlled to uncontrolled blood Phe concentration levels many times. "	The manufacturer does not agree with this suggestion and it does not align to the view of clinical experts that advised the manufacturer. **The manufacturer suggests this statement is removed due to the lack of evidence justifying this proposal.**	The manufacturer is concerned that the ERG has based their recommendations on what seems to be one clinician. This has led to recommendations that are contrary to UK clinical opinion. The manufacturer undertook a series of expert meetings in July 2020 which involved three specialist adult metabolic physicians (collectively experienced in the care of approximately 50% of the UK adult PKU population), two-specialist paediatric metabolic physicians (collectively experienced in the care of approximately 20% of the UK paediatric PKU population), and an advanced practitioner in metabolic disease and experienced metabolic dietitian. This combined experience represents a significant portion of UK PKU clinical management. The experts agreed to yearly cycles and hence the suggestion from the ERG, based on what seems to be one clinician, does not in our view usurp the depth of expertise that has supported the recommendation of yearly cycles. The ERG position is also suggesting that patients may switch from controlled to uncontrolled Ph levels multiple times in a year. The ERG has not stated what the likely Phe levels this would be nor the age groups. The manufacturer must therefore assume this applies to all Phe levels and all patients. The	The ERG appreciates that there is a lack of evidence to support the frequency with which patients' blood Phe concentration levels fluctuate within a given year and have, therefore, amended the text as follows: In clinical practice, within a given year, a patient may switch from having controlled to uncontrolled blood Phe concentration levels

		corollary of this is that patients could move from, for example 2000micromol/L to <600micromol/L and then back again to 2000 micromol/L multiple times in a year. The ERG has not provided evidence from the literature in support of this variance in Phe level nor has it supported this position from a group of clinical experts. There is also a notable lack of specificity to the recommendation. The manufacturer does not agree with this approach. The manufacturer is not aware of situation where patients could move from, for example, 2000 micromol/L to 600 micromol/L and then back again to 2000 micromol/L multiple times in a year. A review of the literature also does not support this possibility of all Phe ranges potentially moving from controlled to uncontrolled states. Furthermore UK clinical experts have also stated that whilst some fluctuation in blood Phe levels are possible e.g. well controlled patients might occasionally get a high level (usually with intercurrent illness) and poorly controlled patients who are mostly uncontrolled but might occasionally get a good level, it is not realistic to see significant swings in Phe levels. **As such, given this lack of validity, lack of specificity, lack of evidence and lack of**	

		clinical validation by a group of experts, the manufacturer cannot support this proposal.	

Issue 2 There is a wealth of comparative data available via the PKUDOS registry

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states "The value of the evidence from the three RCTs that are relevant to this appraisal is limited due to the short duration of the trials (10-13 weeks). " The ERG also states on p11 section 1.4 that "A long-term RCT that compares treatment with sapropterin+PRD versus PRD would provide the optimal data for decision-making; there are no comparative trials available of this kind and there are no known plans to conduct such a trial. Effectiveness data from the currently available	This is not a fair reflection of the challenges in undertaking long term RCTs in a rare disease such as PKU. The manufacturer suggests the ERG amends this to state: "the manufacturer has undertaken a large number of RCTs in this rare disease and undertaken numerous registry studies, the totality of which demonstrates that sapropterin offers considerable value, highlighting a consistent	There is a lack of recognition of the challenges in undertaking long term RCTs in a rare disease such as PKU. Kuvan has been granted orphan designation on the basis of this rarity. However despite this, the manufacturer has undertaken a clinical development programme that includes studies across phases II, III and IV and has been undertaken across a range of patient groups (such as those below the age of 4 years, maternal PKU for example) and includes a range of patient relevant endpoints (such as reduction in Phe levels, Phe	This is not a factual inaccuracy. No change required.

RCTs are limited by their short durations”	picture of the value of sapropterin in PKU patients” And “A long-term RCT that compares treatment with sapropterin+PRD versus PRD would provide the optimal data for decision-making. However given the challenges of undertaking long-term RCTs, this data provides the best available evidence to support decision making.”	tolerance and neurological outcomes for example). These studies are captured below: **Phase II studies:** PKU-001 (screening study) **Phase III studies**: PKU-003 (Pivotal Phase III); PKU-004 (Ph III extension); PKU-006 (Diet study); PKU-016 (Neurocognitive study); PKU-008 (Phase III OLE from PKU004 and PKU006); SPARK (<4 age group); PKU-015 (young children) **Phase IV studies:** ENDURE; PKUDOS; PKUMOMS; KAMPER; KOGNITO The clinical trial and registry evidence thus capture strong evidence across a range of endpoints and populations. Given the backdrop of a rare disease, it is therefore incorrect and unfair to state there is limited evidence available. In regard to long term evidence, a paper by Longo et al, 2015[1] states that: “Sapropterin has been assessed in long-term clinical studies. Burton et al. reported the safety of sapropterin and maintenance of blood Phe reduction in a population with PKU (N = 111,	

[1] *Molecular Genetics and Metabolism 114 (2015) 557–563*

		age range: 4 to 50 years) **for up to 2.6 years** at doses of 5 to 20 mg/kg/day" Furthermore, the PKUDOS registry (reported by Longo et al, 2015) captures data for 5 years (as stated in the publication) and >9 years today. **The data exists despite the rarity of PKU and the challenges of undertaking long term RCTs in a rare disease.**	
The ERG states there are no alternative datasets available that can be used to address the decision problem (page 10, issue 1.3)	This is factually incorrect. The PKUDOS registry data is available and has been submitted as part of the CS.	The Phenylketonuria Demographics, Outcomes and Safety (PKUDOS) registry is a phase 4 voluntary observational study designed to provide up to 15 years of data from adult and maternal[2] subjects with PKU who are (or have been) treated with sapropterin. Subjects must have a diagnosis of PKU and have previously received sapropterin, are currently receiving sapropterin, or intend to	This is not a factual inaccuracy. The ERG has noted that the PKUDOS registry study is of good methodological quality and includes a large number of patients followed over a number of years. However, the PKUDOS study was not designed to enable a comparison of treatment with sapropterin+PRD versus PRD. There are no alternative datasets available that would enable a comparison of treatment with sapropterin+PRD versus PRD.

[2] *D.K. Grange, R.E. Hillman, B.K. Burton, S. Yano, J. Vockley, C. Fong, J. Hunt, J.J. Mahoney, J.L. Cohen-Pfeffer, Sapropterin dihydrochloride use in pregnant women with phenylketonuria: an interim report of the PKU MOMS sub-registry, Mol. Genet. Metab. 112 (2014) 9–16.*

		receive sapropterin therapy within 90 days of enrolment. The data underpinning PKUDOS has been presented in the CS. On the one hand, the ERG has recognised the value of the registry data. The ERG states on page 32, table 6, last row that “The registries provide long-term data that are more representative of usual clinical practice than trial data. The ERG agrees that the registries are the most appropriate data sources to inform conclusions relating to long-term efficacy and safety outcomes” But then paradoxically, the point is made that there is insufficient data available. **The manufacturer asserts that the PKUDOS data is an appropriate dataset to use**	

The ERG report states (page 43): "The ERG notes that the number of patients contributing longer-term blood Phe concentration level data to the PKUDOS registry study is small; for example, 998 patients (51.9% of the safety analysis set) contribute blood Phe concentration level results at 2 years, 586 patients (30.5%) contribute results at 5 years and only 83 patients (4.3%) contribute results at the latest follow-up time of 9 years." Similarly, the reports states on page 48 (heading "Blood Phe Concentration" second sentence) "The number of patients contributing longer-term blood Phe concentration level data to the KAMPER registry is small"	This is not a fair reflection of the challenges in undertaking long term data collection in a rare disease such as PKU. The manufacturer suggests the ERG amends this to state: "**The ERG notes that the number of patients contributing longer-term blood Phe concentration level data to the PKUDOS registry study is significant given the rarity of the disease; for example, 998 patients (51.9% of the safety analysis set) contribute blood Phe concentration level results at 2 years, 586 patients (30.5%) contribute results at 5 years and 83 patients (4.3%) contribute results at the latest follow-up time of 9 years."**	There is a lack of recognition of the challenges in undertaking long term studies in a rare disease such as PKU. However despite this, the manufacturer has undertaken a clinical development programme that includes studies across phases II, III and IV and has been undertaken across a range of patient groups (such as those below the age of 4 years, maternal PKU for example) and includes a range of patient relevant endpoints (such as reduction in Phe levels, Phe tolerance and neurological outcomes for example). The clinical trial and registry evidence, specifically PKUDOS, has captured considerable evidence in 1922 patients and over a period of up to10 years. In KAMPER the population size is 576 patients Given the backdrop of a rare disease, it is therefore unfair to criticise the patient numbers in the registry and the duration of data available.	This is not a factual inaccuracy. No change required.

Issue 3 The challenges of capturing QoL data are not reflected or considered by the ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that no HRQoL data is presented in the CS. This is factually inaccurate. (page 10, issue 2)	The manufacturer has provided in the CS details of a Swedish TTO study undertaken in excess of 1000 patients capturing QoL data. **The manufacturer recommends the ERG remove the sentence stating no HRQoL data is presented.**	Capturing QoL data in PKU patients is extremely challenging due to PKU patients' disability paradox. Patients with PKU are less able to report their own quality of life due to reduced executive function and neurological and neurocognitive impairment which contributes significantly to hidden disabilities in these patient groups. This manifests as difficulties in planning, organizing and reduced processing speed for example. As a result, patients are less able to undertake a subjective evaluation of his or her own functioning and emotional well-being. These challenges are also observed in other diseases areas such as psychiatry. Reliability and validity of reporting QoL in psychiatric disorders has been questioned because of the cognitive impairments and distortions that characterize several mental health conditions.[3] There are no quality of life tools successfully validated in PKU. Attempts have been made in the past to try and address this with, for example, the PKU-QoL tool (a PKU disease	The ERG has added text to clarify that there are no HRQoL data that are collected directly from patients with PKU.

[3] *Bullinger M, Quitmann J. Quality of life as patient-reported outcomes: principles of assessment. Dialogues in clinical neuroscience 2014;16(2):137*

		specific tool). However, this has been unsuccessful. Initial psychometric validation of the tool shows poor content and construct validity. There has been further psychometric evaluation of this instrument but no clinically important difference (CID) estimates have been derived. Furthermore, generic tools such as SF36 or EQ5D have been unsuccessful in capturing the impact of PKU. The limited data on the use of the SF-36 in PKU has shown the tool to be insensitive. Attempts to map PKU-QoL to SF36 have also been unsuccessful and has been shown to have poor correlation between PKU-QoL and SF36. It is clear therefore that capturing QoL in PKU presents significant challenges. The manufacturer has managed to finally address this with a Swedish TTO that does show in over 1000 members of the general public, categorically, the impact PKU on quality of life, by Phe level. **An understanding of the challenges of capturing QoL data are not reflected or considered by the ERG in their report.**	
The ERG states on page 76 that there are unrealistically	The manufacturer does not accept the ERG's	In terms of methodology, the Swedish TTO study is based on a robust sample size of over	This is not a factual inaccuracy. No change required.

low utility values associated with uncontrolled PKU **"**The ERG considers that the disutilities applied for uncontrolled PKU in the company model lead to unrealistically low patient utilities. For example, in the model, a person aged 20 years old with uncontrolled PKU has a utility value of [redacted]. This is caused by the very low utility values in the Swedish TTO study, particularly for the utility value associated with severe symptoms ([redacted]), which is very close to the utility associated with death (0.0). Whilst severe PKU symptoms may lead to a substantial reduction in HRQoL, the ERG considers that there is a lack of validity in the model assumption that a patient with such a poor HRQoL would remain uncontrolled for many years, rather than modifying	viewpoint regarding the utility values. **The manufacturer recommends this statement is withdrawn**	1000 respondents from the general population. The health state vignettes were developed based on a Delphi panel of PKU experts in the US, a targeted review of the literature and feedback from internal medical expertise from the manufacturer. The draft vignettes were then reviewed by three European health care professionals (HCPs) with experience of treating PKU patients. A revised version based on their comments were constructed after the review, presented, and discussed with the HCPs during a follow-up interview. After the follow-up interview, a final version of the vignettes was constructed (the TTO study report was provided in the CS). Uncontrolled PKU is characterised by symptoms that have a profound impact on daily living and patients' quality of life. Caregivers/ partners of these patients with sustained high level of blood Phe often report severe symptoms. These patients also suffer from what has been termed as hidden disabilities (Gentile 2010) and end up in a vicious downward spiral where patients need to resume therapy (such as the Phe-restricted diet) but are hindered from doing so due to neurological and neurocognitive impairment caused by elevated blood Phe levels. These levels continue to rise if sapropterin and / or the Phe-restricted diet is not initiated. If not initiated, the blood Phe levels rise	

their diet and/or starting or returning to take sapropterin.”		further leading to worsening neurological and neurocognitive impairment. A degree of executive functioning ability is required for the planning and organising the highly restrictive Phe-free diet. The utility data was validated by UK clinical experts in July 2020 which involved three specialist adult metabolic physicians (collectively experienced in the care of approximately 50% of the UK adult PKU population), two-specialist paediatric metabolic physicians (collectively experienced in the care of approximately 20% of the UK paediatric PKU population),and an advanced practitioner in metabolic disease and experienced metabolic dietitian. This combined experience represents a significant portion of UK PKU clinical care and as such provides strong and confirmatory support for the applicability of these utility results from the TTO study to a UK perspective. It remains unclear what scientific evidence was reviewed, or clinical rationale gained, or indeed systematic literature search was applied/undertaken by the ERG to state that patients with low utility values would not modify their diet and/or start or return to take sapropterin. This highlights a lack of understanding of the disease.	

		Patients with this level of disease severity have significant cognitive and executive function impairment. It is not possible for them to rationalise the cause of their 'fogginess' and impaired quality of life, and to then make an informed judgement about the best course of action to take that will best address the source of their impairment. **As such, the manufacturer does not accept the ERG statement that a patient with such poor HRQoL would rather modify their diet and/or start or return to take sapropterin than stay in an uncontrolled state.**	

Issue 4 The ERG model lacks credibility, is not validated and does not align to the clinical pathway for PKU as opposed to the manufacturers model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states on p12, section 1.5 that they have "undertaken an alternative approach to modelling cost effectiveness that relates only to the period when patients are taking	The ERG developed model does not align to the clinical pathway for PKU, does not seem to have been validated by a group of clinical experts and suffers from multiple issues all of which undermine	The manufacturer believes the model developed by the ERG suffers from multiple issues: 1. The ERG model has not been validated by a group of clinical experts across various disciplines	This is not a factual inaccuracy. No change required. Due to the limitations of the company's model, the ERG presented an alternative approach to assessing cost effectiveness. This simple calculation of

sapropterin. This negates the need to model for a complex pathway.”	the approach of the ERG. The model has not been shared with the manufacturer hence a more detailed critique has not been possible. **The manufacturer therefore recommends all reference to the ERG developed model and its outputs be removed.**	2. Does not reflect the disease course of PKU nor consider PKU in the real world 3. Fails to appreciate the benefits of sapropterin over the longer term even if treatment with sapropterin is ceased 4. Seems to be an overly simple decision tree model which does not address the complexity of PKU 5. Many of the inputs to the model are not evidence-based and lack clinical validation 6. The model itself has not been made available to the manufacturer and therefore we are basing our critique on the limited description in the ERG report The ERG has, it seems, contradicted itself with the statement that says: “The ERG considers that the company model structure and parameterisation are both too simplistic for the complexity of the condition being modelled. However, the ERG considers that the model is too complex for the decision problem that needs to be addressed” Yet the ERG has then developed a model of its own that is overly simple and does not reflect the complexity of the disease. This goes against the point the ERG just made (in inverted commas). The manufacturer is also concerned	the costs and benefits to a patient whilst they take sapropterin+PRD focusses the discussion on the drivers of the cost effectiveness of sapropterin+PRD versus PRD, namely a reduction in the costs of PRD and a gain in HRQoL from not having to follow a PRD so rigidly and potentially a lower PKU symptom burden.

		by what seems to be a lack of validation by a group of multidisciplinary clinical experts. The model does not consider the long-term benefits of sapropterin. The model submitted by the manufacturer has been fully validated by a multi-disciplinary team of clinical experts in England, reflects the disease pathway and clinical practise of managing PKU patients. The ERG model does not reflect the benefits of treatment over the longer term and fails to acknowledge that there are longer term benefits of sapropterin that continue even if the treatment is stopped. As such this is factually incorrect and invalidates the ERG model. **As has been responded later on p30, and repeated here -** Treatment with sapropterin lays down foundations that prevent future complications and as such the benefits do accrue over time. For example, treatment with sapropterin will help children achieve better metabolic control and as such there will be benefits that are maintained and carried forward into adult life even if treatment is subsequently stopped. Elevated blood Phe leads to neurological and neurocognitive disorders. It can also lead to neurotransmitter imbalance and structural	

		deformities of the brain. If left untreated, PKU can result in severe intellectual impairment. It is therefore clear that by preventing these neurological and neurocognitive disorders one can prevent intellectual impairment, IQ loss etc. that could inhibit educational attainment in school and university. This can then impact work prospects and other life chances, job opportunities. Clinical expert state that brain development continues into mid-20s for many individuals and brain remodelling occurs throughout life. From a neurotransmitter imbalance perspective, the role of dopamine changes over time and insufficient dopamine will have a different impact at a young age compared to a young adult for example. With elevated blood Phe levels, this can lead to a reduction in other neurotransmitters including dopamine. The pre-frontal cortex develops in later life which is dependent on dopamine hence a lack of dopamine at 5 years of age is vastly different to lack of dopamine at 15years or 20 years of age for example. Dopamine has a critical role to play in critical thinking, decision making and higher orders of thinking rely on dopamine. As the pre-frontal cortex develops as a young adult, the ability to undertake more complex and higher order thing increases. A lack of dopamine at this stage (due to elevated blood Phe) can then lead to	

		executive function impairment, reduced speed of processing, poorer working memory etc. This could then manifest as poorer exam results for example, poor decision making in the workplace, inability to retain information thus limiting one's true potential at critical points in life. **As such, the manufacture does not accept the ERG position that the benefits of sapropterin cease once treatment is ceased and therefore invalidates, in our view, the ERG model.**	
The ERG states on p12, issue 7 that "..the company transition probabilities are unreliable and are of limited use to inform decision-making"	The manufacturer does not accept the ERG's viewpoint regarding the transition probabilities (TPs). **The manufacturer recommends this statement is withdrawn**	The transition probabilities are based on PKUDOS (a registry initiated in 2008 and currently includes 1997 patients). At the last data-cut in February 2018, there were 1,867 patients that had been followed since 2008. The transition was based on a robust sample size of 221 patients in the 'Sapropterin+diet', and 557 in the 'diet only' arm. The Transition probabilities were calculated based on actual counts of patients moving from one of the two health states (controlled and uncontrolled) over the period of 6 years for the 2 arms (saproptetin+diet and diet only) to the destination health states (controlled and uncontrolled). Uncontrolled PKU is defined by Phe levels being above the target Phe levels	This is not a factual inaccuracy. No change required.

		described in the European PKU guidelines. Controlled PKU is defined by Phe levels being within the target range. Full and transparent calculations have been provided to the ERG by the manufacturer in response to questions from August 2020.	
The ERG states on p71, final sentence "The ERG considers that the model structure is too simplistic to reflect the complexities of the lives of patients with PKU due to the 1-year cycle length and the implausibility of time and age invariant health state transition probabilities."	The manufacturer does not accept the view of the ERG regarding simplicity of the model **The manufacturer recommends this statement is withdrawn**	The manufacturer does not accept the ERG viewpoint that 1-year cycle lengths are too long. UK clinical experts have stated that an annual cycle is when clinical reviews generally happen and clinicians then look over an annual period to get a measure of control. The age variants structure of the manufacturer model reflects the disease etiology and management where irreversible damage to the brain happens in the early years of life (pre-adolescence). Patients with PKU needs to be managed more closely in these early years of life (before the brain is structurally fully developed). Also, these younger patients are managed in pediatric metabolic clinics to the age of 18 before they transition to adult clinics. These age variants were further validated by clinical experts in England. **Given this feedback from UK clinical experts we suggest the one-year cycle length is retained.**	This is not a factual inaccuracy. No change required.

The ERG states on page 72, under Cycle length that "Clinical advice to the ERG is that PKU symptoms may signal a lack of control of dietary protein, leading patients to alter their diet. For example, a patient who has increased the natural protein content of their diet may begin to feel sick or have headaches and this may incentivise them to control their dietary intake of protein"	The ERG report does not state in whom this ability to consciously self-manage natural Phe intake. Nor does the ERG state what Phe levels are patients able to make this alteration. There is considerable lack of clarity to this suggestion. As such, the manufacturer suggests: "Clinical advice to the ERG is that PKU symptoms may signal a lack of control of dietary protein. For example, a patient who has increased the natural protein content of their diet may begin to feel sick or have headaches and this may incentivise them to control their dietary intake of protein. **However in clinical practice this does not happen".**	The ERG report does not state in which patients this ability to consciously self-manage natural Phe intake is possible. Nor does the ERG state at what Phe levels are patients able to self - manage. Patients with elevated Phe, with symptoms such as those described by the ERG with headaches and sickness causes people to become "foggy" and this fogginess makes it much harder for patients to be incentivised to control their dietary intake. Also, this also does not align to UK clinical opinion. Patients who get symptoms of poor control rarely notice this themselves – it is others around them who notice changes in behaviour, irritability, poor concentration and these changes by their very nature make self-directed changes to dietary control very difficult. For example, an adult living by themselves, who is getting poorly controlled will find it very hard to motivate themselves/organise themselves to make the changes needed to get their dietary control better if their levels are high, because of the effect of high Phe levels. This 'fogginess' that occurs in PKU patients with elevated Phe makes it much harder for patients	The company is not disputing the factual accuracy of the ERG statement. However, the statement that the company considers should be added to the ERG report is a matter of opinion. No revision required.

		to be incentivised to make changes to their dietary intake. Indeed, many patients are habituated to suboptimal control and therefore don't always recognise their control needs to improve. Others may not have the executive function to effect dietary control when needed. As such it is recognised that this is not a statement that can made as a general comment for the PKU population as a whole. **Hence in clinical practice, it is not likely that patients will make the changes suggested by the ERG.** Furthermore, given the challenges of adhering to the PRD, which becomes even more challenging as patients age and begin to gain independence (Jurecki et al, 2017[4], Walter et al, 2002[5]) the proportion of patients able to self-manage in this way is likely to be very small. A systematic review undertaken by Enns, 2010[6] highlights the suboptimal outcomes in patients treated with diet alone. It is therefore clear that the ability of patients able to self-manage in this way is extremely limited otherwise the	

[4] *Molecular Genetics and Metabolism 120 (2017) 190–197*
[5] *THE LANCET • Vol 360 • July 6, 2002*
[6] *Molecular Genetics and Metabolism; Volume 101, Issues 2–3, October–November 2010, Pages 99-109*

		suboptimal outcomes reported by Enns in the systematic review would not be observed. Similarly, a publication by Bilder et al, 2017[7] highlighted the range of neurologic and psychiatric disorders, including intellectual disability, anxiety, depression, and neurocognitive dysfunction observed n PKU patients. This study was undertaken in the US. Rutsch et al, 2018[8] presented evidence from a German claims database where the top 50 most common comorbidities in the PKU population were assessed, those with a PR >1.5 for the PKU vs. control population included major depressive disorders (recurrent), reaction to severe stress and adjustment disorders, other anxiety disorders, chronic ischemic heart disease, infectious gastroenteritis and colitis, unspecified diabetes mellitus, and asthma; this higher risk in the PKU population was maintained for the majority of these conditions when the top 50 most common comorbidities in the control population were assessed. **This is further evidence of the complications PKU patients face and again suggests that patients are not self-managing their PKU well. The suggestion of the ERG that patients self-manage is not borne out by the**	

[7] *Molecular Genetics and Metabolism 121 (2017) 1–8*

[8] *Presented at the Society for the Study of Inborn Errors of Metabolism 2018 Annual Symposium: 4–7 September, 2018, Athens, Greece*

		literature, registry data or UK clinical opinion.	
The ERG states on page 72, "The time invariant transition probabilities, lack of health state memory and zero probability of resuming treatment with sapropterin mean that the company model produces implausible results"	The manufacturer does not accept the view of the ERG regarding these points. **The manufacturer recommends this statement is withdrawn**	The ERG themselves developed a model without these features that they claim adequately represents PKU, therefore we consider that the ERG must not deem them necessary and therefore this statement is contradictory of other sections of the ERG report.	This is not a factual inaccuracy. No change required.
The ERG states on page 73 section 5.2.2. "Due to these concerns, the ERG considers that the company transition probabilities are unreliable and have limited use for decision making."	The manufacturer does not accept the view of the ERG regarding the transition probabilities. **The manufacturer recommends this statement is withdrawn**	The CS cost-effectiveness model is a cohort-based Markov model, where patients' movement between health state is driven by transition probabilities. PKUDOS is the only source of long-term comparative data between 'sapropterin+diet' and 'diet only'. It may be noted that PKUDOS doesn't only follow patients who are on drug (sapropterin+diet'), but also patients who are on standard of care (diet only). The Transition probabilities were calculated based on actual counts of patients moving from one of the two health states (controlled and uncontrolled) over the period of 6 years for the 2 arms (saproptetin+diet and diet only) to the destination health states (controlled and uncontrolled). Rom the company standpoint, this	This is not a factual inaccuracy. No change required.

		is most reliable, long-term comparative data from which transition probabilities have been calculated. The ERG contention that transition probabilities are 'unreliable and have limited use' is unfortunate. The company would be happy to incorporate any other source (other than PKUDOS), which ERG can suggest would be more reliable and robust source of comparative data.	
The ERG states on page 74 under the heading of attrition rate that: "The ERG considers that the attrition rate in the model (i.e., the annual rate at which patients stop receiving sapropterin) is unreliable and, furthermore, the methods used to incorporate the attrition rate into the model is inappropriate"	**The manufacturer recommends this statement is withdrawn**	The manufacturer responded to questions from NICE in relation to attrition rate. The response is reproduced below: Following further analysis of various data sources, we observe there is some variance in the range of discontinuation rates observed in the real world. For example, we see a rate from the most recent CSR for KAMPER (European registry) calculated [redacted] (see *Section 1* below) and data from Rohr et al, 2014 (attached) stating a figure of 29% (Table 1). In addition, anecdotally we are aware of real-world data from the US suggesting a figure closer to 10%. **Given this variance, our original submission figure of [redacted] reflects a mid-point of rates observed.**	This is not a factual inaccuracy. No change required. The extra analyses provided by the company highlight that treatment with sapropterin+PRD becomes [redacted] cost effective as the discontinuation rate [redacted].

We have applied the rates of 4.1% and 29% discontinuation as sensitivity analyses in *Section 2* below.

Table 1 Rohr et al 2014

Table 1
Characteristics of patients with PKU who responded to sapropterin therapy.

	Remained on drug	Discontinue drug
Number of sapropterin responders	29	12
Mean age (years)	19.7	19.9
Age range (years)	0.5–54	3–47
Male	17	4
Female	12	8
Experienced side effects	8	10
Severity of PKU		
Mild hyperphenylalaninemia	1	0
Mild PKU	9	2
Moderate PKU	16	7
Severe PKU	3	3
Diet		
Tolerated more dietary PHE	24	7
Mean protein intake (SD) before sapropterin therapy (g/day)	11.3 (7.7)	8.8 (1.8)
Mean protein intake (SD) after sapropterin therapy (g/d)	31.8 (17.4)	17.2 (4.6)

Section 1 KAMPER data

The attrition rate reported earlier were based on 7th interim analysis of KAMPER, dated 9th June, 2017. However, since then we have a new CSR from KAMPER, dated 29 June 2020 (10th Interim Report: 08 December 2009 through 31 January 2020). As per the latest CSR, there were [redacted] patients in the Safety Analysis

		Set, data were analysed for [redacted] patients with HPA associated with PKU ([redacted] paediatric and [redacted] adult) and [redacted] patients with HPA associated with BH4 deficiency ([redacted] paediatric and [redacted] adult). A total of [redacted] ([redacted]) patients, including [redacted] BH4-deficient patients, were reported to discontinue the study as presented in Figure 1 below. The most common reasons for study discontinuation (including designation of "[redacted]" free-text responses) were [redacted] (n=[redacted]), [redacted] (n= [redacted]), and [redacted] (n=[redacted] [redacted]). [redacted] patient was reported to discontinue the study due to [redacted]. In recent years, the number of discontinuation reports from the registry was the following: [redacted] patients in 2011, [redacted] patients in 2012, [redacted] patients in 2013, [redacted] patients in 2014, [redacted] patients in 2015, [redacted] patients in 2016, [redacted] patients in 2017, [redacted] patients in 2018, and [redacted] patients in 2019. For the [redacted] PKU patients, the median calculated study duration was [redacted] days (about [redacted] years). The minimum study	

		duration was [redacted] days, and the maximum study duration was [redacted] days. Using data from the latest CSR, risk of discontinuation over [redacted] period is [redacted]. This probability of discontinuation, converted to annual rate will work out to be [redacted]. KAMPER, being a drug registry, only included patients who were responsive to sapropterin treatment (i.e. ≥30% reduction in blood Phe level). The attrition rate calculation shown did not specifically include patients who were not controlled with sapropterin+diet treatment. Figure 1: Reasons for discontinuation	

[redacted]

Section 2 Updated Economic Analyses

The revised deterministic ICER for the base case as reported in Table 72 in the main *ID1475 Sapropterin Company evidence submission Final* is presented below with a 4.1% discontinuation rate.

Table 2 base-case results (All years, with PAS, discontinuation rate 4.1%)

Treatment	Total costs	Total LL	Total QALL	Δ costs	Δ QALYs	ICER (£/QALY gained)

		YG*	**Ys**			
Sapropterin + Protein-restricted diet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protein-restricted diet	[redacted]	[redacted]	[redacted]			

* Undiscounted values; Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

<u>Updated with 29% discontinuation rate</u>

The revised deterministic ICER for the base case as reported in Table 72 in the main *ID1475 Sapropterin Company evidence submission Final* is presented below with a 29% discontinuation rate.

Table 3 base-case results (All years, with PAS, discontinuation rate 29%)

		Treatment / **Total costs** / **Total LYG*** / **Total QALYs** / **Δ costs** / **ΔQALYs** / **ICER (£/QALY gained)** Sapropterin + Protein-restricted diet: [redacted] Protein-restricted diet: [redacted] * Undiscounted values; Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years	
The ERG states on page 75, under section 5.2.3 that:	The manufacturer does not accept the view of the ERG regarding utility values.	The ERG states that the utility values derived from the Swedish TTO study are “unrealistically low” (page 14, issue 9) and unlikely to reflect the	This is not a factual inaccuracy. No change required.

"The ERG considers that the utility values used in the company model are unlikely to reflect the HRQoL of patients with PKU who are treated in the NHS. The ERG's four areas of concern are around the: • methods used by the company to elicit health state utility values • mismatch between Swedish health state descriptions and company model health states • unrealistically low utility values associated with uncontrolled PKU • method used to map Swedish health state utilities to company model health states."	**The manufacturer recommends this statement is amended to** **"the ERG considers that the utility values used in the company model are based on robust evidence from a large Swedish TTO study and subsequently validated by UK clinical experts. As such, this data offers the best perspective of utility values for PKU patients across the disease spectrum"**	experience of NHS patients with PKU (page 14, issue 9, heading). It is unclear on what basis has the ERG stated the utility figures are 'unrealistically low'. The Swedish TTO study was undertaken in over 1000 patients consisting of individuals from the general population and individuals with experience of PKU (i.e. individuals with PKU/parents to individuals with PKU/individuals with other experience of PKU). Based on these surveys, the utility values were determined and the results highlight that both diet- and disease-related attributes associated with PKU have a significant impact on the quality of life of PKU patients. These data were then validated by UK clinical experts in July 2020 which involved three specialist adult metabolic physicians (collectively experienced in the care of approximately 50% of the UK adult PKU population), two-specialist paediatric metabolic physicians (collectively experienced in the care of approximately 20% of the UK paediatric PKU population),and an advanced practitioner in metabolic disease and experienced metabolic dietitian. This combined experience represents a significant portion of UK PKU clinical care and as such provides strong and confirmatory support for the applicability of	

		these utility results from the TTO study to a UK perspective. It remains unclear what scientific evidence was reviewed, or clinical rationale gained, or indeed systematic literature search was applied/undertaken by the ERG to then state these utility values are “unrealistically low”. Greater clarity on this point would be appreciated. This does raise a concern with the manufacturer that the ERG has not fully appreciated the severity of PKU despite expert clinical opinion, literature, clinical studies, registries and claim database studies, and patient organisation perspectives highlighting this. Patients with PKU suffer from a range of neurological and neurocognitive impairments not limited to for example tremors, anxiety, depression, impaired executive function, cognitive impairment. The manufacturer notes that utility values of 0.30 are observed in other disorders such as severe depression.[9] **As such, the manufacturer does not accept the ERG statement that the utility figures are “unrealistically low”. The ERG has not**	

[9] *Fitzgibbon et al, 2019; Can J Psychiatry,2019 Jul 1; ():706743719890167*

		provided a justification from the literature or clinical opinion to support the claim that the utilities are 'unrealistically low'. Without any evidence supporting this ERG claim, it must be assumed that this is purely just an opinion and therefore remains baseless.	
The ERG states on Page 77 that "..clinical advice to the ERG is that it is likely that even if patients could reduce their intake of low protein foods, they would be advised to maintain their intake of protein supplements. It may, therefore, be the case that use of sapropterin in the UK may lead to no reduction in patient intake of protein supplements." And The ERG states on Page 77 that "..the evidence from the PKUDOS registry study	The manufacturer does not accept the view of the ERG regarding protein supplement intake. **The manufacturer recommends this statement is removed.** **The manufacturer also recommends that the cost-effectiveness estimated based on 0% reduction in protein supplement intake be removed.**	This does not reflect UK clinical opinion nor published literature. UK clinical experts aim to meet protein requirements by a combination of natural protein and PKU phe free amino acid mixtures/protein substitutes. If phe tolerance increases then a greater proportion of the daily protein requirements can be met by dietary natural protein. The requirement for protein substitutes is then reduced. Clinical experts state that they would expect to see a 50% reduction in protein supplement use, and with good responders potentially going even further. Indeed, this is one of the major incentivising factors for many children is that they are able to take less amino acid mixture which is perceived by a child, for example, as a far greater benefit than having to consume additional protein substitute. Protein substitutes tend not to be removed entirely to allow for some buffer for illness (even if it's only 10g) and to ensure patients do not forget the taste or technique associated with	This is not a factual inaccuracy. No change required.

suggests that a 71.2% reduction in low protein food and protein supplements may be optimistic.		protein substitute intake should they need additional protein particularly in times of illness. A poster by Yilmaz et al, presented at ESPKU, reports the following: *"8 centers from 8 countries reported the dietary management of 291 saproterin responsive patients. More than half (n=163, 56.0%) of the sapropterin treated patients achieved WHO/FAO/UNU safe levels of protein intake. Of 291 sapropterin responsive patients, 82 (28%) did not require a L-AA supplements and in the remaining patients L-AA dosage reduced by 60%. Only 26% (n=75) patients used low protein milk, and 6% (n=33) low protein foods like bread. Only 30% were prescribed vitamin/mineral supplements."* It is clear that some patients were able to remove their Phe-free protein supplements entirely and others reduced their intake by 60%. There are many further publications that highlight the reduction in amino acid (AA) supplements as a result of sapropterin (Scala, 2015[10], Thiele, 2012[11], Singh, 2010[12], Burlina	

[10] *Scala et al. Orphanet Journal of Rare Diseases (2015) 10:14*
[11] *JIMD Rep. 2013;9:31-40*
[12] *J Inherit Metab Dis (2010) 33:689–695*

		2009[13]) which all highlight the reductions observed in AA mixture. **As such, the manufacturer suggests both statements from the ERG are factually incorrect and should be removed. The resulting cost-effectiveness estimates based on 0% protein reduction should also be removed.**	
The ERG states on page 75, section 5.3 that "..the ERG notes that there are no long-term benefits of treatment with sapropterin in terms of survival, and there is no evidence, or clinical reason, to consider that the effectiveness of sapropterin changes over time.	The manufacturer does not accept the view of the ERG regarding utility values. **The manufacturer recommends this statement is amended to** **" the ERG accepts that there are long-term benefits of treatment with sapropterin and there is evidence, or clinical reason, to consider that the effectiveness of sapropterin changes over time."**	This is factually incorrect. There are longer term benefits of sapropterin that continue even if the treatment is stopped. Treatment with sapropterin lays down foundations that prevent future complications and as such the benefits do accrue over time. For example, treatment with sapropterin will help children achieve better metabolic control and as such there will be benefits that are maintained and carried forward into adult life even if treatment is subsequently stopped. Elevated blood Phe leads to neurological and neurocognitive disorders. It can also lead to neurotransmitter imbalance and structural deformities of the brain. If left untreated, PKU can result in severe intellectual impairment.	This is not a factual inaccuracy. No change required.

[13] *J Inherit Metab Dis (2009) 32:40–45*

		It is therefore clear that by preventing these neurological and neurocognitive disorders one can prevent intellectual impairment, IQ loss etc. that could inhibit educational attainment in school and university. This can then impact work prospects and other life chances, job opportunities. Clinical experts state that brain development continues into mid-20s for many individuals and brain remodelling occurs throughout life. From a neurotransmitter imbalance perspective, the role of dopamine changes over time and insufficient dopamine will have a different impact at a young age compared to a young adult for example. With elevated blood Phe levels, this can lead to a reduction in other neurotransmitters including dopamine. The pre-frontal cortex develops in later life which is dependent on dopamine hence a lack of dopamine at 5 years of age is vastly different to lack of dopamine at 15 years or 20 years of age for example. Dopamine has a fundamental role to play in critical thinking, decision making, higher orders of thinking for example which rely on dopamine. As the pre-frontal cortex develops as a young adult, the ability to undertake more complex and higher order thing increases. A lack of dopamine at this stage (due to elevated blood Phe) can then lead to executive function impairment,	

		reduced speed of processing, poorer working memory etc. This could then manifest as poorer exam results for example, poor decision making in the workplace, inability to retain information thus limiting one's true potential. **As such, the manufacturer does not accept the ERG position that the benefits of sapropterin cease once treatment is ceased.**	
The ERG states on page 78, section 5.3.1 that "The company has stated that the mean dose for children is 10mg/kg and the mean dose for adults is 12.5mg/kg. The evidence base for these doses is not robust. " The ERG goes on to state (3rd sentence) that: "This suggests that the values used in the company model may be	The manufacturer does not accept the view of the ERG. **The manufacturer recommends this statement is amended to "The recommendation for the Kuvan dosages came from UK clinical experts representing NHS England's clinical reference group (CRG)"** And	The dosages come directly from NHS England's Clinical experts sitting on the Clinical Reference Group (CRG) and published in NHS England's Integrated impact Assessment report. **The manufacturer has merely cited the view of NHS England's clinical experts** With regard to the second statement from the ERG which states "This suggests that the values used in the company model may be underestimates of real-world dosages" the manufacturer would highlight that the dosages observed in KAMPER reflect the countries that are part of the registry which consist of 8 countries including Austria, France, Germany, Italy, the Netherlands, Slovakia, Spain, and Sweden. The UK is not part of this registry.	This is not a factual inaccuracy. No change required.

underestimates of real-world dosages"	**"This suggests that the values used in the company model are reflective of the recommendation by NHS England's Clinical Reference Group (CRG)"**	**As such the opinion of NHS England's Clinical Reference Group better reflects UK clinical opinion than the average dosage from a registry that does not include the UK.**	
The ERG states on page 20, section 2.4.1 that according to clinical advice "that adhering to a PRD can be time- and resource-consuming and burdensome for patients with PKU and their caregivers" The ERG further states on p84 section 5.5 that these values were not included in their model and that "Inclusion of parent/carer disutilities could double the QALY gain"	The manufacturer considers this a major limitation of the model that is counter to the clinical evidence that the ERG received. **The manufacturer does not accept the ERG model, and notwithstanding this point, the manufacturer would flag that the ERG model, as a minimum, should be updated to reflect parent/carer disutilities as the base case**	The ERG acknowledges that it received clinical advice "that adhering to a PRD can be time- and resource-consuming and burdensome for patients with PKU and their caregivers", and that the "Inclusion of parent/carer disutilities could double the QALY gain". While the ERG acknowledges this limitation of their model, it further confirms that their model is overly simplistic and may be drastically under-estimating the health benefits that clinical advice to the ERG has confirmed**. The manufacturer believes the ERG's conclusions on cost effectiveness should be read with extreme caution** since the ERG model underestimates the QALY gains of taking sapropterin by more than 50% due to this single omission alone.	This is not a factual inaccuracy. No change required.

(please cut and paste further tables as necessary)

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.	
Page 19 3rd paragraph	Sapropterin is dispensed as 100mg sapropterin dihydrochloride soluble tablets and as 100mg and 500mg sapropterin dihydrochloride powder for oral solution. The sapropterin tablets and powder are dissolved in water and taken orally.[27]	Sapropterin is dispensed as 100mg sapropterin dihydrochloride soluble tablets. The sapropterin tablets are dissolved in water and taken orally	Thank you for the clarification. The ERG report has been changed as suggested.
Page 20 para 1	The criteria for responsiveness to sapropterin are either, i) a ≥30% reduction in blood Phe concentration levels, ii) a reduction in blood Phe concentration levels to within the target range recommended in the European PKU guidelines[4] (see Table 1) or iii) as recommended by the treating clinician.	The SmPC should be referenced here which states: "A satisfactory response is defined as a ≥30 percent reduction in blood phenylalanine levels or attainment of the therapeutic blood phenylalanine goals defined for an individual patient by the treating physician. Patients who fail to achieve this level of response within the described one month test period should be considered non-responsive and should not receive treatment with Kuvan."	Thank you for the clarification. The ERG report has been updated as suggested.
Page 22, table 2 row 4, column 4	No health-related quality of life data are available	Suggest this removed. HRQoL data has been provided in the CS (details of a Swedish TTO study undertaken in excess of 1000	The ERG has added text to clarify that there are no HRQoL data that are collected directly from patients with PKU.

		patients capturing QoL data has been presented in the CS)	
Page 25, para 2	Neither the PKUDOS registry study nor the KAMPER registry study include data describing current clinical management without previous exposure to sapropterin and therefore do not provide evidence for a comparison of sapropterin+PRD versus PRD	Suggest removal. The PKUDOS registry captures data for patients who are sapropterin responsive and non-sapropterin responsiveness. The Longo et al 2015[14] paper states "Sapropterin responsiveness was found for 71% in the uninterrupted use population, 27% in the short-term use population, and 57% for these two populations."	This is not a factual inaccuracy. The PKUDOS registry does not provide evidence for a comparison of sapropterin+PRD versus PRD. See ERG response to Issue 2 for further details.
Page 25, paragraph 3	The ERG states that blood Phe is a poor efficacy outcome measure in PKU and should only be considered in conjunction with dietary Phe intake.	Rephrase to: "clinical advice to the ERG is that blood Phe concentration level is a validated measure of efficacy"	See ERG response to issue 1 for further details.
Page 11, issue 3	The ERG states that blood Phe is a poor efficacy outcome measure in PKU and should only be considered in conjunction with dietary Phe intake.	On page 11, issue 3 should be amended to "The ERG recognises that blood Phe is the most widely used and	See ERG response to issue 1 for further details.

[14] *N. Longo et al. / Molecular Genetics and Metabolism 114 (2015) 557–563*

		accepted outcome measure in PKU”	
Page 44, last sentence and **Page 49 paragraph 1, last sentence and** **Page 53, sixth bullet**	Clinical advice to the ERG is that blood Phe concentration level alone is a poor measure of efficacy and should only be considered in conjunction with dietary Phe intake	Rephrase to: “clinical advice to the ERG is that blood Phe concentration level is a validated measure of efficacy”	See ERG response to issue 1 for further details.
Page 59, sixth row	HRQoL values used in the model were derived from the general public and not from patients with PKU	Suggest this is reworded to: HRQoL values used in the model were derived from the general public and not from patients with PKU which is a reasonable approach given the challenges of PKU patients being able to rate their own quality of life.	This is not a factual inaccuracy. No change required.
Table 1, page 8, issue 3	Blood Phe concentration level is a poor measure of efficacy	This heading should be reworded to: Blood Phe concentration level as a measure of efficacy	Thank you. The heading has been changed to: Blood Phe concentration level as a measure of efficacy
Page 11, issue 3 heading	Issue 3 Blood Phe concentration level is a poor measure of efficacy	This heading should be reworded to: Blood Phe concentration level as a measure of efficacy	Thank you. The heading has been changed to: Blood Phe concentration level as a measure of efficacy

Technical engagement response form

Sapropterin for treating phenylketonuria [ID1475]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: **30 November 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**BioMarin International Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Limited relevance of the registry data to the decision problem	**NO**	The Phenylketonuria Demographics, Outcomes and Safety (PKUDOS) registry is a phase 4 voluntary observational study designed to provide up to 15 years of data from adult and maternal[1] subjects with Phenylketonuria (PKU) who are (or have been) treated with sapropterin. We maintain that the PKUDOS registry is a relevant dataset to use to support the assessment of long-term comparative benefit of sapropterin and as such is relevant for the decision problem. To be eligible to enter the PKUDOS registry, subjects must have a diagnosis of PKU and have previously received sapropterin, are currently receiving sapropterin, or intend to receive sapropterin therapy within 90 days of enrolment. The PKUDOS dataset is available with comparable data in a population of approximately 1922 patients with some patients' data available since 2008. The data has been published by Longo et al, 2015 (Molecular Genetics and Metabolism 114 (2015) 557–563) and numerous posters all of which are referenced in the company submission. PKU is a rare disease and as such it is difficult and impractical to collect long term data as an RCT from a small limited patient population. The ability to capture long- term evidence from the PKUDOS registry by the manufacturer (9 years in some cases) is testament to the commitment of the manufacturer to continue to expand the evidence base supporting PKU. On the one hand, the ERG has recognised the value of the registry data. The ERG states on page 32, table 6, last row that "The registries provide long-term data that are more representative of usual clinical practice than trial data. The ERG agrees that the registries are the most

[1] *D.K. Grange, R.E. Hillman, B.K. Burton, S. Yano, J. Vockley, C. Fong, J. Hunt, J.J. Mahoney, J.L. Cohen-Pfeffer, Sapropterin dihydrochloride use in pregnant women with phenylketonuria: an interim report of the PKU MOMS sub-registry, Mol. Genet. Metab. 112 (2014) 9–16.*

		appropriate data sources to inform conclusions relating to long-term efficacy and safety outcomes" but then paradoxically, the point is made that there is insufficient data available. **Given the patient numbers, the length of available data, and the comparable evidence, the dataset represents a substantial body of evidence for patients with PKU who have previously received sapropterin, are currently receiving sapropterin, or intend to receive sapropterin therapy within 90 days of enrolment.**
Key issue 2: Outcomes not addressed in the company submission	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 3: Blood phenylalanine concentration level as a measure of efficacy	**YES**	• **We would argue that blood Phe concentration level is a validated measure of efficacy and is the most widely used measure of efficacy in clinical practice.** We do not therefore accept the proposal of a composite endpoint (as suggested by the ERG). There is no scientific or clinical basis to support this composite endpoint nor is there clinical support for such an approach. • **In addition to blood Phe being the most widely used measure of efficacy in clinical practice, it is also the dominant measure widely referenced across literally hundreds of publications and referred to in national and international guidelines.** **Blood Phe is used across the globe as a target measure to reach to demonstrate improvement in disease outcomes.** o For example, the European guidelines recommend target blood Phe levels between 120 and 600 µmol/l for patients older than 12 years – clearly an endorsement of the importance of blood Phe. o The American College of Medical Genetics and Genomics (ACMG) guidelines in the US (Vockley et al, 2014) state a goal of maintaining blood phenylalanine in the range of 120–360 µmol/l, again recognition of the importance of using blood Phe as a measure to assess disease outcome. **The body of literature is substantial in relation to the use of blood Phe and indeed, it's impact on other outcomes.** o For example, ten Hoedt et al, 2011 highlights the findings from a randomised double-blind placebo-controlled trial showing that "high plasma Phe levels have a direct negative effect on both sustained attention and on mood in adult patients with PKU." o Waisbren et al, 2007 states in her systematic literature review and meta-analysis that "Blood phenylalanine (Phe) levels provide a practical and reliable method for the diagnosis and monitoring of metabolic status in patients with phenylketonuria (PKU)." o This is further reinforced by Lindegren 2012 in her Comparative Effectiveness review 2012 which states "Increasing Phe is clearly associated with decreased IQ, with a probability of IQ less than 85 exceeding the population probability (approximately 15 percent) at

		blood Phe over 400 µmol/L and levelling off at about 80 percent at 2,000µmol/L. This finding supports the typical target goal for blood Phe levels in individuals" o The reliance on the use of blood Phe can be found in publications regarding co-morbidities (Bilder, Rutsch), cognition (Lindegren, Romani, Jahja) and neuropsychological deficit (Bik-Multanowski) to name just a few. This list is by no means exhaustive. The clinical papers are extensive and too numerous to list here. • **Whilst emphasising the criticality of blood Phe, we do also recognise the importance of Phe intake which is why this was captured in our clinical trials (e.g. in the SPARK study); however they cannot be used as a composite endpoint as suggested by the ERG.** o The outcome of poor nutrition results in elevated Phe, which reinforces the use of blood Phe as the dominant outcome measure. o In addition, Phe intake influences blood Phe levels which therefore invalidates their use as a composite outcome measure (notwithstanding the lack of clinical rationale for such a measure). This was also recognised by the ERG which states on page 41 that "Clinical advice to the ERG is that a known confounder of sapropterin treatment on clinical outcomes is dietary adherence" o The majority of UK clinical opinion is also aligned to the manufacturer position. Maintenance of blood Phe levels in, for example, paediatrics is very clear that blood Phe levels below 360 micromol/L is linked to good neuropsychological outcomes. The EU guidelines have a threshold of 600 micromol/L for patients over the age of 12 years and maintaining Phe levels below 600 micromol/L will help prevent IQ loss, with implications on education, speed of processing and executive function. This will in turn also affect patients' quality of life, their ability to maintain relationships, engage in social interactions, operate effectively in a work environment etc. o The other huge advantage of Phe being the primary outcome measure is that it is readily measurable and consistent. All patients can measure it and can measure it frequently. • The evidence above had been presented during the review of the ERG report by the manufacturer. The clinical advice to the ERG must be considered and weighed in conjunction with the robust body of literature and clinical opinions of experts consulted by the manufacturer (including three specialist adult metabolic physicians (collectively experienced in the care of approximately 50% of the UK adult PKU population), two-specialist paediatric metabolic physicians (collectively experienced in the care of approximately 20% of the UK paediatric PKU population),and an advanced practitioner in metabolic disease and experienced metabolic dietitian) which express a view that blood Phe concentration level is a validated measure of efficacy.

Key issue 4: Limited randomised controlled trial data available	**NO**	There are significant challenges in undertaking long term RCTs in a rare disease such as PKU. Kuvan has been granted orphan designation on the basis of this rarity. However, notwithstanding this, the manufacturer has undertaken an extensive clinical development programme that includes studies across phases II, III and IV and undertaken across a range of patient groups (such as those below the age of 4 years, maternal PKU for example) and includes a range of patient relevant endpoints (such as reduction in Phe levels, Phe tolerance and neurological outcomes for example). **As such, the data exists despite the rarity of PKU and the challenges of undertaking long term RCTs in a rare disease.** The studies are captured below: **Phase II studies:** PKU-001 (screening study) **Phase III studies**: PKU-003 (Pivotal Phase III); PKU-004 (Ph III extension); PKU-006 (Diet study); PKU-016 (Neurocognitive study); PKU-008 (Phase III OLE from PKU004 and PKU006); SPARK (<4 age group); PKU-015 (young children) **Phase IV studies:** ENDURE; PKUDOS; PKUMOMS; KAMPER; KOGNITO The clinical trial and registry evidence thus capture strong evidence across a range of endpoints and populations. Given the backdrop of a rare disease, it is therefore incorrect and unfair to state there is limited evidence available. In regard to long term evidence, a paper by Longo et al, 2015[2] states that: "Sapropterin has been assessed in long-term clinical studies. Burton et al. reported the safety of sapropterin and maintenance of blood Phe reduction in a population with PKU (N = 111, age range: 4 to 50 years) **for up to 2.6 years** at doses of 5 to 20 mg/kg/day" Furthermore, the PKUDOS registry (reported by Longo et al, 2015) captures data for 5 years (as stated in the publication) and >9 years today.
Key issue 5: Unrealistic company model pathway	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 6: Implausible time and age	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

[2] *Molecular Genetics and Metabolism 114 (2015) 557–563*

invariant health state transition probabilities		
Key issue 7: Methods used to calculate transition probabilities	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 8: Annual rate that patients stop taking sapropterin (attrition rate)	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 9: Utility values used in the model are highly unlikely to reflect the experience of NHS patients with phenylketonuria	**NO**	The utility figures used in the model have been derived by a Time Trade Off (TTO) study undertaken in Sweden based on a sample size of over 1000 respondents from the general population. These figures were subsequently validated by UK KOLs and as such reflects the experience of NHS patients with phenylketonuria. In terms of methodology, the Swedish TTO study is based on a robust sample size of over 1000 respondents from the general population. The health state vignettes were developed based on a Delphi panel of PKU experts in the US, a targeted review of the literature and feedback from internal medical expertise from the manufacturer. The draft vignettes were then reviewed by three European health care professionals (HCPs) with experience of treating PKU patients. A revised version based on their comments were constructed after the review, presented, and discussed with the HCPs during a follow-up interview. After the follow-up interview, a final version of the vignettes was constructed (the TTO study report was provided in the CS). Uncontrolled PKU is characterised by symptoms that have a profound impact on daily living and patients' quality of life. Caregivers/ partners of these patients with sustained high level of blood Phe often report severe symptoms. These patients also suffer from what has been termed as hidden disabilities (Gentile 2010) and end up in a vicious downward spiral where patients need to resume therapy (such as the Phe-restricted diet) but are hindered from doing so due to neurological and neurocognitive impairment caused by elevated blood Phe levels. These levels continue to rise if sapropterin and / or the Phe-restricted diet is not initiated. If not initiated, the blood Phe levels rise further leading to

		worsening neurological and neurocognitive impairment. A degree of executive functioning ability is required for the planning and organising the highly restrictive Phe-free diet. The utility data was validated by UK clinical experts in July 2020 which involved three specialist adult metabolic physicians (collectively experienced in the care of approximately 50% of the UK adult PKU population), two-specialist paediatric metabolic physicians (collectively experienced in the care of approximately 20% of the UK paediatric PKU population), and an advanced practitioner in metabolic disease and experienced metabolic dietitian. This combined experience represents a significant portion of UK PKU clinical care and as such provides strong and confirmatory support for the applicability of these utility results from the TTO study to a UK perspective. Patients with PKU suffer from a range of neurological and neurocognitive impairments including but not limited to for example tremors, anxiety, depression, impaired executive function, and cognitive impairment. The manufacturer notes that utility values of 0.30 are observed in other disorders such as severe depression.[3] **As such, the manufacturer does not accept the statement that the utility figures are highly unlikely to reflect the experience of NHS patients with PKU. It remains unclear what scientific evidence was reviewed, or clinical rationale gained, or indeed systematic literature search was applied/undertaken by the ERG to then state these utility values do not reflect UK patients' experience. Greater clarity on this point would be appreciated.**
Key issue 10: Effect of sapropterin on protein-restricted diet	**YES**	The manufacturer does not accept the view of the ERG regarding protein supplement intake. The ERG report states: "It may, therefore, be the case that use of sapropterin in the UK may lead to no reduction in patient intake of protein supplements." UK clinical experts aim to meet protein requirements by a combination of natural protein and PKU phe free amino acid mixtures/protein substitutes. If phe tolerance increases, then a greater proportion of the daily protein requirements can be met by dietary natural protein. The requirement for protein substitutes is then reduced. **Clinical experts state that they would expect to see a 50% reduction in protein supplement use, and with good responders potentially going even further.** Indeed, this is one of the major incentivising factors for many children is that they are able to take less amino acid mixture which is perceived by a child, for example, as a far greater benefit than having to consume additional protein substitute. Protein substitutes tend not to be removed entirely to allow for some buffer for illness (even if it's only 10g) and to ensure patients do not forget the taste or technique associated with protein substitute intake should they need additional protein particularly in times of illness. A poster by Yilmaz et al, presented at ESPKU, reports the following:

[3] *Fitzgibbon et al, 2019; Can J Psychiatry,2019 Jul 1; ():706743719890167*

"8 centers from 8 countries reported the dietary management of 291 sapropterin responsive patients. More than half (n=163, 56.0%) of the sapropterin treated patients achieved WHO/FAO/UNU safe levels of protein intake. Of 291 sapropterin responsive patients, 82 (28%) did not require a L-AA supplements and in the remaining patients L-AA dosage reduced by 60%. Only 26% (n=75) patients used low protein milk, and 6% (n=33) low protein foods like bread. Only 30% were prescribed vitamin/mineral supplements."

It is clear that some patients were able to remove their Phe-free protein supplements entirely and others reduced their intake by 60%.

There are further publications that highlight the reduction in amino acid (AA) supplements as a result of sapropterin (Scala, 2015[4], Thiele, 2012[5], Singh, 2010[6], Burlina 2009[7]) which all highlight the reductions observed in AA mixture. The table below captures the range of studies that have explored the impact of sapropterin on phe-tolerance and the studies also highlight the reduction in protein supplement intake (see appendix 1 for fuller details).

				Phe tolerance		
Reference and centre	**n**	**Age**	**Mean Dose**	**Pre-sapropterin(g)**	**Post-sapropterin(g)**	**% increase**
Belanger 2007, Spain	7	0-18 years	12.5	32.5	104	220%
Burlina 2009, Italy	12	0-7 years	10	52.5	175	233%
Hennerman 2005, Switzerland	5	0-3 years	10	9.5	75	689%
Singh 2010, Atlanta	6	5-12 years	20	42.1	147	249%
Thiele 2012, Germany	8	5-16 years	20	62.9	213.1	239%
Vilaseca 2010, Spain	13	4-14 years	10		64.15	
Muntau 2002, Germany	5	4-14 years	8.9	18.7	61.4	228%
Muntau 2017, Germany	25	0-4 years	15			
Thiele 2015, Germany	8	6-17 years	14.5	49.3	220.8	348%
Tansek 2016, Slovenia	9	2-10 years	13.05	55	150	173%
Scala 2015, Italy	17	14 years	10	58.3	279.8	380%
Mean			13.09	42.31	149.03	307%

[4] *Scala et al. Orphanet Journal of Rare Diseases (2015) 10:14*
[5] *JIMD Rep. 2013;9:31-40*
[6] *J Inherit Metab Dis (2010) 33:689–695*
[7] *J Inherit Metab Dis (2009) 32:40–45*

Additional Issue: 11 The challenges in obtaining quality of life data in PKU patients and recognition of the evidence provided	**NO**	Capturing quality of life (QoL) data in PKU patients is extremely challenging due to the small patient population and range of disease states. Patients with PKU are less able to report their own quality of life due to reduced executive function and neurological and neurocognitive impairment which contributes significantly to hidden disabilities in these patient groups. This manifests as difficulties in planning, organizing and reduced processing speed for example. As a result, patients are less able to undertake a subjective evaluation of his or her own functioning and emotional well-being. These challenges are also observed in other diseases areas such as psychiatry. Reliability and validity of reporting QoL in psychiatric disorders has been questioned because of the cognitive impairments and distortions that characterize several mental health conditions.[8] As such, there are no quality of life tools successfully validated in PKU. Attempts have been made in the past to try and address this with, for example, the PKU-QoL tool (a PKU disease specific tool). However, this has been unsuccessful. Initial psychometric validation of the tool shows poor content and construct validity. There has been further psychometric evaluation of this instrument but no clinically important difference (CID) estimates have been derived. Furthermore, generic tools such as SF36 or EQ5D have been unsuccessful in capturing the impact of PKU. The limited data on the use of the SF-36 in PKU has shown the tool to be insensitive. Attempts to map PKU-QoL to SF36 have also been unsuccessful and has been shown to have poor correlation between PKU-QoL and SF36. It is clear therefore that capturing QoL in PKU presents significant challenges. The manufacturer has captured data from a Swedish time trade-off (TTO) study in over 1000 members of the general population and PKU patients across a range of clinically validated disease states. Whilst this was undertaken in Sweden, UK clinical experts have confirmed that it is transferable to the UK. The TTO study is based on a robust sample size of over 1000 respondents from the general population. The health state vignettes were developed based on a Delphi panel of PKU experts in the US, a targeted review of the literature and feedback from internal medical expertise from the manufacturer. The draft vignettes were then reviewed by three European health care professionals (HCPs) with experience of treating PKU patients. A revised version based on their comments were constructed after the review, presented, and discussed with the HCPs during a follow-up interview. After the follow-up interview, a final version of the vignettes was constructed (the TTO study report was provided in the CS). Uncontrolled PKU is characterised by symptoms that have a profound impact on daily living and patients' quality of life. Caregivers/ partners of these patients with sustained high level of blood Phe often report severe symptoms. These patients also suffer from what has been termed as hidden disabilities (Gentile 2010) and end up in a vicious downward spiral where patients need to resume therapy (such as the Phe-restricted diet) but are hindered from doing so due to neurological and neurocognitive impairment caused by elevated blood Phe levels. These levels continue to rise if sapropterin and / or the Phe-restricted diet is not initiated. If not initiated, the blood Phe levels rise further leading to worsening

[8] *Bullinger M, Quitmann J. Quality of life as patient-reported outcomes: principles of assessment. Dialogues in clinical neuroscience 2014;16(2):137*

		neurological and neurocognitive impairment. A degree of executive functioning ability is required for the planning and organising the highly restrictive Phe-free diet. The utility data was validated by UK clinical experts in July 2020 which involved three specialist adult metabolic physicians (collectively experienced in the care of approximately 50% of the UK adult PKU population), two-specialist paediatric metabolic physicians (collectively experienced in the care of approximately 20% of the UK paediatric PKU population),and an advanced practitioner in metabolic disease and experienced metabolic dietitian. This combined experience represents a significant portion of UK PKU clinical care and as such provides strong and confirmatory support for the applicability of these utility results from the TTO study to a UK perspective. It remains unclear what scientific evidence was reviewed, or clinical rationale gained, or indeed systematic literature search was applied/undertaken by the ERG to state that patients with low utility values would not modify their diet and/or start or return to take sapropterin. Patients with this level of disease severity have significant cognitive and executive function impairment. It is not possible for them to rationalise the cause of their 'fogginess' and impaired quality of life, and to then make an informed judgement about the best course of action to take that will best address the source of their impairment.
Additional Issue: 12 Mean dose recommendation from experts deemed as not robust	**NO**	The dosages come directly from NHS England's Clinical experts sitting on the Clinical Reference Group (CRG) and published in NHS England's Integrated impact Assessment report. The manufacturer has merely cited the view of NHS England's clinical experts. With regard to the second statement from the ERG which states "This suggests that the values used in the company model may be underestimates of real-world dosages" the manufacturer would highlight that the dosages observed in KAMPER reflect the countries that are part of the registry which consist of 8 countries including Austria, France, Germany, Italy, the Netherlands, Slovakia, Spain, and Sweden. The UK is not part of this registry.
Additional Issue: 13 Long term benefits of sapropterin treatment have not been accepted	**YES**	There are longer term benefits of sapropterin that continue even if the treatment is stopped. Treatment with sapropterin lays down foundations that prevent future complications and as such the benefits do accrue over time. For example, treatment with sapropterin will help children achieve better metabolic control and as such there will be benefits that are maintained and carried forward into adult life even if treatment is subsequently stopped. Elevated blood Phe leads to neurological and neurocognitive disorders. It can also lead to neurotransmitter imbalance and structural deformities of the brain. If left untreated, PKU can result in severe intellectual impairment

		It is therefore clear that by preventing these neurological and neurocognitive disorders one can prevent intellectual impairment, IQ loss and intellectual disability that could inhibit educational attainment in school and university. This can then impact work prospects and other life chances, job opportunities. Clinical experts state that brain development continues into mid-20s for many individuals and brain remodelling occurs throughout life. From a neurotransmitter imbalance perspective, the role of dopamine changes over time and insufficient dopamine will have a different impact at a young age compared to a young adult for example. With elevated blood Phe levels, this can lead to a reduction in other neurotransmitters including dopamine. The pre-frontal cortex develops in later life which is dependent on dopamine hence a lack of dopamine at 5 years of age is vastly different to lack of dopamine at 15 years or 20 years of age for example. Dopamine has a fundamental role to play in critical thinking, decision making, higher orders of thinking for example which rely on dopamine. As the pre-frontal cortex develops as a young adult, the ability to undertake more complex and higher order thing increases. A lack of dopamine at this stage (due to elevated blood Phe) can then lead to executive function impairment, reduced speed of processing, poorer working memory etc. This could then manifest as poorer exam results for example, poor decision making in the workplace, inability to retain information thus limiting one's true potential and reduced lifetime earning capability. Given the risk of intellectual disability associated with elevated blood Phe levels, the company economic model has been refined into a decision tree model that better captures this impact. Please see appendix 2 for a report on this revised model structure and justification

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	**Company's base case before technical engagement**	**Change(s) made in response to technical engagement**	**Impact on the company's base-case ICER**
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
			[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Subgroups** / **Incremental QALY gain** 0-3 years-Mild [redacted] Moderate [redacted] Severe [redacted] 0-17 years-Mild [redacted] Moderate [redacted] Severe [redacted] ≥18 years-Mild [redacted] Moderate [redacted] Severe [redacted] Woman of child-bearing age-Mild [redacted] Moderate [redacted] Severe [redacted]	**Subgroups** / **Incremental cost gain** 0-3 years-Mild [redacted] Moderate [redacted] Severe [redacted] 0-17 years-Mild [redacted] Moderate [redacted] Severe [redacted] ≥18 years-Mild [redacted] Moderate [redacted] Severe [redacted] Woman of child-bearing age-Mild [redacted] Moderate [redacted] Severe [redacted]	**Subgroups** / **ICER** 0-3 years-Mild [redacted] Moderate [redacted] Severe [redacted] 0-17 years-Mild [redacted] Moderate [redacted] Severe [redacted] ≥18 years-Mild [redacted] Moderate [redacted] Severe [redacted] Woman of child-bearing age-Mild [redacted] Moderate [redacted] Severe [redacted]

Appendix 1

Review of evidence - impact of sapropterin on phe-tolerance and low protein foods

				Phe tolerance		
Reference and centre	**n**	**Age**	**Mean Dose**	**Pre-sapropterin(g)**	**Post-sapropterin(g)**	**% increase**
Belanger 2007, Spain	7	0-18 years	12.5	32.5	104	220%
Burlina 2009, Italy	12	0-7 years	10	52.5	175	233%
Hennerman 2005, Switzerland	5	0-3 years	10	9.5	75	689%
Singh 2010, Atlanta	6	5-12 years	20	42.1	147	249%
Thiele 2012, Germany	8	5-16 years	20	62.9	213.1	239%
Vilaseca 2010, Spain	13	4-14 years	10		64.15	
Muntau 2002, Germany	5	4-14 years	8.9	18.7	61.4	228%
Muntau 2017, Germany	25	0-4 years	15	50.1	80.6	61%
Thiele 2015, Germany	8	6-17 years	14.5	49.3	220.8	348%
Tansek 2016, Slovenia	9	2-10 years	13.05	55	150	173%
Scala 2015, Italy	17	14 years	10	58.3	279.8	380%
Mean			13.09	423.09	142.8	282%

Reference & Name of centre	Number of the patients on BH4	Age of patients at the beginning of BH4 treatment	Duration of BH4 treatment	Dose of BH4 and dosing time	Phe tolerance		Use and dose of protein substitute & low protein foods +notes	Phe levels	
					pre BH4 (mg/kg/d)	*post BH4 (mg/kg/d)*		*Before BH4 (µm/L)*	*With BH4 (µm/L)*
Belanger,2007, Spain	7	8 months-18 years	5-18 months	5-20 mg/kg/d 1-3 doses	20-45	75-133	?	200-520	145-530
Burlina, 2009, Italy	12	2-16 years	6 months-7 years	10 mg/kg/d Twice a day	350-700 mg/d	800-2700 mg/d	7 of them free diet 5 of them combined (low phe-100 mg/kg-no amino acid mixture)	433-12115	Drop below defined threshold levels
Hennermann, 2005, Switzerland	5	0,5-42 months	5.5-29 months	10 mg/kg Twice a day	?-19	30-120		77-208	190-314
Singh, 2010, Atlanta	6	5-12 yrs	24 months	20 mg/kg/d	421±128 mg/d	1470±455 mg/d	3 out of 6 no longer required any medical food No patient required SLPF	120-360	120-360
Thiele, 2012, Germany	8	5-16 yrs (11.13±4.4)	<3 months	20 mg/kg/d	629±476 mg/d	2131±1084 mg/d	Decreased consumption of SLPF Increased consumption of high protein foods. 6 out of 8 patients no longer take AAM, remaining 2 of them reduced	283±145	304±136
Ziesh, 2012, Germany	*Looks like the same results and method with Thiele, 2014.*								
Vilaseca, 2010, Spain	13		1-6 yrs	5-15 mg/kg/d	No inf	34.8-93.5			
Muntau, 2002, Germany*	5	4-14 yrs	166-263 days	7.1-10.7 mg/kg/d	18.7±8.6 mg/kg	61.4±27.9	*This study consists of 2 different part. I just took long term results of BH4 therapy which was briefly mentioned.	366±120	378±173
Muntau, 2017, Germany/ SPARK Study	25	<4 yrs	26 week	10-20 mg/kg/d	Mean change: 36.9±27.3 mg/kg/d		Significantly improved dietary phe tolerance		300.1±115.2

Thiele, 2015, Germany	8	6.0-16.6 yrs (10.5±3.8)	3 yrs	10-19 mg/kg	493.2±161.8	After 3 months: 2208.9 ±1336.4 After 2 yrs: 2021.9 ± 897.4	*4 out of 8 patients entirely stopped AAM. Remaining 4 reduced AAM dosage *Markedly increased intake of normal, protein rich food, primarily bread, potatoes, pasta and rice during short-term follow-up over a three month period *The mean consumption of special low protein products significantly declined further in long-term follow up. No changes detected regarding the consumption of edible fats as well as sweets and snacks	262.2±129.4	1st yr: 337.1±129.6 2nd yr: 382.7±148.1 3rd yr: 371.7 ±119.8
Tansek, 2016, Slovenia	9	2-10 yrs	Min 2 yrs	15.5 (starting dose) 10.6 (after 2 yrs follow up)	400-700 mg	1000-2000 mg	No significant change on blood Se, Zn and B12 levels. Improves quality of life. Cost effective.	191-302	135-285
Scala, 2015, Italy	17	14.4±4.5	60-84 month*1 patient discontinued after 12 months	10 mg/kg/d	583±443	2798±1568	9 out of 17 patients don't need AA and vitamin supplements. 2 of the patients need them only small amounts.	468 (204-570)	432 (210-600)

Ref & Name of centre	**How many patients on BH4**	**Age of patients at the beginning of BH4 treatment**	**Duration of BH4 treatment**	**Dose of BH4 (mg/kg/d) and dosing time**	**Phe tolerance**		**Use and dose of protein substitute & low protein foods**	**Phe levels**		**Results**
					pre BH4 (mg/kg/d)	*post BH4 (mg/kg/d)*		*Before BH4 (µm/L)*	*With BH4 (µm/L)*	
Belanger 2007 Spain, Hospital Ramon y Cajal,	7	18 yrs	18 months	10-2 doses	20	100 (free)		520	530	Oral BH4 is well tolerated and no side effects Normal weight gain and growth of the patients Normal psychomotor Development Great improvement in the quality of life
		12 yrs	18 months	5-1 doses	44	111 (free)		420	470	
		12 yrs	5 months	10-2 doses	44	120 (free)		300	245	
		8 yrs	18 months	15-2 doses	20	133 (free)		330	230	
		3 yrs	10 months	10-2 doses	30	75		300	280	
		8 months	5 months	20-3 doses	45	133		200	300	
		8 months	5 months	15-3 doses	45	90		200	145	

Ref & Name of centre	How many patients on BH4	Age of patients at the beginning of BH4 treatment	Duration of BH4 treatment	Dose of BH4 (mg/kg/d) and dosing time	Phe tolerance		Low phe diet	Phe levels		Results
					pre BH4 (mg/d)	*post BH4 (mg/d)*		*Before BH4 (µm/L)*	*With BH4 (µm/L)*	
Burlina, 2010 University Childrens Hospital Padua, Italy	12	3 yrs	3 yrs	10 mg/kg/d Twice a day	400	1000	Combined*	561	Phe drop below defined threshold levels (e.g. 360 mmol/L during the first 12 years of life and 600 mmol/L up to 17 years	-BH4 therapy allowed the introduction of high-protein foods such as meat -Their psychomotor development was normal and it has been adequate for each patient`s age -All patients and their families indicate great improvement in their quality of life.
		3 yrs	6 yrs		650	2700	No	502		
		2 yrs	3 yrs		350	1400	Combined*	564		
		10 yrs	2 yrs		600	2000	No	490		
		11 yrs	3 yrs		350	1400	No	564		
		2 yrs	6 mo		370	1600	No	433		
		3 yrs	3 yrs		400	1000	Combined*	605		
		2 yrs	2 yrs		550	800	Combined*	1215		
		9 yrs	7 yrs		700	2000	No	684		
		2 yrs	5 yrs		500	1200	No	649		
		16 yrs	4 yrs		500	1400	No	961		
		4 yrs	4 yrs		350	1200	Combined*	716		

- *Low-Phe (100 mg/kg, without amino acid mixture) and BH4 (10 mg/kg) treatment

Ref & Name of centre	How many patients on BH4	Age of patients at the beginning of BH4 treatment	Duration of BH4 treatment	Dose of BH4 (mg/kg/d) and dosing time	Phe tolerance		Use and dose of protein substitute & low protein foods	Phe levels		Results
					pre BH4 (mg/kg/d)	*on BH4 (mg/kg/d)*		*Before BH4 (µm/L)*	*With BH4 (µm/L)*	
Hennermann, 2005 Switzerland	5	18 months	24 months	10mg/kg bw twice a day	19	35		143 (18–557) n= 65	299** (61–1065) n=78	-No side effects during BH4 short- and long-term treatment - Growth, length, and head circumference were within the percentiles for age and sex. - Normal mental and motor development -Increase in quality of life
		1.2 months	29 months		19	80		77 (30–157) *n*=6	314 (36–726) n=52	
		0.5 months	8 months		-*	40		-*	293 (30–720) n=49	
		0.5 months	5.5 months		-*	30		-*	190 (30–490) *n*=21	
		42 months	24 months		18	120		208 (18–775) n=75	249** (54–799) *n*=51	

*In patients 3 and 4, BH4 treatment was started already at the age of 2 weeks. Therefore data on treatment before BH4-treatment do not exist.
** The slight increase of median phe serum concentrations on long-term BH4 treatment is associated with commencement of kindergarten and subsequent recurrent febrile infections.

Ref & Name of centre	How many patients on BH4	Age of patients at the beginning of BH4 treatment	Duration of BH4 treatment	Dose of BH4 (mg/kg/d) and dosing time	Phe tolerance		Use and dose of protein substitute & low protein foods	Phe levels		Results
					pre BH4 (mg/d)	*post BH4 (mg/d)*		*Before BH4 (µm/L)*	*With BH4 (µm/L)*	
Singh, 2010 Atlanta	6	5-12 yrs	24 months	20 mg/kg/d	421±128	1470±455	-3 of the 6 patients no longer required any medical food# in the remaining medical food prescribed but less than baseline -No patient required special low protein food	120-360	120-360	Dramatic increase in phenylalanine tolerance and the ability to consume intact protein Improved quality of life
Results	-By the third month of BH4 therapy, three patients were consuming a reduced proportion of their original medical food prescription (50%, 20%, and 38%, respectively). The other three patients no longer required medical food. -Total protein intake, the sum of intact protein and medical food, remained at approximately 1.0±0.08 g/kg per day (43.7±4.2 g/day) throughout the 24 months of the study. -Consumption of intact protein over 24 months increased significantly (p=0.0006), with a corresponding significant decline in medical-food intake (p=0.0002). -Mean dietary phenylalanine prescription (mg/kg per day) increased 3.3-fold within the 24-month study period, whereas patients' blood phenylalanine concentrations remained between 120 and 360 µmol/L -By month 3, the phenylalanine prescription had increased from a baseline average of 11.9±4.1 mg/kg to 39.9±11.5 mg/kg (p=0.001), and phenylalanine intake from food increased from 15.9±5.3 mg/kg to 34.2±13.8 mg/kg (p=0.007). -There were no significant changes in mean plasma tyrosine concentration over the 2-year study period -Serum albumin and total serum protein were within reference range -Hemoglobin and hematocrit concentrations began to improve after 9 months of BH4 treatment (p<0.001), stabilizing after 12 months -Total serum cholesterol increased slightly during the first 6 months on BH4, from 131±9.9 to 138±15.0 mg, without reaching statistical significance -Mean height-for-age Z score of study participants increased significantly over the 24-month follow-up									

Ref & Name of centre	How many patients on BH4	Age of patients at the beginning of BH4 treatment	Duration of BH4 treatment	Dose of BH4 (mg/kg/d) and dosing time	Phe tolerance		Phe levels	
					pre BH4 (mg/d)	*post BH4 (mg/d)*	*Before BH4 (µm/L)*	*With BH4 (µm/L)*
Thiele 2014 Germany	8	5-16 yrs	<3 months	20 mg/kg/d	629±476	2131±1084	283±145	304±136
Results	-Decreased consumption of special low protein products and fruit while increased consumption of high protein foods such as processed meat, milk and dairy products. - Intake of vitamin D (P ¼ 0.016), iron (P ¼ 0.002), calcium (P ¼ 0.017), iodine (P ¼ 0.005) and zinc (p=0.046) significantly declined during BH4 treatment while no differences in energy and macronutrient supply occurred. - During follow-up six of the eight BH4- sensitive patients could end any AAM supply. In the other two BH4-sensitive patients the dosage could be reduced. - Under classical dietary treatment, the BH4- sensitive PKU patients showed a higher mean intake of vitamin D, iron, calcium and iodine, but a lower mean intake of vitamin C and vitamin B12. Under BH4 treatment the supply of almost all micronutrients proved to be markedly lower compared to the healthy German children.							

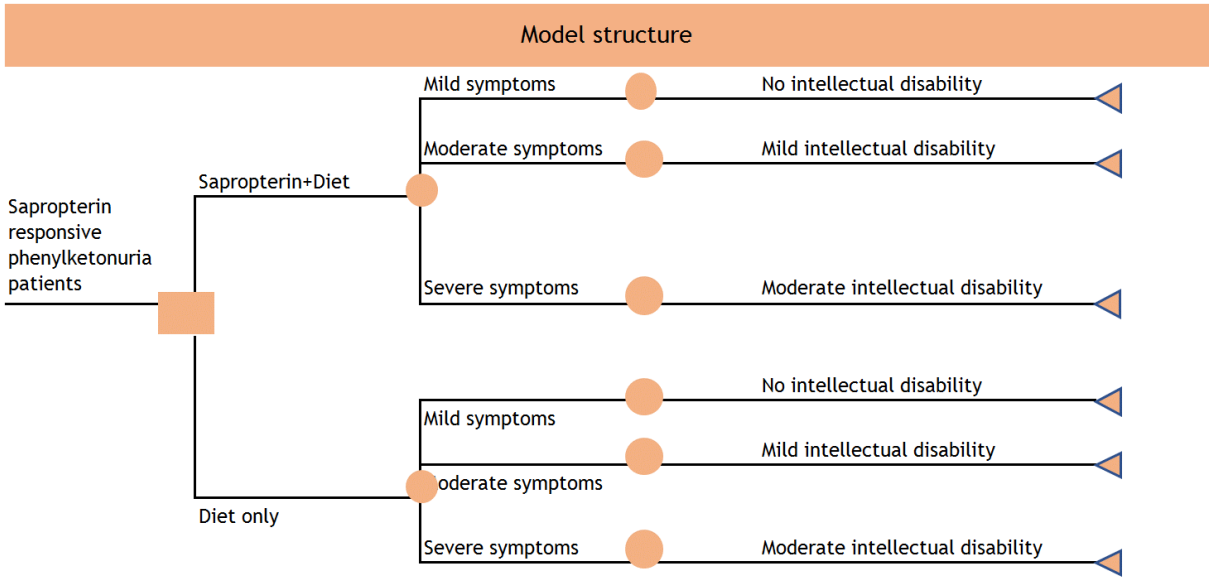
****Ziesch,2012 is looks like the same.

Ref & Name of centre	How many patients on BH4	Age of patients at the beginning of BH4 treatment	Duration of BH4 treatment	Dose of BH4 (mg/kg/d) and dosing time	Phe tolerance	
					pre BH4 (mg/kg/d)	*post BH4 (mg/kg/d)*
Vilaseca, 2010 Spain	13		5.7	5-15	No information	59.7
			5.7			53.5
			5.6			43.9
			5.8			39.3
			5.3			34.8
			6.0			35.4
			5.6			81.2
			5.6			49.1
			5.8			84.1
			6.0			93.5
			2.2			85.0
			1.0			80.2
			1.0			71.1
Results	*LCPUFA status is within the reference values in PKU patients treated with BH4. This translates to a further advantage of BH4 therapy. *Phe tolerance significantly increased after BH4 therapy (Wilcoxon test; p= 0.004; data in baseline conditions not shown).					

Appendix 2 – technical report to support revised company decision tree model

1. **Objective:** What is the incremental cost-effectiveness ratio (ICER) of 'sapropterin+diet' against 'diet only' for different age groups, namely 0-3 years, 0-17 years, 18+ years and 'woman of child bearing age'

2. **Model structure:** A one year decision tree was developed following discussion with NICE and the ERG. Structure of the model is shown below:



Phenylketonuria (PKU) is one of the several rare autosomal recessive condition that is diagnosed at birth through new-born screening programme (heel prick test). As per the SmPC (summary of product characteristics https://www.ema.europa.eu/en/documents/product-information/kuvan-epar-product-information_en.pdf accessed on 01/12/2020), a child born with PKU, after a four week response testing, sapropterin responsive PKU patients are put on treatment of sapropterin. Sapropterin non-responsive patents are put on 'diet only' (standard of care).

3. **Model health states**

Based on blood phenylalanine (Phe) reduction, Phe tolerance and symptoms level achieved, patients are categorised to be in either mild, moderate or severe health states (Okhuoya et al. 2020). Definition of these health states are detailed below:

Mild health state

European PKU guidelines recommend blood Phe between 120-360 µmol/L for children up to 12 years of age and maternal PKUs. The guideline recommends blood Phe between 120-600 µmol/L for >12 years of age (Van Wegberg et al. 2017). The mild symptomatic PKU health state have blood Phe between 600-900 µmol/L. The utility for this health state was derived from a general population in Sweden using TTO methodology (Swedish health utility report 2020 in original submission). The vignette for this state was defined as

You experience the following symptoms associated with PKU:

Emotional symptoms

- You experience **mild** feelings of unhappiness, anxiety, moodiness, irritability and worthlessness.

Cognitive symptoms

- You **occasionally** experience mild concentration issues, slowness of thinking and Forgetfulness.
- This **mildly** affects performance at work/school/home and ability to complete complex tasks (e.g. less productive while at work).

Physical symptoms

- You **occasionally** experience **mild** headaches, **mild** nausea and trembling hands.

In order to control your disease, you need to follow a **restricted, low-protein diet** as it was described in the first health state. [A question mark was included that led to a pop-up box with the diet description].

Moderate health state

The moderate symptomatic PKU health state have blood Phe between 900-1,200 µmol/L. The utility for this health state was derived from a general population in Sweden using TTO methodology (Swedish health utility report 2020 in original submission). The vignette for this state was defined as

You experience the following symptoms associated with PKU:

Emotional symptoms

- You experience **moderate** feelings of unhappiness, anxiety, moodiness, irritability and worthlessness.

Cognitive symptoms

- You **often** experience, **moderate** concentration issues, slowness of thinking and Forgetfulness.
- This **moderately** affects performance at work/school/home and ability to complete complex tasks (e.g. days missed of work).

Physical symptoms

- You **often** experience **moderate** headaches, **moderate** nausea and trembling hands.

In order to control your disease, you need to follow a **restricted, low-protein diet** as it was described in the first health state. [A question mark was included that led to a pop-up box with the diet description].

Severe health state

The moderate symptomatic PKU health state have blood Phe between 900-1,200 µmol/L. The utility for this health state was derived from a general population in Sweden using TTO methodology (Swedish health utility report 2020 in original submission). The vignette for this state was defined as

You experience the following symptoms associated with PKU:

Emotional symptoms

- You experience **severe** feelings of unhappiness, anxiety, moodiness, irritability and worthlessness.

Cognitive symptoms

- You **often** experience **severe** concentration issues, slowness of thinking and forgetfulness.
- This **severely** affects performance at work/school/home and ability to complete complex tasks (e.g. days missed of work and likelihood of unemployment).

Physical symptoms

- You **often** experience **severe** headaches, **severe** nausea and trembling hands.

In order to control your disease, you need to follow a **restricted, low-protein diet** as it was described in the first health state. [A question mark was included that led to a pop-up box with the diet description].

Patients with mild symptoms have lower risk of developing downstream neurological, psychiatric and neuro-cognitive complications. Whereas, moderate and severely symptomatic patients are at relatively higher risk of developing downstream neurological, psychiatric and neuro-cognitive complications. If left untreated, PKU can lead to irreversible intellectual disability (approximately 98% of individuals with untreated PKU fall within the range of global intellectual disability (Christ et al. 2010), as well as microcephaly, motor deficits, eczematous rash, autism, seizures, developmental problems, aberrant behaviour and psychiatric symptoms (Van Wegberg et al. 2017).

4. Key features of the cost-effectiveness model

The key features are summarised in the table below:

Current appraisal	**Chosen values**	**Justification**
Model structure	Decision tree model	The model structure was developed following discussion with NICE and ERG on 12/11/2020. It captures the impact of distinct resource use and patient HRQoL associated with each health state and allows for a cost-utility analysis over one year for a range of age groups. It incorporates a number of consequences of uncontrolled disease that were not accounted for in the ERG model.
Time horizon	One year	Initial manufacturer submission had life-time horizon. Based on the discussion with NICE and ERG on 12/11/2020, this alternative decision tree model has one year time horizon for a range of age groups.
Source of utilities	Elicitation of values from a sample of the overall Swedish population using a TTO exercise	Sample size and scope of work as well as a paucity of published information meant that both the manufacturer and ERG concluded that this was the best available source.
Source of costs	NHS reference costs, BNF, MacDonald	Consistent with the NICE reference case.
Treatment-related adverse events (TRAE)	Not included	The rate of adverse reactions in the clinical development programme for sapropterin was low (see Section B.2.10 of the original company submission). Therefore, adverse events are not a key driver of cost-effectiveness.
Mortality	Not included	Not enough evidence to support the hypothesis that there is an impact of the underlying condition on overall survival.

Abbreviations: BNF: British National Formulary; HRQoL: health-related quality-of-life; NICE: National Institute for Health and Care Excellence; TRAE: treatment-related adverse events.

Model also has checkboxes for selection of PAS (patient access scheme) price of sapropterin, intellectual disability and extra utility for woman of ‘child-bearing age’. The base case is based on PAS and intellectual disability. Scenario analysis is presented with including extra utility for woman of ‘child-bearing age’.

5. Model inputs

A separate model input worksheet captures all the key inputs to the model. These model inputs are presented in the table below:

Parameters	User input	Default value	Reference
Sapropterin Price per 100mg tablet	£19.91	£19.91	British National Formulary. 2019. £597.22 for 30 tablets. Available from: https://bnf.nice.org.uk/medicinal-forms/sapropterin-dihydrochloride.html
PAS	[redacted]	[redacted]	
Price after PAS	[redacted]	[redacted]	
Number of days in a year	365.25	365.25	
Sapropterin Dose (mg/kg) for 0-12 years	10	10	Integrated Impact Assessment Report for Clinical Commissioning Policies, Policy reference number: 1840, Title: Sapropterin for phenylketonuria all ages, interim pending NICE guidance, Proposal for routine commissioning (ref A3.1)
Sapropterin Dose (mg/kg) for 13-17 years	10	10	Integrated Impact Assessment Report for Clinical Commissioning Policies, Policy reference number: 1840, Title: Sapropterin for phenylketonuria all ages, interim pending NICE guidance, Proposal for routine commissioning (ref A3.1)
Sapropterin Dose (mg/kg) for 18+ years	12.5	12.5	Integrated Impact Assessment Report for Clinical Commissioning Policies, Policy reference number: 1840, Title: Sapropterin for phenylketonuria all ages, interim pending NICE guidance, Proposal for routine commissioning (ref A3.1)
Cost of diet (£) for 0-3 years	[redacted]	[redacted]	Anita MacDonald. Protein supplement based the average cost of 3 brands
Cost of diet (£) for 4-17 years	[redacted]	[redacted]	Anita MacDonald. Protein supplement based the average cost of 3 brands
Cost of diet (£) for ≥18 years	[redacted]	[redacted]	Anita MacDonald. Protein supplement based the average cost of 3 brands
Mean reduction in diet cost for patient on sapropterin	71.20%	71.20%	Yilmaz et al. 2018
Baseline utilities- no symptoms, no diet restrictions			
0-17 Years	0.829	0.829	Swedish health utility study in general population 2020
18+	0.816	0.816	Swedish health utility study in general population 2020
Woman of child-bearing age	0.817	0.817	Swedish health utility study in general population 2020
Health state utility values for intellectual disability (lower IQ and its impact over lifetime)			
Mild intellectual disability	0.787	0.787	Phe difference above the threshold (van Wegberg et al. 2017); IQ translation (based on Waisbren et. Al 2007, mid-value of 1.9 to 4.1=3); IQ reduction compared to normative (based on van Vliet et al. 2018, 102); Utility values from

			http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/weight0.aspx accessed in December 2020
Moderate intellectual disability	0.578	0.578	Phe difference above the threshold (van Wegberg et al. 2017); IQ translation (based on Waisbren et. Al 2007, mid-value of 1.9 to 4.1=3); IQ reduction compared to normative (based on van Vliet et al. 2018, 102); Utility values from http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/weight0.aspx accessed in December 2020
Health state utility decrement	0		
0-17 years with mild symptoms	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
0-17 years with moderate symptoms	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
0-17 years with severe symptoms	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
≥18 years with mild symptoms	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
≥18 years with moderate symptoms	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
≥18 years with severe symptoms	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
0-17 years on diet compared to sapropterin	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
≥18 years on diet compared to sapropterin	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
% of patients symptom-free on sapropterin compared to diet	0		Swedish health utility study in general population 2020, ERG Model 2020
0-17 years	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
≥18 years	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
Utility gain associated with sapropterin treatment in women of child bearing age	[redacted]	[redacted]	Maternal PKU syndrome refers to the teratogenic effects of elevated maternal blood Phe on the developing foetus. These high blood Phe levels during pregnancy can lead to growth retardation, microcephaly, intellectual disabilities and birth defects, including congenital heart defects (CHD) (Van Wegberg et al. 2017). The estimated utility gain is based on sapropterin as a treatment option that can bring to mothers and the effect on child over the lifetime

The disease pathophysiology and its manifestations in different subgroups, i.e. children of 0-17 years, adults of 18+ years and woman of 'child-bearing age' are summarised below:

Elevated Phe in children and adolescents

Children 0-11 years old

Blood Phe concentration during childhood is the major determinant of cognitive outcome. If blood Phe levels remain uncontrolled, children with PKU can suffer severe mental retardation and loss of IQ, microcephaly, seizures and tremors, psychological, behavioural and social problems, stunted growth, delayed speech and difficulties with executive thought processes (Kaufman et al. 1989, Huttenlocher et al. 2000).

Children 12-17 years old

Early dietary management to control blood Phe levels is effective in the prevention of severe and irreversible damage to the grey matter of the brain and the resulting mental disabilities caused by high Phe concentrations during brain development in childhood. However, high Phe concentrations in adolescence and adulthood can lead to a number of reversible complications. Good Phe control during childhood thus allows for patients with PKU to have normal/near normal intellectual ability but, with progressive loss of Phe control, patients develop the following complications (Blau et al. 2010, Enns et al. 2010):

- Neurocognitive deficits, largely related to poor executive function (EF), including attention deficits, reduced inhibitory control and reduced speed of response over multiple domains (Bilder et al. 2016, Romani e al. 2017)
- Neuropsychiatric symptoms, including high levels of depression, anxiety and inattention (Bilder et al. 2016, Bilder et al. 2017)
- Psychosocial impairments, including lack of autonomy, social maturity deficits and difficulties forming relationships (Enns et al. 2010, Gentile et al. 2010).

Elevated Phe in adults

The effect of high blood Phe is also detrimental to adults; higher Phe is associated with an increased prevalence of neuropsychiatric symptoms and EF deficits (Bilder et al. 2016). European PKU guidelines state that deficits in EF, attention problems, decreased verbal memory and social and emotional difficulties are observed in adults with PKU, even when treated early (Van Spronsen et al. 2017).

EF refers to higher order cognitive abilities, which encompasses planning, organisation, cognitive flexibility, inhibitory control and working memory. These are considered as EF because they require the integration and processing of information across a range of cognitive domains, sensory modalities and response modalities (Christ et al. 2010).

Poor EF may also impact treatment adherence and, therefore, lead to psychosocial deficits that

are not always visible. These psychosocial aspects include social difficulties and psychosocial problems, such as forming interpersonal relationships, achieving autonomy, attaining educational goals, maintaining steady employment and having healthy emotional development. The key to reducing the risks associated with PKU is improved metabolic control throughout life (Gentile et al. 2010).

The neurological complications observed due to elevated Phe are well documented (Blau et al. 2010, Van Spronsen et al. 2017). Untreated PKU can lead to irreversible intellectual disability (approximately 98% of individuals with untreated PKU fall in the range of global intellectual disability (Christ et al. 2010) as well as microcephaly, motor deficits, eczematous rash, autism, seizures, developmental problems, aberrant behaviour and psychiatric symptoms (Van Wegberg et al. 2017). Furthermore, neuropsychiatric symptoms such as depression, anxiety and attention deficit disorder are higher in PKU patients than the general population (Bilder et al. 2017).

Elevated Phe in women of childbearing age

Maternal PKU syndrome refers to the teratogenic effects of elevated maternal blood Phe on the developing foetus. These high blood Phe levels during pregnancy can lead to growth retardation, microcephaly, intellectual disabilities and birth defects, including congenital heart defects (CHD) (Van Wegberg et al. 2017).

Signs of maternal PKU may be evident at birth, but other signs can be delayed and only observed over the course of an individual's growth and development.

Tight Phe control before conception and continually throughout pregnancy is therefore critically important. Cognitive outcomes in children whose mothers had good Phe control pre-conception are better than in children whose mothers began or resumed dietary Phe restriction after conception (Grange et al. 2014).

The European PKU guidelines (Van Wegberg et al. 2017) recommend the following for maternal PKU:

- Women with untreated Phe level >360 micromol/L must be treated to bring Phe level to 120-360 micromol/L;
- Blood Phe levels before and during pregnancy should be maintained at 120-360 micromol/L;
- Significant effort should be taken to avoid any unplanned pregnancies in PKU women; and
- Education and effective contraceptive methods are key elements.

6. Results

ICER for the base case, based on ERG model, including PAS and intellectual disability is presented in the table below:

Subgroups	Mean sapropterin dosage(mg/kg/day)	Mean sapropterin cost per day	Reduction in daily PRD cost with sapropterin	Incremental daily cost with sapropterin	Annual incremental cost with sapropterin	Symptom severity level	QALY incremental gain with sapropterin	ICER per QALY gained with sapropterin
0-3 years	10mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]
0-17 years	10mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]
≥18 years	12.5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]
Woman of child-bearing age	12.5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]

Scenario analysis: Scenario analysis including extra utility gain that sapropterin will bring to woman of 'child-bearing age' is presented in the table below:

Subgroups	Mean sapropterin dosage(mg/kg/day)	Mean sapropterin cost per day	Reduction in daily PRD cost with sapropterin	Incremental daily cost with sapropterin	Annual incremental cost with sapropterin	Symptom severity level	QALY incremental gain with sapropterin	ICER per QALY gained with sapropterin
0-3 years	10mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]
0-17 years	10mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]
≥18 years	12.5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]
Woman of child-bearing age	12.5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]

7. Summary and conclusions

Treatment of children and adolescents with sapropterin plus diet compared with diet alone is a cost-effective use of NHS resources based on this one-year decision tree model.

Treatment with sapropterin in the 0-3 age group is dominant (more effective and less costly) at PAS price across all disease severity levels, while treatment with sapropterin in the 0-17 age group has an ICER of less than £20,000 per QALY across all disease severity levels (i.e. it is more effective and associated with a modest incremental cost). The use of sapropterin in adults is associated with higher ICERs, however, there may be groups such as women of childbearing age that accrue additional benefits from sapropterin treatment where this ICER is substantially lowered.

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Sapropterin for treating phenylketonuria [ID1475]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Wednesday 16 December 2020**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with phenylketonuria and current treatment options	
About you	
1. Your name	**Anita MacDonald**
2. Name of organisation	**NSPKU /British Dietetic Association**
3. Job title or position	**Consultant Dietitian in Inherited Metabolic Disorders and Honorary Professor in Dietetics**
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? **x**☐ a specialist in the clinical evidence base for this condition or technology? (researcher) **X**☐ other (please specify): Volunteer for the NSPKU
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	**x**☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No links to tabacco industry**
The aim of treatment for phenylketonuria	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	I agree with the submission by the NSPKU
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	I agree with the submission by the NSPKU

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	I agree with the submission by the NSPKU
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	I agree with the submission by the NSPKU
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	I agree with the submission by the NSPKU
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	I agree with the submission by the NSPKU
• What impact would the technology have on the current pathway of care?	I agree with the submission by the NSPKU

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	I agree with the submission by the NSPKU
• How does healthcare resource use differ between the technology and current care?	I agree with the submission by the NSPKU
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	I agree with the submission by the NSPKU
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	I agree with the submission by the NSPKU
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	I agree with the submission by the NSPKU
• Do you expect the technology to increase	I agree with the submission by the NSPKU

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	I agree with the submission by the NSPKU
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I agree with the submission by the NSPKU
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or	I agree with the submission by the NSPKU

ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I agree with the submission by the NSPKU
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I agree with the submission by the NSPKU
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	I agree with the submission by the NSPKU

• Is the technology a 'step-change' in the management of the condition?	I agree with the submission by the NSPKU
• Does the use of the technology address any particular unmet need of the patient population?	I agree with the submission by the NSPKU
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	I agree with the submission by the NSPKU
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	I agree with the submission by the NSPKU
• If not, how could the results be extrapolated to the UK setting?	I agree with the submission by the NSPKU
• What, in your view, are the most important outcomes,	I agree with the submission by the NSPKU

and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	I agree with the submission by the NSPKU
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I agree with the submission by the NSPKU
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I agree with the submission by the NSPKU
22. How do data on real-world experience compare with the trial data?	I agree with the submission by the NSPKU
Equality	
23a. Are there any potential equality issues that should be	I agree with the submission by the NSPKU

taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	I agree with the submission by the NSPKU

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Limited relevance of the registry data to the decision problem	I agree with the submission by the NSPKU
Key issue 2: Outcomes not addressed in the company submission	I agree with the submission by the NSPKU
Key issue 3: Blood phenylalanine concentration level as a measure of efficacy	I agree with the submission by the NSPKU
Key issue 4: Limited randomised controlled trial data available	I agree with the submission by the NSPKU

Key issue 5: Unrealistic company model pathway	I agree with the submission by the NSPKU
Key issue 6: Implausible time and age invariant health state transition probabilities	I agree with the submission by the NSPKU
Key issue 7: Methods used to calculate transition probabilities	I agree with the submission by the NSPKU
Key issue 8: Annual rate that patients stop taking sapropterin (attrition rate)	I agree with the submission by the NSPKU
Key issue 9: Utility values used in the model are highly unlikely to reflect the experience of NHS patients with phenylketonuria	I agree with the submission by the NSPKU
Key issue 10: Effect of sapropterin on protein-restricted diet	I agree with the submission by the NSPKU
Are there any important issues that have been missed in ERG report?	I agree with the submission by the NSPKU

Additional technical team questions	
Does damage to the brain and nervous system happen in children with phenylketonuria managed within the NHS?	I agree with the submission by the NSPKU
What proportion of children go on to develop neurological damage because of uncontrolled phenylalanine levels despite being prescribed a protein restricted diet?	I agree with the submission by the NSPKU
For those children who do develop neurological damage, what other treatments and care (health and social) will these children require?	I agree with the submission by the NSPKU
Does a 71.2% reduction in protein-restricted diet due to treatment with sapropterin reflect the level expected in clinical practice? (see ERG report page 77) If no, what approximate	I agree with the submission by the NSPKU

percentage reduction in protein-restricted die do you anticipate in clinical practice with sapropterin?	
Is a utility level of 0.095 appropriate or realistic for a patient with severe PKU symptoms and on a protein-restricted diet? (see ERG report pages 75 and 76) If no, what level reflects this state in clinical practice?	I agree with the submission by the NSPKU

PART 3 -Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I agree with the submission by the NSPKU
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

Your privacy

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Sapropterin for treating phenylketonuria [ID1475]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Wednesday 16 December 2020**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with phenylketonuria and current treatment options	
About you	
1. Your name	**Robin Lachmann**
2. Name of organisation	**Royal College of Physicians, London**
3. Job title or position	**Consultant in Adult Inherited Metabolic Disease**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for phenylketonuria	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment in PKU is to prevent neurological damage and optimise neurocognitive function in patients with this disease. This is done by reducing phenylalanine (Phe) levels in the blood, and hence in the brain. Left untreated, PKU is a devastating disease characterised by developmental delay, severe learning difficulties, and behavioural problems. The degree of neurological damage seen, as measured by final IQ, is directly related to Phe exposure. If Phe levels can be reduced in the first weeks of life and then maintained at <360 mcmol/L, then the irreversible neurological effects of PKU can be avoided, and final IQ will be at or close to expected values. Interestingly, after the age of 10 IQ is fixed irrespective of subsequent Phe levels, suggesting that there is a critical period in neurodevelopment when the brain is particularly susceptible to the toxic effects of Phe. However, although IQ is fixed, there may be other neurocognitive effects of Phe in adolescents and adults with PKU. Neurocognitive testing consistently shows subtle but statistically significant underperformance on tests of processing speed and executive function but evidence suggests that these deficits are more strongly related to Phe levels in childhood than they are to Phe at the time of testing.

	In the early days of dietary treatment, maintaining Phe levels was more challenging than it is today due to a lack of low protein foods and palatable amino acid supplements. In the 1970s, and into the 1980s, it was standard clinical practice to advise patients to come off dietary treatment and eat normally after the age of 12. Later, the advice was to stay on diet, but to maintain less strict metabolic control with Phe levels below 700 mcmol/L after childhood. In fact, the number of patients succeeding in maintaining Phe levels within target ranges decreases markedly in older age groups. Hence there are many adults with PKU who have either been on unrestricted diets, or on Phe-restricted diets but with Phe levels well above target levels, for many years. Providing metabolic control was good up until the age of about 10, the evidence is that as a group adults with PKU have normal educational and social outcomes and a good quality of life. Nonetheless, there are some patients who find that they feel and perform better with lower Phe levels. Hence, in my view, the aims of treatment in adults with PKU are much more individualised than those for children and patients should be supported to maintain the Phe levels at which they feel they operate best. The oldest patients who were identified on NBS and treated early are now entering their 50s. Some specialists have expressed concern that there may be late effects of having high Phe levels that might include dementia. However, there is currently no evidence to support this. Indeed, patients who were born before the introduction of NBS and were never treated can have severe learning disabilities and other neurological problems but do not have progressive neurological disease. It is essential for women with PKU who are planning pregnancy to maintain Phe levels between 120 and 250 mcmol/L throughout pregnancy in order to avoid the teratogenic effects of Phe. This group of patients, who normally go onto a highly restricted diet before conception, would potentially be very useful for studying the neurocognitive effects of different Phe levels on adults with PKU. Unfortunately, to date very few studies have been done.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	It has been suggested that response to treatment could be measured in two ways; an absolute reduction in Phe levels and/or an increase in Phe tolerance (the amount of dietary protein intake required to maintain a given Phe level). A treatment which was started in the neonatal period and was able to maintain normal Phe levels throughout life would be the gold standard. Dietary treatment fits this definition. It is, however, a treatment that has major lifestyle

or a reduction in disease activity by a certain amount.)	effects for both the patient and their family. Therefore, adjuvant treatments which can allow patients to eat more normally whilst maintaining target Phe levels could provide extra benefits for the patient. Although there are some patients with hyperphenylalaninaemia who obtain Phe levels <360 mcmol/L with sapropterin treatment alone, for the large majority sapropterin will be an adjunct to dietary treatment. Sapropterin responsiveness, however, has been defined in terms of Phe reduction (a decrease in plasma Phe of 30%) rather than in terms of increase in protein tolerance. A reduction of 30% in Phe will not have the same clinical significance for all patients. A child with hyperphenylalaninaemia and an untreated Phe of 500 mcmol/L who obtained Phe of 330 mcmol/L on sapropterin would have a highly significant response (in Switzerland sapropterin is only reimbursed for patients who when treated achieve target Phe levels without the need for any protein restriction {https://serval.unil.ch/resource/serval:BIB_71A05CAD5FB7.P001/REF}). An individual with mild PKU and untreated levels of 700 mcmol/L who obtained levels of 470 mcmol/L on sapropterin would only have to follow a mild protein restriction in childhood and could follow a normal diet as an adult (although it could be argues that they could follow a normal diet in adulthood even without sparopterin). The significance of reducing levels from 1500 mcmol/L to 1000 mcmol/L in a patient with classical PKU, for instance, is less clear. In reality, the higher the untreated baseline Phe level, the less likely the patient is to show any reduction in Phe with the addition of sapropterin. The argument for using sapropterin as an adjunct to diet is that it makes it easier for patients to maintain target Phe levels because dietary restriction can be less severe and/or the amount of protein substitute can be reduced. It is very difficult to define what a clinically significant increase in protein tolerance is. In effect you are trying to measure the effect of dietary restriction and having to take unpalatable amino acid supplements on the quality of life of the patient and their family. This will vary between families: for any given baseline Phe level there are families who maintain metabolic control relatively easily and others who really struggle. It should also be noted that for any individual patient Phe tolerance changes over time, increasing as they get older. Two thirds of adolescent patients were able to considerably liberalise their diets whilst still maintaining Phe levels in target range (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6566391/). My personal experience is also that many young people transitioning from paediatric to adult services are excessively restricting their natural protein intake and

	can significantly increase it without an adverse effect on their Phe levels. Therefore, if Phe tolerance is to be used as a clinical response, it is essential that patients are challenged with protein and an accurate baseline is measured before sapropterin is commenced.
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Dietary treatment is highly effective and safe, but it is complex and demanding, for patients, their families and the healthcare professionals who support them. There is a need for a cure (which might be provided by gene therapy in the future) or, failing that, a pharmacological treatment which would not require dietary modification.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Neonates are diagnosed on newborn screening and referred to their local paediatric metabolic service for confirmation of the diagnosis and initiation of treatment with a Phe restricted diet and amino acid supplements. Families are taught how to collect blood spots at home so that Phe levels can be monitored. Treatment is supervised by specialist dieticians and doctors. Between the ages of 16 and 18, patients will transition to an adult metabolic service which will take over supervision of treatment. All medical foods and PKU supplements are provided by the NHS.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The last UK guidelines were published by the MRC Working Group on PKU in 1993 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1793880/). Currently there are no PKU treatment guidelines which are approve by either NHSE or the British Inherited Metabolic Disease Group. I think that most centres broadly follow the 2017 European PKU Guidelines (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639803/), certainly for children.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The pathway from NBS to initiation of treatment is well defined. Lifelong care should be under the supervision of a unit fulfilling the NHSE service specification for Metabolic Disorders (adults or children). On the whole care across the UK will be uniform. There are disagreements treatment goals for adults who do not achieve the target levels set by either the 1993 (<700 mcmol/L) or 2017 (<600 mcmol/L) guidelines.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It would require the introduction of testing for responsiveness into the pathway. It would also be necessary to develop protocols to monitor response to sapropterin and measure Phe tolerance. Both of these would require significant clinical and laboratory resource.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It would be used as an adjunct to current care.
• How does healthcare resource use differ between the technology and current care?	There might be a reduced requirement for medical foods and PKU supplements for some patients. There would be increased clinical time required for testing for responsiveness and monitoring Phe tolerance as an outcome. Additional lab resource would be required, particularly if genotyping was part of the pathway for responsiveness testing.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics only
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Development of protocols for testing for sapropterin responsiveness and reliably measuring Phe tolerance. Extra specialist dietetic resource in particular will be required.
13. Do you expect the technology to provide clinically meaningful	Not for the majority of patients. There may however still be a small minority of families who are not able to establish adequate metabolic control by dietary therapy and whose children with PKU may have sub-optimal outcomes due to

benefits compared with current care?	higher Phe levels in early life. It remains to be demonstrated, however, that addition of sapropterin either improves metabolic control or clinical outcomes in this population.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	I don't expect it to significantly increase the health-related quality of life for most patients (it is already comparable to the general population). It could however have significant effects on other aspects of quality of life for both patients and their families.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes. It will be essential to clearly define the group of patients who are sapropterin responsive as they are the only ones who may benefit. Unfortunately, response to sapropterin is not binary. It can also be measured in a number of different ways: measuring absolute Phe or measuring Phe tolerance; testing response after a single dose or after a period of treatment. It will also be necessary to define what treatment goals need to be met in the long-term.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	For most patients this will involve taking extra daily medication while they to continue on their dietary treatment.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes. These are crucial. There will have to be responsiveness testing. I also think stop criteria need to be developed to avoid using this expensive medication in patients who are not maintaining acceptable control of their Phe levels.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I think most if not all benefit will not be picked up by the QALY calculation. It will also be important to take into account effects on families and carers.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	No. This is just an adjunct to our current management. The simplest way to think of it is that in some patients it can reduce the baseline Phe level.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No. A small number of babies with hyperphenylalaninaemia might be able to avoid dietary treatment in childhood.
• Does the use of the technology address any particular unmet need of the patient population?	Only partially. Most patients will still need to maintain a low protein diet.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Sapropterin seems to be very well tolerated.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. They look at the effects of adding sapropterin onto dietary treatment.
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	Phe levels were measured in every study. Phe tolerance is less well studied.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Phe is a surrogate marker. It is an excellent predictor of long-term neurological outcomes when measured in children. In adults, its relationship to long-term outcomes is not clear. Many adults have been off diet for many years with Phe>1500 and are leading normal lives.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Given that Kuvan has been licensed for 10 years, there is some published real life experience of the use of sapropterin in PKU. However, this is disappointingly sparse and much of it is industry sponsored.
22. How do data on real-world experience compare with the trial data?	They are broadly comparable
Equality	

23a. Are there any potential equality issues that should be taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Limited relevance of the registry data to the decision problem	There is a major problem in not including patients who are on PRD only. I also don't think the registries are necessarily representative of UK practice. UK practice is probably very similar to European practice (patients are identified by NBS and started on PRD immediately) but very different from US practice where there are major issues in obtaining PRD, and consequently long-term outcomes are not as good. I would be concerned that the adult patients included in PKUDOS would be significantly different from the UK cohort of adults with PKU.
Key issue 2: Outcomes not addressed in the company submission	What evidence there is suggests that neurocognitive function in adults is stable and that the deficits which have been described in PKU are more strongly related to historical Phe levels than to Phe at the time of testing (https://pubmed.ncbi.nlm.nih.gov/24071437/). Therefore I don't think it is surprising that there is no data to support improved neurocognitive outcomes with sapropterin treatment as compared to PRD alone. Concerns about poor nutrition in PKU do not apply to those who are following a PRD and taking their supplements, which are designed to be nutritionally complete. The risk of nutritional deficiency arises when patients relax or stop their PRD and stop or reduce their supplement intake. This is safe as long as they increase their intake of natural protein of high biological value,

	which can then provide sufficient nutrition. Unfortunately, some people with PKU who have been treated with PRD since birth never acquire a taste for such high protein foods and instead choose a diet of processed, often high carbohydrate foods which puts them at risk of nutritional deficiency, particularly B12 deficiency. It is possible that if sapropterin were introduced early in life, so that responsive infants and young children could follow a more varied diet in early life, they then might make better food choices if they were to relax their diets further in adulthood. Again, this would require lifelong study and it is not surprising that this data does not exist.
Key issue 3: Blood phenylalanine concentration level as a measure of efficacy	The aim or treating PKU is to maintain plasma Phe within the target range whilst meeting patients' nutritional requirements. Controlling dietary Phe intake is the tool that is used to decrease Phe levels, and the amino acid and nutritional supplements that patients take ensure full nutritional requirements are met. So with a PRD dietary Phe intake is the intervention and the efficacy measure is the Phe concentration, and there is a dose response relationship. The effect of sapropterin in responsive patients is to alter this dose response relationship such that with any given degree of protein restriction, a lower plasma Phe level will be obtained. Thus, to properly assess the effects of using sapropterin as an adjunct to a PRD, you need to see data both on Phe levels and dietary protein intake.
Key issue 4: Limited randomised controlled trial data available	The clinical trials are of remarkably short duration. Even if you accept that Phe levels are a good surrogate for the neurological outcomes in PKU (which I do), it is surprising that regulators did not want evidence that they could be maintained in the long-term. Long-term data on protein intake is also needed for a proper assessment of efficacy.
Key issue 5: Unrealistic company model pathway	I agree that Phe levels can fluctuate markedly within a relatively short period of time due to factors which include protein intake and intercurrent illness. Although some patients report headache with sudden changes in Phe levels, in reality such fluctuation will actually often be asymptomatic. You will only know they are happening if you measure the blood Phe levels. Monitoring is carried out frequently in young children, and in pregnancy where we do levels three times a week, but many adolescents and adults only have their Phe levels measured when they attend clinic, which will be only once or twice a year.

Key issue 6: Implausible time and age invariant health state transition probabilities	Certainly there are many adults who function well with high Phe levels and see no need to control them. Many of these people will have had excellent control in childhood (which is why they function normally as adults).
Key issue 7: Methods used to calculate transition probabilities	
Key issue 8: Annual rate that patients stop taking sapropterin (attrition rate)	
Key issue 9: Utility values used in the model are highly unlikely to reflect the experience of NHS patients with phenylketonuria	NBS for PKU followed by early institution of a PRD is a highly effective intervention and utility values for people living with PKU in England today will be very high. Almost all patients treated with a PRD from an early age are self caring, independently mobile, and have educational, occupational and relationship outcomes comparable to the population. Although the PRD is challenging for patients and their families, I think it is very unlikely that the effects of following it would have a significant detrimental effect on utility values.
Key issue 10: Effect of sapropterin on protein-restricted diet	The effect which taking sapropterin has on the degree of protein restriction any individual patient needs to follow in order to maintain target blood Phe levels is crucial to any assessment of its efficacy and cost effectiveness. It is going to be different for every patient and is in fact the key to how one defines sapropterin responsiveness. It sems to me that for the company model to apply you would have to define sapropterin responsiveness as being the ability to achieve a 71.2% reduction in the intake of LP foods and PKU supplements whilst maintaining target Phe levels. That would be very different to the definition which I think they are using, which is to obtain a 30% reduction in Phe levels when sapropterin is added to PRD.

Are there any important issues that have been missed in ERG report?	I think there needs to be much more detail on how sapropterin responsiveness is defined and on what constitutes a clinically significant response to sapropterin treatment in the long-term.
Additional technical team questions	
Does damage to the brain and nervous system happen in children with phenylketonuria managed within the NHS?	Yes, but it is related to adherence to treatment rather than the availability of treatment. Furthermore, the degrees of neurological damage we see in those who struggle to control their Phe levels are nowhere near as severe as was seen in the days before treatment was available or that we still see patients who were born in countries where they do not have effective NBS programmes.
What proportion of children go on to develop neurological damage because of uncontrolled phenylalanine levels despite being prescribed a protein restricted diet?	This isn't easy to answer as it depends on your definition of neurological damage. Very few will have significant learning disabilities. More will have scores which fall more than 1.5 SD below the mean on neuropsychological tests of executive function and processing speed, but the clinical significance of such findings is unclear. It is also an issue of adherence (not everyone who is prescribed a PRD achieves levels within the target range) and the degree to which levels are uncontrolled (we think neurological damage relates to both the level of Phe and the duration of exposure, the area under the curve of the plot of Phe against time)
For those children who do develop neurological damage, what other treatments and care (health and social) will these children require?	Even adults with untreated or late treated PKU, born before the introduction of NBS, have very different needs. Most are not able to live independently due to learning disability, but most do not require institutional care and are looked after in the community, either by their families or in residential settings. Some do live independently with jobs and families of their own.

Does a 71.2% reduction in protein-restricted diet due to treatment with sapropterin reflect the level expected in clinical practice? (see ERG report page 77) If no, what approximate percentage reduction in protein-restricted die do you anticipate in clinical practice with sapropterin?	One of the major issues here is that we don't have the data to answer this question. It will be entirely dependent on how you define sapropterin responsiveness. I'm sure you could find a population of patients who could achieve a 71.2% reduction in PRD when treated with sapropterin, but they would be a small minority of the PKU population as a whole and would mostly have hyperphenylalaninaemia rather than classical PKU. The question is really what percentage reduction in PRD is regarded as clinically significant and then, is sapropterin treatment a cost effective way of achieving that reduction.
Is a utility level of 0.095 appropriate or realistic for a patient with severe PKU symptoms and on a protein-restricted diet? (see ERG report pages 75 and 76) If no, what level reflects this state in clinical practice?	No. Most if not all patients with untreated PKU would have utility values considerably greater the this. I have found data on health-related quality of life and the burden of prolonged seizures in noninstitutionalized children with epilepsy (https://www.sciencedirect.com/science/article/pii/S1525505019300186). This population has a degree of learning disability and neurodisability that would be close to those with untreated PKU. Mean utility values for this population as judged by both clinicians and parents were just above 0.5. There is little comparison between even the most severe symptoms seen in children diagnosed on NBS and the disease seen in untreated patients.
PART 3 -Key messages	
In up to 5 sentences, please summarise the key messages of your statement:	

- NBS for PKU with early institution of dietary treatment is a highly effective intervention which has transformed the outcomes for people with PKU.
- Sapropterin has limited effectiveness and is an adjunct to PRD.
- Its efficacy will vary between individual patients and is related to the *PAH* mutations they carry.
- In making decisions about its place in treatment it is essential to precisely define what constitutes sapropterin responsiveness, both in terms of blood Phe levels and of protein tolerance.
- It is also essential to decide what constitutes a clinically meaningful response to long-term sapropterin treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Sapropterin for treating phenylketonuria [ID1475]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Wednesday 16 December 2020**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with phenylketonuria and current treatment options	
About you	
1.Your name	**Patient Expert**
2. Are you (please tick all that apply):	☐ a patient with phenylketonuria? ☐ a patient with experience of the treatment being evaluated? **x**☐ a carer of a patient with phenylketonuria? x☐ a patient organisation employee or volunteer? x☐ other (please specify): a carer with experience of the treatment being evaluated
3. Name of your nominating organisation.	National Society for Phenylketonuria
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement x☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

	This is a composite submission from NSPKU and the carer nominated by NSPKU
5. How did you gather the information included in your statement? (please tick all that apply)	x☐ I am drawing from personal experience. x☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: In my work for NSPKU I have been involved in : - **Conducting research on patient's experiences of living with PKU** - **Assisting with queries to the charity helpline for individuals/families living with PKU** - **Assisting people with PKU or their carers make applications for Disability Living Allowance or Personal Independence Payment or advising on other welfare issues** - **Communicating with NHS and other organisations in relation to services for people with PKU and the experiences of people with PKU** - **The above work has given me an overview of different experiences of living with PKU.** x☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with phenylketonuria?	[redacted]

If you are a carer (for someone with phenylketonuria) please share your experience of caring for them.	My son is 12 years old and was diagnosed via newborn screening with “Classical PKU” with levels of almost 2000 micromols at diagnosis. My son was treated solely by a phenylalanine restricted diet until the age of 5 when he started taken Kuvan. The difficulty of living with PKU is misunderstood. The responsibility of caring for a child with PKU is enormous as the burden of ensuring your child develops normally falls entirely on you; the parents are the “front line” of delivering the treatment. Healthcare professionals provide background advice and support. [redacted] The dietary treatment is limited and complex. It is very difficult to eat outside the home and this restricts many activities; travelling and days out and allowing other people to care for your child. Organising and preparing food which your child is able to eat becomes a dominant activity of life. Food for people with PKU consists of prescribed wheat starch (which is similar to cornflour) which is made into bread, and recipes which are presented as “burgers” “sausages” or even an “omelette” made with wheat starch and yellow colouring. My son had very little appetite or enthusiasm for this food and meals could be stressful. Hunger can be a problem and sweets and fizzy pop were a way of filling him up. My other children ate normal and tastier food; my son

	found this upsetting at times. Food in the house has to be controlled and monitored in a very unnatural way. The dietary treatment assumes precise amounts of food can be "administered" like medicine but in everyday life this is extremely hard and potentially impossible, e.g. when he dropped food on the floor you are supposed to sweep it up and weigh it on digital scales and then offer an equivalent value of phenylalanine in another form having calculated the amount using a phenylalanine chart, a calculator and scales. The diet is also very detailed and easy to get wrong, e.g. 35g of kale is one exchange of phenylalanine whereas broccoli is 60g. Consequently nearly all food needs to be checked, considered and weighed. There is a high amount of anxiety and guilt around food which affected the whole family. Understanding of the condition is very limited, amongst GPs, chemists, teachers and other people you rely on for keeping your child safe. My GP restricted the food he was recommended by his specialist dietitian. Obtaining prescribed foods is hard as the NHS system is not designed for people who get most of their food on prescription. [redacted] My son started Kuvan on the KOGNITO trial aged about 5 and a half and has now taken it for 6 and half years. His phenylalanine tolerance is now about 30 exchanges, increased from 10. He does not require food to be specially prepared and eats a wide variety of food, eg wholemeal bread, eggs, pulses, quorn and cheese. He does not eat prescribed food and has low doses of protein supplement. It is no longer necessary to weigh phenylalanine exchanges and this is very liberating for him and me as a carer. He can eat most food to appetite. His growth and BMI are good. Gastric symptoms he had experienced improved.

	His phenylalanine levels are very stable and it is rare for him to have levels out of range except when he has an infection. Eating at school or other people's homes is not a problem as he can have normal vegetarian options and this means PKU is a very marginal issue in his life. 
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for phenylketonuria on the NHS?	The current treatment is the complex low phenylalanine diet with blood monitoring which individuals or families self-administer at home with supervision from hospitals. This care largely avoids the catastrophic brain damage that occurred in people with PKU before newborn screening. However there is still a wide range of outcomes amongst people with PKU including some outcomes that are tragically poor for a treatable disease in a high income country. This is because controlling phenylalanine levels through avoiding eating phenylalanine, which is within almost all foods, is extremely difficult to sustain over the long term. NHS services for people with PKU in England are variable with geographical inequality. Some of the best patient focused services are dependent on NHS staff working through goodwill. Patients may experience a variety of barriers to accessing the services they need, for example many patients with PKU have problems with organisation and lack confidence to travel to city centre metabolic clinics. There is a lack of ready access to psychological support to help patients and caregivers across England. The statement (page 20 ERG report) that a multi-disciplinary team is involved in the clinical management of patients with PKU is the

	paradigm but is not always the reality. Patients in “shared care” arrangements typically lack access to psychologists and specialist nurses and their dietitians may be non-specialist. Blood phenylalanine reporting in shared care services can be significantly slower. Many patients attending Highly Specialist Metabolic centres lack routine counselling/mental health help or routine neurocognitive testing. Many patients find it a struggle to consistently access all the dietary products they require. **Research gaps**: PKU is a rare disease and its effects in the brain and body are hard to study. Many patients describe having concurrent high phenylalanine as having brain fog, feeling detached, irritable and tetchy, or changes in phenylalanine causing intense headaches. Subtle problems like tremor or fatigue are also seen even in young early treated patients but patients feel these issues are too easily dismissed by their doctors. **Range of outcomes;** There is no UK patient registry and there is a lack of high quality data that is not compromised by participation bias. There is no reliable picture of the outcomes of the entire patient cohort in the UK. The survey conducted by NSPKU (*Ford S, O'Driscoll M, MacDonald A. Living with Phenylketonuria: Lessons from the PKU community*. Mol Genet Metab Rep. 2018 Oct 18) is the largest survey of PKU experiences. Individuals with PKU who are older than 50 may be late treated or untreated and have significant care needs. There is a concern that this generation is often reliant on family care arrangements but their parents are now elderly. The outcomes and care experience of late treated/untreated people with PKU in the UK has not been reliably surveyed. A large number of patients with PKU (more than 50%) are lost to follow up. Early treated patients, who are unable to manage their phenylalanine levels in adulthood appear to have a range of outcomes. At the more severe end, there are early treated people with PKU less than 40 years old who are disabled due to PKU

	related brain injury and/or malnutrition. Some families may have multi-generational poor outcomes, e.g mothers with PKU with impaired outcomes who have one or more children affected by Maternal PKU syndrome. These families can require significant help from the NHS and social services. Experiences which are commonly seen amongst adults with PKU are social anxiety (which can be in a range from not leaving the house at all to having unusually restricted social activities), depression, panic attacks, forgetfulness. In 2017 NSPKU interviewed a young woman who vividly described how she felt with high phenylalanine levels "*I feel like I am in a bubble, and I can't process what is going on around me. I stop speaking, struggle with balance, lose my train of thought and stop speaking and just stare into space*." These symptoms can be varied among patients but can have a significant impact upon the ability to work, enjoy life or care for dependents. NSPKU provides welfare advice and an expected outcome from the DWP Personal Independence Payment process for symptomatic adults with PKU will be awards of higher rate "daily living" and lower rate "mobility" which reflects the significant impairments which can be experienced. At NSPKU we see patients who can experience a downward spiral where poor daily functioning affects social and economic outcomes, and in turn, poverty and insecure housing is an additional obstacle to being able to cope with PKU treatment. However some adult patients who have high phenylalanine levels have much milder problems or generally function well. There are also patients who successfully control their phenylalanine levels in adulthood through dietary treatment despite the difficulty of this. **Women with PKU, Maternal PKU and sexual and reproductive experiences:** Phenylalanine is highly teratogenic to the foetus and this means women with PKU are advised to have very tightly controlled phenylalanine before conception. There is no recent published peer reviewed data from UK metabolic clinics on pregnancy outcomes. A poster presentation from 2017 provides useful outcome data. *Journal of Inborn Errors of Metabolism & Screening or JIEMS 2017, Volume 5: 1–*

	413 Abstracts presented at 13th International Congress of Inborn Errors of Metabolism - ICIEM 2017 266 - Analysis of the West of Scotland Maternal Phenylketonuria Clinic Sarah Adam Royal Hospital for Children, NHS Greater Glasgow And Clyde, Glasgow, United Kingdom This showed that only 11 of the 20 pregnancies were planned. The birth outcomes showed 23% of infants presented with congenital birth defects (cardiac, cleft palate, dysmorphic features, microcephaly, larynglomalacia, lower intestinal anomalies, other). The survey had a small sample size. The analysis did not include long term follow up of the infants' outcomes as issues such as low IQ and behaviourial issues might manifest later. It is believed that high rates of unplanned pregnancies are also experienced at other metabolic clinics. NSPKU regards the current arrangements for accessing sapropterin in pregnancy https://www.england.nhs.uk/wp-content/uploads/2013/04/e12-p-a.pdf as inadequate as patients are required to (a) be already pregnant (b) have failed to establish metabolic control before response testing with sapropterin will be attempted. Therefore in a patient with poorly controlled PKU valuable time will elapse where the foetus is exposed to teratogenic phenylalanine before sapropterin is accessible. In addition, some women with PKU report stressful pregnancy experiences which might have been alleviated by sapropterin, for example vomiting protein substitute. Understandably many women fear Maternal PKU and this can affect their sexual and reproductive choices in a negative way (*Ford, 2018 Reproductive experiences of women living with PKU* https://pubmed.ncbi.nlm.nih.gov/30416967/). Some women described intense feelings of fear and shame even to the extent that this affected the ability to form intimate relationships in their comments to the NSPKU survey. Women also described that PKU affects their ability to manage their PKU and care for small children.

	Children and young people: Children's outcomes are dependent upon how well their caregivers are able to cope with administering the dietary treatment. This can lead to children being removed from parents by social services as a very high level of parental coping skills are required. Children almost always attend mainstream school but there appears to be a higher prevalence of learning disorders. Dietary treatment will affect children's life experiences depending on how successfully parents are able to organise/advocate around the obstacles. Discrimination and bullying around the dietary treatment and failures with administering the dietary treatment in educational settings are issues commonly reported. Adolescence and young adulthood is an extremely challenging time for people with PKU. Older children become hungrier but phenylalanine tolerance will still be limited. Teenagers are vulnerable to peer pressure and smelly amino acid supplements and special foods can be embarrassing. At the same time, children's food intake can no longer be reliably monitored by parents/carers. This can cause poor adherence by children and young people at a crucial time in their education and personal development. It also can strain relationships within the family. Parents can describe their children spiralling out of control by eating biscuits and crisps in the same manner that others talk about teenagers taking drugs or alcohol. Overall the current treatment is flawed for children and young people. Outcomes will depend entirely on their ability to control their own *natural* urges to eat food, not consume unpleasant protein substitutes and to fit in with the social group. However children and young people inherently lack the ability to control impulses and make good assessments of risk. Parents/carers try to monitor and supervise dietary treatment but it will always depend to some extent on the co-operation of the child/young person. **Burden of dietary treatment - carers:** Administering dietary treatment is very burdensome for carers. It is time-consuming, causes many parents to alter their working arrangements to accommodate their caring duties. It can cause

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	psychological distress (*Medford E, Hare DJ, Carpenter K, Rust S, Jones S, Wittkowski A. Treatment Adherence and Psychological Wellbeing in Maternal Carers of Children with Phenylketonuria (PKU). JIMD Rep. 2017*). The need to provide care and support often extends into patient's adulthood. Research suggests that carers spend on average 19 hours a week administering dietary treatment (*MacDonald A, Smith TA, de Silva S, Alam V, van Loon JM. The personal burden for caregivers of children with phenylketonuria: A cross-sectional study investigating time burden and costs in the UK. Mol Genet Metab Rep. 2016).* In NSPKU's survey (*Ford et al, ibid*) 75% of carers reported that looking after a child with PKU affected their well-being. **Burden of dietary treatment – individuals with PKU:** Living with such extreme dietary restrictions and artificial foods and supplements can have many physical and mental affects. Disordered eating patterns seem prevalent but under treated. Many patients are made anxious by weighing phenylalanine exchanges and the severity of the restrictions can create a relationship with food which is very abnormal. The protein supplements are described as "unpalatable" but many patients find these really difficult to take; either repellent, or causing nausea, diarrhoea, stomach problems, mouth ulcers and dental problems. Social anxiety, anxiety or depression is also commonly reported and observed. Some people with PKU eat restricted diets without reliably consuming their protein substitutes and have symptoms relating to malnutrition. Weight control is also very challenging among many patients. The impact on quality of life of adhering to a PKU diet must not be understated. Pleasure in food can be removed. Many people with PKU report feeling hungry all the time or having intense cravings for food. Food needs planning and hours of food preparation for food which might not be particularly appetising. Most social occasions, or travel, will involve food and this becomes a constant obstacle to be

	dealt with. The PKU diet requires a relentless level of self-control to avoid eating the majority of all normal foods that is hard to sustain in the long term. There appears to be broad consensus that there are high levels of unmet need in the PKU community and a need for new treatments in addition to the low phenylalanine diet. Sapropterin is used on a large scale across the developed world and in lower income countries indicating a wide acceptance of the need for other new treatment options amongst both patients and metabolic clinicians. NHS England's Metabolic CRG has recommended the use of sapropterin in 2015, 2018, 2019 and 2020. A gene therapy trial for PKU started this year for adults with PKU, recognising the unmet need for new treatments in adults with PKU. https://www.uhb.nhs.uk/news/uhb-recruits-first-patient-in-world-to-pioneering-gene-therapy-trial.htm
Advantages of this treatment	
9a. If there are advantages of sapropterin over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others?	9 (a) In 2018, NSPKU surveyed carers of children in the UK accessing Kuvan. In addition this question has also been put to an adult with PKU who is now taking sapropterin after BioMarin allowed access to patients who had participated in pre-licensing clinical trials after 10 years without access. This response draws upon their comments **Sapropterin makes it easier to control phenylalanine levels in a long term and sustainable way**. Dietary treatment is rigorous and relentless. Sapropterin increases phenylalanine tolerance, decreases the need for protein substitutes and low phenylalanine prescribed food – all these factors improve long term treatment adherence. Sapropterin makes the task of controlling phenylalanine less arduous

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does sapropterin help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	and a more realistic goal. *"I did not really understand what PKU was about or how to manage the diet. I was a young single mum. … I struggled with every aspect. Phenylalanine levels were always up and down. When he went on Kuvan it was a different story. My boys phe levels were steady and I did not need to worry about restricting anything." (Parent of 6 year old child)* *"He had 50% of blood Phe levels outside target levels without Kuvan. He rarely has a blood Phe level outside target with Kuvan" (Parent of 8 year old)* *"Before Kuvan my days were a constant battle with myself and agonising over why I couldn't be happy, pain free, heathy and keep all of the plates spinning whilst 'doing the pku regime'. My PKU was always last on my list of priorities and constantly overlooked. It was just too hard to do and too easy to ignore. Everything suffered because I was never able to function as the person I should be. PKU is not a diet." (Adult with PKU)* **Increase in quality of life for patients** – This is felt in different ways. *Mental health improvements* : Patients who are not reliably controlling their phenylalanine levels have a variety of different problems, but depression, low mood, anxiety and impaired executive functioning are commonly seen. *"I knew Kuvan was working when I laughed out loud at something on the radio. It felt strange. I found over time I could explain exactly what I meant verbally, follow the path of a conversation , look people in the eye, remember things and hold my body up rather than drag my limbs. My sleep improved and my concentration and focus returned. I felt like I had been regenerated. My dark thoughts disappeared. The mental health benefits far outweigh the food benefits for me because quite simply, I feel like Kuvan has saved me, my marriage and who I will be in the future."* (Adult with PKU)

	"He is calmer, more settled/content. He has less distressing melt downs" (Parent of 8 year old) *"He is much more confident and less anxious." (Parent of 7 year old)* <u>Improvements in social relationships with family and peers and ability to take part in social occasions:</u> *"We have less fights about food [between mother and son] and he is being bullied less." (Mother of 10 year old)* "*Life is just easier – going out for the day, eating together as family. School lunches – he could not stay for school dinner before, being with his dad and relatives is easier. He can stay with his dad and I don't have to worry what he eats like before" (Mother of 10 year old)* "*My daughter goes on holiday, goes to restaurants, attends social occasions, stays with family – and eating away from home is not an issue. There is always plenty for her to choose. She does not get teased about her diet anymore." (Father of 10 year old)* *"Pre Kuvan we would have excluded him from activities as we would not have trusted others to get the diet right." (Mother of 8 year old)* <u>Improvement in diet and reduction in health symptoms associated with dietary treatment:</u> Carers described their children as eating a wide variety of food, having increased enjoyment in food and less stress around food. The parents described their children as having reduced volumes of protein substitute and no/virtually no low

	protein prescribed food. Gastric problems were reduced. The reduction in the volume of protein substitutes was perceived as a strong benefit. *"She will eat some sausage, chicken, ham, fish, ordinary bread, ordinary milk. Her diet has changed from being very abnormal to normal." (Mother of 7 year old)* "*My son suffered a lot with stomach problems from being small – diahorrea. He does still occasionally have this, but much less frequently, as his diet is more balanced*." (Mother of 10 year old) *"He has gained weight and grown. He is not hungry."* (Mother of 7 year old) <u>Reduction for burden of care for adult patients:</u> Managing to control phenylalanine levels requires hours of work, pre-ordering and collecting prescribed foods, planning meals and preparing food with weighed exchanges. This work is not necessary in patients taking sapropterin. <u>Reduction in burden of care/quality of life for carers and other family members</u> Carers described sapropterin as significantly reducing the amount of work they had to do to manage their child's PKU, which freed them to work, study or care for other children. Arranging childcare was more feasible. They also describe feeling less stressed. They also described siblings as enjoying positive spillover effects from their parents having more time and the family more freedom. The reduced volume of protein substitute was described by a parent as reducing the burden of administering this aspect of the treatment from a "*constant battle*" to something "*not overwhelming any more*". This reduction in the treatment burden will also apply to carers of adult patients.

	"Life is much easier for me since my daughter has been on Kuvan….I worry less about my daughter having PKU and so there is much less stress. I was able to go to college and study since she started Kuvan and I finish my studies this year. Without Kuvan I would have been less likely to leave my daughter with family members." (Mother of 9 year old) *"I was able to return to work and work more hours as a consequence of my boy being on Kuvan so financially we have been better off." (Mother of 8 year old)* 9(b) The benefits of the treatment all inter-relate. The central issue is that sapropterin makes it easier to control phenylalanine levels in a long term and sustainable way. The adult patient we consulted specified the improvement in her mental health rather than increased dietary freedom as the key gain. 9(c) Yes, sapropterin is easy to use and makes controlling phenylalanine levels easier to achieve, reducing the treatment burden, improving nutrition, improving quality of life for patients, carers and families and lessening the health impacts of a long-term artificial diet. NHS England accepted that the reduction in the treatment burden from adopting sapropterin would help protected/vulnerable groups (see question 12 below).
Disadvantages of this treatment	
10. If there are disadvantages of sapropterin over current treatments on the NHS please describe these? For example, are there any risks with sapropterin? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	Carers/patients we surveyed did not report problems using or administering sapropterin or side effects. All described it as very advantageous.

Patient population	
11. Are there any groups of patients who might benefit more from sapropterin or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	There are no sub-groups which can be carved out of the overall patient cohort in responsible and appropriate way. Some patients may be at higher risk of non-adherence to standard dietary treatment, but this includes socio-economic, ethnic and clinical factors. This is described below (Question 12). NSPKU also considers that using sapropterin with stopping criteria based on age or other factors is inappropriate and potentially dangerous. Patients who have used sapropterin will become accustomed to a different diet and may be less likely to have coping mechanisms which enable them to control their phenylalanine levels through dietary means alone. Commissioning sapropterin on a start/stop basis was strongly condemned by the adult patient who had herself experienced this.
Equality	
12. Are there any potential equality issues that should be taken into account when considering phenylketonuria and sapropterin? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race,	NICE is required to have regard to the need to reduce health inequalities, this is a much wider concept than protected groups under the Equality Act and the public sector equality duty, and also includes socio-economic disadvantage and geographical inequalities. As the only treatment currently available for PKU is a complex self managed treatment there are groups which are particularly disadvantaged. These factors are detailed in the Equality and Health Inequalities Impact Assessment published by NHS England. The final version of this report produced after public consultation and published by NHS England is endorsed by NSPKU. They include:

religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	Disability – people with learning disabilities, sensory impairment and cognitive impairment are at higher risk of being unable to control their phenylalanine due to the nature and complexity of the treatment. People with learning difficulties are more prevalent in this patient cohort. Race and ethnicity – non English speakers, Roma/travellers, may have greater risk controlling phenylalanine for social and cultural reasons Religion – may impact on women who need to avoid unplanned pregnancy. Sex – women are more likely to be the primary carers of people with PKU. Low income, living in a deprived area and insecure housing – these social vulnerabilities are risk factors for being unable to sustain a low phenylalanine diet.
Other issues	
13. Are there any other issues that you would like the committee to consider?	Yes, see question 19 and Key Issue 2 below.

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

ERG report key issues	
Key issue 1: Limited relevance of the registry data to the decision problem	Sapropterin is a treatment for a rare disease which was licensed by the FDA in 2007 and the EMA in 2008. The statement (p 19 of the ERG Report) that marketing authorisation was granted in 2015 is incorrect, this was the date of an extension in the license to include children under 4. Marketing exclusivity has expired in both the EU and USA. This is an old drug for a rare disease which is already routinely commissioned in most countries. Accordingly the prospect that a further long term RCT of the type suggested by the ERG will ever be conducted is minimal. This appraisal needs to be conducted in a way which is realistic about the rarity of the condition and the overall market context rather than adopting a threshold for the evidence which can never be achieved.
Key issue 2: Outcomes not addressed in the company submission	NSPKU considers the following outcomes to be relevant, and which were referred to in the NHS England analysis of sapropterin – Stability of blood phenylalanine concentrations – the 2018 NHSE clinical evidence review found evidence that sapropterin improves blood phenylalanine stability but did not review evidence on the significance of stable blood phenylalanine levels. There is evidence that blood phenylalanine stability is a predictor of long term cognitive outcomes. Children's executive functioning and inattentiveness – the 2018 NHSE clinical evidence review noted these improvements found in the Burton (2015) study. These are highly relevant improvements for patients which potentially impact on children's educational potential, life chances, quality of life and the lives of carers.

Key issue 3: Blood phenylalanine concentration level as a measure of efficacy	The European Guidelines state that blood phenylalanine levels is the best available surrogate marker for the goals of PKU treatment. However it is agreed that increased dietary phenylalanine intake is important for quality of life, nutrition, the health benefits of a better diet and reduction in burden of care for patients and carers.
Key issue 4: Limited randomised controlled trial data available	The NICE Medicines and Technologies Programme has already reported on the clinical evidence for sapropterin in 2018 and 2020 (e.g https://www.england.nhs.uk/wp-content/uploads/2018/12/Evidence-Review-Sapropterin-for-Phenylketonuria.pdf) and described the RCTs for sapropterin as "high quality".
Key issue 5: Unrealistic company model pathway	With regard to the statement at page 72 of the ERG report "*Within any given year, a patient may switch between having controlled and uncontrolled blood phenylalanine levels (…) a one year cycle model is too long to reflect the true experience of patients with PKU*" - It is agreed that there are many adult patients who are trying to adhere to dietary treatment who have variable blood phe results over a year. - However the goal of PKU treatment is sustained and stable low phenylalanine treatment. The assumption that a person with very variable blood phe results within a year is moving between "controlled" and non-controlled" states is inappropriate.
Key issue 6: Implausible time and age invariant health state transition probabilities	
Key issue 7: Methods used to calculate transition probabilities	

Key issue 8: Annual rate that patients stop taking sapropterin (attrition rate)	
Key issue 9: Utility values used in the model are highly unlikely to reflect the experience of NHS patients with phenylketonuria	With regard to the statement at page 76 of the ERG report that there is a lack of validity in the model assumption that a person with a poor quality of life would remain uncontrolled for many years rather than modifying their diet: - At NSPKU we observe that individuals with uncontrolled PKU typically have a range of issues which inhibit their ability to achieve control of their phenylalanine levels; eg depression, anxiety, fatigue and impaired executive functioning. - This issue was confirmed in the NHS England CCP "In adults, neurocognitive and executive function deficits leads to inability to sustain dietary treatment, causing chronic poor blood phenylalanine control with negative impacts on mental health, quality of life, and daily functioning"
Key issue 10: Effect of sapropterin on protein-restricted diet	Our evidence from patients using sapropterin in the UK is that they eat no prescribed low phenylalanine food at all or very small amounts. This was due to their increased phenylalanine tolerance allowing them to eat normal food. Patients also had a reduction in prescribed protein substitute. Patients are also highly motivated to substantially reduce use of both protein substitutes and prescribed food as patients typically strongly dislike them.
Additional technical team questions	
14. Does damage to the brain and nervous system happen in children with phenylketonuria managed within the NHS?	NSPKU does not agree with the assertion that close clinical management ensures that blood phenylalanine levels remain controlled in all but exceptionally rare cases. There are still children with PKU who experience long periods of uncontrolled phenylalanine levels. As example of such as case is evidenced in the judgment of the High Court in R (on the application of SB) v NHS England [2017] EWHC 2000 in which the parents of a 7 year old child with chronically uncontrolled phenylalanine levels brought a judicial review for individual funding for Sapropterin. It was accepted that the child was at risk of neurological harm.

	NSPKU is aware of other cases of chronic poor adherence in children occurring in England. There is clear evidence that children with PKU suffer neurological damage which reduces their IQ potential. The 4-7% drop in IQ compared to unaffected siblings is referred to in successive NHS England draft clinical commissioning policies from 2015, 2018, 2019 and 2020. Changes in white matter integrity, which are linked to decreases in IQ and executive functioning are observed in early treated children with PKU, González, M.J., Polo, M.R., Ripollés, P. *et al.* White matter microstructural damage in early treated phenylketonuric patients. *Orphanet J Rare Dis* **13,** 188 (2018). NSPKU is also aware of tremor being reported by children and young people with PKU to the extent that it can interfere with the ability to undertake usual tasks, for example fine motor tasks like writing and painting. This observation is confirmed by recent research which found high levels of early onset tremor in patients with PKU*, Francesca Nardecchia, Filippo Manti, Sabrina De Leo, Claudia Carducci, Vincenzo Leuzzi, Clinical characterization of tremor in patients with phenylketonuria, Molecular Genetics and Metabolism, Volume 128, Issues 1–2, 2019, Pages 53-56.* NSPKU disagrees with the view that there is no evidence of neurological harm in children with PKU or that damage resulting from drops in IQ potential has no value in an ICER. This appraisal should also consider the issue of cumulative harm as very poor outcomes seen in some adults will have been caused by harm occurring before the age of 18.
15a. What proportion of children go on to develop neurological damage because of uncontrolled phenylalanine levels despite being prescribed a protein restricted diet?	There is no registry data in the UK. Studies suggest a high proportion of early treated paediatric patients have changes in white matter integrity, reductions in IQ potential and executive functioning deficits. Damage may be cumulative and manifest in adulthood.

15b. For those children who do develop neurological damage, what other treatments and care (health and social) will these children require?	Input to improve dietary adherence – see answer at 19 below. Children with neurological damage will require input from an educational psychologist, additional support at school and counselling. Social services – Children with poor adherence at risk of neurological damage or who have sustained neurological damage may become subject to child protection arrangements. There is no data for this due to the inherent difficulty of studying this but consultation with paediatric dietitians and our helpline/welfare work at NSPKU strongly suggests that children with PKU are vulnerable to being removed into care at a much lower threshold than children without a disability. It is likely that serious damage is more likely to become manifest in adulthood with accumulated exposure to phenylalanine and/or malnutrition. In 2017 NSPKU interviewed a 42 year old adult patient who described having poorly controlled phenylalanine levels in childhood. She had two disabled children affected by Maternal PKU. She described nerve damage, problems with memory and organisation which affected simple tasks, shaky hands, problems putting shoes on, an inability to work and relying on her partner for care and support. We are aware through our helpline work of early treated patients who require significant care packages however prevalence of poor outcomes is hard to study.
16. Does a 71.2% reduction in protein-restricted diet due to treatment with sapropterin reflect the level expected in clinical practice? (see ERG report page 77) If no, what approximate percentage reduction in protein-restricted die do you anticipate in clinical practice with sapropterin?	Yes. The evidence from patients using sapropterin in the UK is that they eat no prescribed low phenylalanine food at all, or very small amounts. This was due to their increased phenylalanine tolerance allowing them to eat normal food. Patients also had a reduction in prescribed protein substitute.

17. Is a utility level of 0.095 appropriate or realistic for a patient with severe PKU symptoms and on a protein-restricted diet? (see ERG report pages 75 and 76) If no, what level reflects this state in clinical practice?	
Technical engagement questions	
18a. Are the comparators (the current treatment available in the NHS) in the company submission used in the NHS for treating phenylketonuria?	Some patients with PKU have no access to treatment at the moment due to issues such as learning disabilities impairing their ability to adhere to treatment. It should not be assumed that patients with uncontrolled phenylalanine levels are exercising a free choice to not treat their PKU.
18b. Is the assessment tool used in the clinical trial appropriate for assessing the severity of phenylketonuria?	18 b – This question is unclear. What is being referred to?
18c. What are the main benefits of sapropterin for patients? If there are several benefits please list them in order of importance. Are there any	18 (c) See answer given at 9 a above. Benefits not captured (i) Many parents report that their children had improved mood and attention on sapropterin and these anecdoctal results are also confirmed by the Burton (2015) study which found improvements in ADD symptoms. The Burton study was included in the 2018 evidence

benefits of sapropterin that have not been captured? 18d. What are the benefits of sapropterin for carers?	review performed by NICE for NHS England. (ii) Carer disutility is ignored. (iii) Quality of life improvements is not captured in the ERG Report. 18 (d) – See answer given at 9 a above.
19. Are there any important issues that have been missed in ERG report?	This appraisal could risk producing a distorted picture of the value of sapropterin for several reasons. <u>The methodology for costing the current dietary treatment is flawed as the resources used in delivering current dietary treatment are undervalued.</u> At page 65 of the ERG report it is suggested that the average resource use is 3.3 consultant led appointments for an "uncontrolled" child and 4 appointments which are non-consultant led. However an uncontrolled child would require: - Regular telemedicine consultations between a dietitian and the carer about phenylalanine results, issues being experienced, changes to the diet, etc - Home visits to assess reasons for non-compliance, multi-disciplinary interventions and the involvement of social services would also be required. These are not captured in the calculations. - In addition, trying to get non-adherent children to have controlled phenylalanine levels will have a huge impact on carers, requiring hours of their time and skills. This is costed at zero but this work will dominate the life of the carer. - NSPKU strongly endorses the statement at page 31/32 of the Company Submission that the costs of delivering the treatment is not captured by local tariffs. - Finally, there is substantial unmet need in patients with PKU. As an example, children and young people with Type 1 diabetes have access to mental health professionals with an understanding of the condition https://www.nice.org.uk/guidance/qs125/chapter/Quality-statement-6-Access-to-mental-health-professionals-with-an-understanding-of-type-1-or-type-2-diabetes There is an equivalent need for this provision in patients with PKU who

	have similar levels of disease and treatment related distress. However this is not readily accessible to most patients with PKU. Adult patients who cannot adhere to dietary treatment receive very little support. - PKU treatment is under resourced in the UK. NICE should not under-price the incremental cost per QALY of sapropterin by accepting that services needed by patients on dietary treatment are either provided by NHS staff for free or not provided at all. - The Metabolic CRG including costs savings from resource use within their Preliminary Policy Proposal. This stated "*Those that struggle to maintain the unpalatable diet and require extra intervention from dietician and psychologists to help their dietary control; this is estimated as 7-10% of the PKU population."* NSPKU understands these savings were not included in NHS England impact assessment calculations. - NICE should include such savings and should rectify failures in the tariff by according an appropriate value to telephone contact between metabolic teams and patients. <u>Health related quality of life</u> NSPKU also endorses the concerns raised in the Company Submission that many people with PKU are likely to fail to articulate their health related quality of life. We are also concerned that research across PKU is often distorted by failing to capture the experiences of people who are not in long term follow up or have the functional impairments which are likely to inhibit their likelihood to volunteer for research. <u>Carer disutility</u> At page 84 of the ERG report is stated that inclusion of parent/carer disutility would reduce the size of the ICER gained for children by 50%. NSPKU also considers that many adult patients are reliant on others to help them manage their treatment or daily functioning. For example we have seen many patients who rely upon partners to help them cope with executive functioning deficits and managing their dietary therapy.

	The failure to appropriately value the carer disutilty has an obvious distorting effect on this appraisal unless this is rectified. Model does not account for cumulative harm The statement "*in general the costs and benefits associated with treatment with sapropterin only occur while a patient takes sapropterin and stops when a patient stops taking sapropterin*" is too crude. High and varying phe levels (particularly in childhood, adolescence and early adulthood) can cause permanent harm and co-morbidity. Maternal PKU The prevention of neurological damage to unborn children and improvements to the pregnancy experiences of women is not properly accounted for. Also refer to the issues stated under Key Issue 2.

PART 3 -Key messages

20. In up to 5 sentences, please summarise the key messages of your statement:

- The existing treatment for PKU is inadequate and associated with low rates of adherence, health problems associated with the diet and poor quality of life.
- Sapropterin allows patients to control their phenylalanine levels in a long term and sustainable way which will improve cognitive outcomes, health and daily functioning.
- PKU is a rare disease which is hard to study and this appraisal should approach uncertainties in the evidence within this context.
- Disregarding parent/carer disutility will significantly distort the ICER gained for patients of all ages.

- Patients using sapropterin report that the treatment had a transformative effect on ability to adhere to treatment, quality of life, mental health, nutrition and the lives of their families.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Sapropterin for treating phenylketonuria [ID1475]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Wednesday 16 December 2020**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with phenylketonuria and current treatment options	
About you	
1.Your name	**Sharon Buckley**
2. Are you (please tick all that apply):	☐ a patient with phenylketonuria? ☐ a patient with experience of the treatment being evaluated? ☒ a carer of a patient with phenylketonuria? ☐ a patient organisation employee or volunteer? ☒ other (please specify): Administrator of a PKU Facebook support group with over 3000 members
3. Name of your nominating organisation.	The National Society for Phenylketonuria
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: Administrator of a PKU Facebook support group with over 3000 members ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with phenylketonuria? If you are a carer (for someone with phenylketonuria) please share your experience of caring for them.	I am the parent to two young adults living with Phenylketonuria (PKU); my daughter is 23 years old and remains on the diet as best she can, and my son is 21 years old and is off diet. Both my children were diagnosed via new-born screening with classical PKU after having levels slightly above 3000 micromols at diagnosis. Prior to having children, I worked full-time, but not long after my daughter was born, it became obvious that I could not return to work full-time. [redacted] Managing the demands of the PKU diet is time consuming: attending hospital appointments, creating and baking low protein substitute foods, ordering/collecting prescriptions, scouring supermarkets, and educating those involved in their care; for example, parties, sleepovers, tea at a friend's, holidays and school trips. I was determined that my children had to lead a 'normal' life and I had to reduce the impact PKU had on their childhood. In a study

	that examined the parental experience of caring for a young child with PKU, Carpenter et al, 2018 identified, that the strife for a “normal” life for their child was a coping behaviour often carried out by parents of young children with PKU. However, I didn’t feel like I was coping, there simply was not enough hours in the day. I would go to bed thinking about PKU, worrying about what more could I do, and I would wake up thinking about PKU. When my daughter started school, I became a lunch time supervisor at her school as I was convinced that her diet would not be managed adequately by the school. I returned to part-time work when my children were 6 and 4 years old and to assist me, my mother-in-law would do some of the cooking, i.e. making bread and my mum would do child-care duties. It was fortunate that I had family close by. When my son began high school, he shied away from letting people know that he had PKU, he felt awkward and ashamed of his special low protein foods. He wanted to fit in and be able to eat the same foods as his peers. Subsequently, from around the age of 13 his phenylalanine (Phe) levels were recurrently beyond 600 µmol/L. Living with a teenager that was not following the diet was a tremendous strain, life was a constant battle of utilising varying strategies aimed to make him accept the boundaries of the diet. The arguments over food negatively impacted on the fun, laughter and trust that I had with my son (who was otherwise a polite, witty and caring boy). His rising Phe levels also affected his schooling; I was often called into school to discuss his inattentive and impulsive behaviour. As his Phe levels rose, so too did his weight. Across his teenage years at his various metabolic appointments, my son spoke about how he could not tolerate PKU and the 4 grams of protein he was supposed to be limited to. His clinic said that, “doing his own thing was to be expected and that he would find his own way back”. My son was advised by his metabolic team to stop the PKU diet shortly before his 16th birthday as his weight had (apparently) become the most compromising issue to his health and he was unable to manage Phe levels within target range. As yet, there is no approved prevention, or

	treatment intervention for overweight and obese people with PKU. My husband and I was not warned by the medical team that they were going to recommend coming off the diet, and when my son heard the words that he could stop the diet, he felt like all his dreams had come true. The team advised that he stop all amino acid supplementation when desisting from the diet. The first off diet food that I cooked for my son was a bacon sandwich. Whilst I cooked that bacon, I cried so very much, I was heartbroken; cooking a high protein meal for my son cut through everything I knew that was about keeping my son safe. A month after being completely off the PKU diet (that was intended to aid weight loss) he began to gain weight. It became increasingly obvious that he was unable to be selective amongst such a wide range of foods that he was now 'allowed' to eat. Whilst I had thought that controlling his food consumption in his younger teenage years was difficult, it had nothing on his new and increasing appetite. Less than 10 months after stopping the PKU diet he had gained 3 stone. Within a year of being off diet, whilst on a family holiday to Spain my son became feared for his safety; he believed he was going to be robbed, kidnapped or blown up. His paranoia was so extreme that whilst in Spain an urgent referral to a mental health unit was made and he was assessed as having psychosis and placed on anti-psychotic medication. We also started him back on the PKU diet and amino acid supplements, though as he became more mentally settled, he desisted from the diet. My son is no longer paranoid, but he does now have agoraphobia, suffers from panic attacks, he has socially withdrawn and suffers from mood swings. Before his psychological breakdown, my son was due to do a Btec level 2 at college. However, he was unable to do this and barely left the house because of anxiety. We have had intervention from our local mental health team, be it from a psychiatrist, family therapy, cognitive behavioural therapy and an individual support worker (funded by the NHS and privately). But in terms of support from the PKU clinic, there has been little help, as these services are not integrated within routine metabolic care.

	Five years later, my son has had many attempts at getting back on diet but fails to remain on diet. He still lives at home and he has the best support network in us (I had to stop working as a lecturer to care for him) and his sister (with PKU). Between us, when he wants to be on the diet, we run and respond to his every food need. However, that is not enough! When it comes to the PKU prescription foods, I can only describe it as, that my son has a phobic response in the desire and ability to eat PKU prescription food and anything else low protein. That in itself is one big reason as to why my son cannot remain on the diet as he quickly becomes very hungry after a few days and then binge eats protein! He's never had a problem in taking the protein supplements (which is unusual to most people's experiences, for example, my daughter struggles with recurrent bouts of acid reflux due to the supplements and it causes her to have time off work). Another major problem my son has when returning to diet is the major crashing headaches and general overall body aches. The way he describes these pains are an upper body tingling with pins and needles in the lower arms. His metabolic clinic said that the return to diet was altering his neurochemistry and that his sensory system was wakening up from the 'fog'. High Phe levels reduce "*glutamatergic neurotransmission, which results in reduced synaptic plasticity, and in turn atrophy",* (Ashe et al, 2019). The longest return to diet that he has had was two months before Christmas 2019 and it was the worst experience of our lives (even worse than his original psychotic episode). Between October (2019) to February (2020) he had 20 visits to accident & emergency and possibly as many as 20 GP appointments. This was because he was convinced, he was dying of something (what it was changed each time). These health anxieties were really debilitating to him and us too! It is not that my son has a lack of discipline or family support that prevents him doing the diet. But that, trying to get on the diet makes him feel so very poorly (physically and psychologically). Our last experience of trying to help him back on diet has left us feeling scarred and fearful. I strongly believe that he would need to be admitted as a hospital inpatient, or to a rehabilitation clinic in order to be successfully

	transitioned on to the PKU diet. Possibly, if his brain could be given the opportunity to function without the deleterious effects of high Phe he could find confidence in life. [redacted] My son's adult metabolic team know that he cannot cope with a full phenylalanine restricted diet and as a way forward, they have advised him to return to taking amino acid supplements to help mitigate some of the negative effects of being off diet. This advice is contrary to the advice he was given when he was originally taken off the diet. He was told to not take amino acid supplements as there was little point in him having them without being on the PKU diet. From attending various NSPKU conferences and speaking with other patients, I know many with PKU share a similar story. Living life with the burden of Phenylketonuria is consuming. The current diet only therapy has failed my son, he was told to come off the therapy with no alternatives. When my son was born, I held dreams of him growing into a strong, healthy, happy and independent man. He is none of these; I do not see a time when he will live independently. Maintaining my own mental wellbeing is something I have to work very hard with. *Ashe, K., Kelso, W., Farrand, S., Panetta, J., Fazio, T., Jong, G. D., & Walterfang, M. (2019). Psychiatric and Cognitive Aspects of Phenylketonuria: The Limitations of Diet and Promise of New Treatments. Frontiers in Psychiatry, 10. doi:10.3389/fpsyt.2019.00561.* Carpenter, K. Wittkowski, A. Hare, D. J. Medford, E. Rust, S. Jones, S. A., and Smith, D. M. (2018). Parenting a Child with Phenylketonuria (PKU): an Interpretative Phenomenological Analysis (IPA) of the Experience of Parents: *Journal of Genetic Counseling*, 1-13.

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for phenylketonuria on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	7a. The current dietary treatment option available for all PKU patients on the NHS relies on dietary adherence. Maintaining an optimal low protein diet coupled with the unpalatable synthetic protein substitutes is arduous and super restrictive amongst 21st century living. Research depicts that 30% of children under 10 years of age and 80% of patients in their mid-teens do not have Phe levels within target range, (Walter, 2002). For these people, that are viewed as not complying to the diet, there is a lack of interventions that aid treatment compliance. For example, psychological support that promotes resilience and wellbeing in patients or caregivers is not a fundamental part of routine care. Though the statement on pg 20 of the ERG report outlines that, “a multidisciplinary team is involved in the clinical management of patients with PKU, including consultants, psychologists, specialist nurses and dieticians.” In reality, gaining access to the various elements of the ‘team’ is not achievable. Managing the PKU diet with the current dietary therapy is a tricky balance; in the UK the diet is managed using a traffic light system; Red for completely forbidden foods; Amber for counted exchange foods; Green for uncounted free foods. The amber listed foods are a constant source of difficulty, as a person can only eat from this list if they have enough protein allowance. The foods on the amber list have to be given to patients as this is where they get their natural protein from. However, as blood Phe levels change the amount allowed of these foods can vary dramatically, and consequently a prior allowed food can become a forbidden food (and vice versa). There are foods on this list that my son for example, ate routinely as a baby and consequently developed a liking for that food. For example, when my son was a baby, 20 grams of baked beans (equals 1 gram of protein) was adequate for his appetite, but as he became older, 20 grams of beans went nowhere to filling him up. When my child was younger, he had a small appetite due to the amount of medication he was required to drink. Consequently, foods from

	the amber list needed to be chosen based on low volume and higher exchanges. But the older he got his appetite became bigger and the amber food list became a constant source of difficulty. The current treatment takes away spontaneity. For example, if a child wants to have tea at a friend's house after school, or if an adult wants to go for a social meet up after work, this cannot be done without lots of previous planning. My daughter, currently manages her diet by making weekly menu plans, but how does a person plan for the unplanned? Planning and organisation does rely on good executive function as well as not having time pressures. I also do much of my daughter's prescription requests, supermarket shopping and home baking of low protein foods. There is not enough time in the day/week for my daughter to work full time and manage adequately the PKU dietary treatment. Not remaining on diet has been associated with constraints on time, stress linked with food preparation time, limits on social time and record keeping, (Bilginsoy et al, 2005). Another difficulty to the current treatment is that food manufacturers can often change recipes and ingredients. This can lead to mistakes being in made. This has been the case with the introduction of the sugar tax and the inclusion of the artificial sweetener Aspartame. This makes it very difficult for patients to be able to pick up a drink or snack when out and about. Another difficulty in managing protein intake can be that nutritional values that are often shown on packaging per 100g or they can be shown as 100ml, so calculations must be done and often a food will need to be weighed to find out exactly how many exchanges are contained in 1 portion. Another difficulty with managing protein intake based on food labelling relates to labelling inaccuracies. A recent study by Kraleva et al (2020), found that protein labelling is frequently erroneous. Protein labelling information was assessed for 462 food items, as much as 55% of items were either wrong or misleading. "*There was a high rate of incomplete, misleading, or inaccurate data affecting the interpretation of the protein content of food items on supermarket websites. This could adversely affect metabolic control of patients with PKU".*

	The availability and ordering of prescription foods also leads to difficulty. If a patient wants a pizza for a tea, it is not a simple case of going to the supermarket or even ordering a local pizza delivery; bases must be ordered from the chemist or made at home. Even to make a pizza base, a low protein mix must be ordered on prescription from the GP. The last request I sent to our GP for low protein items took 3 weeks before I actually received the items, meaning my daughter had to wait 3 weeks before she got the pizza she wanted for tea. Some doctors refuse many low protein prescription requests, stating that biscuits for example, are a luxury item. The current system of measuring Phe via the taking of blood spots at home and posting off to hospital labs is inadequate for the reliable monitoring of the diet. It can be at least four days before a patient gets their Phe result. Manging Phe levels also gets more complicated as a person ages due to protein no longer being used for growth and cell renewal. An adult that has been compliant to the diet can become disheartened and have internalised feelings of failure when they repeatedly have high levels due to no fault of their own. This can also lead a person to think, what is the point of being on diet? Often this circle of thinking leads many adults not to be on diet. Many women with PKU are petrified of becoming pregnant (whether planned or not) in case their Phe levels would be damaging to the unborn child, (Ford, O'Driscoll, & MacDonald, 2018, https://pubmed.ncbi.nlm.nih.gov/30416967/). For ladies that cannot maintain target Phe levels in pregnancy, then being able to access Sapropterin is a welcome option. However, the idea that a pregnant lady has to have unacceptable Phe levels before being able to access Sapropterin is unethical and puts an unborn child at risk. All women of childbearing age should be routinely allowed a trial of Sapropterin, and if found to be responsive to

	Sapropterin, then it should be part of their pregnancy care plan and ultimately available to them for the rest of their PKU treatment. 7b. Across the PKU community there is general agreement that there is a need for new treatments. This is borne from the many unmet needs that the current diet only therapy does not address and the difficulties that the diet places on people's lives. Since 2012, I have been the administrator of a Facebook group that was set up to provide support to people with PKU and their carers/families. This has over 3000 members, mostly from the UK and Ireland. There are a few observations that I can make from having reviewed posts on this community site: • Many posts are about trying to find things to eat or check if things are safe to eat. It is clear that people find it hard to cope with the dietary restrictions and that practical support is not readily available from the NHS for many patients. Many people cannot cope with maintaining the restrictions amongst every day life - for example going to work. • Parents frequently post about the difficulty they are faced with in trying to coerce their child to drink their amino acid supplement. • Many posts are about the lack of understanding they face, in trying to make sure schools and nurseries keep children safe or not being accommodated in cafes or restaurants. • It is a concern that many adult patients with PKU are not going to clinic. It is not uncommon for people to join the group because they are concerned about symptoms they are experiencing. Sometimes family members express worry that a person with PKU is clearly not doing well - e.g. has mental health problems, but will not go to clinic. • Many posts on the group indicate there is a high level of unmet need in the community of people living with PKU, with lots of people struggling with mental health, disordered eating patterns, health problems and an inability to cope with the current standard treatment for PKU.

	The majority of developed nations already use additional treatments such as Sapropterin and this further serves to frustrate and add burden to PKU patients and their families. (Bilginsoy, C., Waitzman, N., Leonard, C. O., & Ernst, S. L. (2005). Living with phenylketonuria: Perspectives of patients and their families. *Journal of Inherited Metabolic Disease, 28*(5), 639-649. doi:10.1007/s10545-005-4478-8). *Kraleva, D., Evans, S., Pinto, A., Daly, A., Ashmore, C., Pointon-Bell, K., . . . Macdonald, A. (2020). Protein Labelling Accuracy for UK Patients with PKU Following a Low Protein Diet. Nutrients, 12(11), 3440. doi:10.3390/nu12113440* Walter, JH, White, FJ, Hall, SK, MacDonald, A, et al. How practical are recommendations for dietary control in phenylketonuria? Lancet 360[9326], 55-57. 2002.
8. If there are disadvantages for patients of **current NHS treatments** for phenylketonuria (for example how sapropterin is given or taken, side effects of treatment etc) please describe these	There are many disadvantages for patients with the current NHS treatment of diet therapy. As well as my providing an answer here, the answer I provided in question 7 highlights the disadvantages of current NHS treatments. Essentially, following and complying to the diet is very difficult due the poor palatability of the low protein prescription foods and amino acid supplements. There is the possibility of nutritional deficiencies occurring because of the restrictive diet and use of medical foods. The nutritional deficiencies can result in increased risk of obesity, heart disease and bone pathology (Enns, 2010). Despite treatment, the current NHS treatment does not remedy neurological and psychosocial issues. Research has demonstrated that poor Phe control in childhood and adulthood leads to attention deficit, mood disturbance and impaired executive function. It is also unknown what the long-term effects of high phenylalanine levels have on morbidity and ageing.

	There is also a financial burden that families and patients endure. For example, the price of a packet of 4 gluten free (typically lower in protein) wraps can be as much as £3. Compare that to the cost of a packet of 6 regular wraps at £0.80p. The financial burden is further complicated by the change of household income due to the main caregiver often reducing their working hours. Enns, GM, Koch, R, Brumm, V, Blakely, E et. al. Suboptimal outcomes in patients with PKU treated early with diet alone: revisiting the evidence. Mol Genet Metab 101[2-3], 99-109. 2010.
Advantages of this treatment	
9a. If there are advantages of sapropterin over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does sapropterin help to overcome/address any of the listed disadvantages of current treatment that	9a. I have not been given the opportunity to know through experience the advantages of Sapropterin. The current NHS treatment of dietary management fails patients in all age groups. It is practically impossible for most patients to follow and maintain optimum neurological function, sustain Phe levels within range, and eat a diet of natural protein. Page 19 Of the ERG report, states that Sapropterin: 1) Increases the availability of neurotransmitters, such as dopamine, noradrenaline and serotonin. 2) Sapropterin can help patients with PKU to control and maintain their blood Phe concentration levels within, or closer to, the blood concentration levels recommended in the European PKU guidelines. 3) Sapropterin can also allow some patients to increase their daily natural protein intake and reduce their need to take low-protein and Phe-free medical foods, which can be unpalatable. Thus, all three of the above points are the advantages of Sapropterin.

you have described in question 8? If so, please describe these.	Whether you are a person with PKU or a carer of someone with PKU (irrespective of their age) the quality of life that you lead is directly negatively impacted throughout all areas of life. I refer back to the answer I gave in question 6, where I clearly highlight that PKU negatively affected my son's education, ability to work and to be part of society as a whole. Patients that can sustain Phe levels within target range see improvements in cognitive function, don't report as having psychiatric problems and are thus able to be more productive with improved quality of life, (Jahja, 2014). My son never leaves the house without the company of either my husband, myself, or his 82 yr old grandma. My son from the age of 13, rarely had Phe levels within target range. He suffers from panic attacks, agoraphobia (this does not mean that he is only scared to be outdoors, he's scared of being in any situation that he can't accurately predict what may happen), from a psychosocial perspective he can not maintain friendships (online or otherwise), he has an inability to see another person's perspective. He constantly lives with the feeling of being a failure and being inadequate. From the perspective of my daughter, PKU affects the amount of hours that she is able to work. She is a learning support assistant with a permanent contract of 25 hours per week. She has tried to take on more full-time work, however when she does, her ability to adequately manage the PKU diet is compromised as she is not left with enough hours to do all of her prescription orders, shopping and cooking. Not having enough hours to manage the diet ultimately results in a vicious cycle, whereby her Phe levels rise, resulting in a downturn of mood (including anger and frustration), which further leads to a reduced ability to focus and organise the diet. My daughter also feels excluded from many social situations, be it with friends or colleagues. Not being able to eat a diet with an higher amount of protein can often mean that my daughter will exclude herself from socialising in situations that involve food and drink. This leads to a lot of upset. As I stated in answer to question 6, my ability to work has been dramatically restricted in being the caregiver to my children (in childhood and adulthood). I

	am/was a research psychologist and lecturer in cognitive psychology, but I no longer work. I could not work the hours required or have that level of responsibility as I did not know when I would be up all night managing my son's distress or when I would have hospital appointments. Employers just don't give the level of flexibility needed. There is a lack of research when it comes to PKU and the caregivers lived experienced. However, It is acknowledged that in caregivers of children with diabetes mellitus, overwhelming stress occurs as a result of making sense of the condition, loss and grief, learning about the condition, monitoring symptoms and responding to changes in a child's condition, as well as interacting with health professionals. It is no different for the parents of children diagnosed with PKU. The permanent worry about PKU and the development of my children's brain has robbed me of ever feeling settled. The guilt and wonder of what more I could have done for my children is overwhelming. Indeed, greater levels of depression, anxiety, and perceived stress are frequently reported in caregivers managing children with chronic conditions. Caregivers are also reported as having higher levels of C-reactive protein (CRP). High levels of CRP is a risk factor for cardiovascular-related diseases and has also been linked to diabetes. [redacted] If my children had been given a treatment option that helped maintain optimum neurological function, sustain Phe levels within range, and have been able to eat a diet with more natural protein, then the quality of all our lives would have dramatically improved. 9b.

	It is too difficult to extrapolate one advantage and consider just one as more important than another as the advantages of having optimum neurological function, sustained Phe levels within range, and being able to eat a diet with more natural protein are all interconnected. 9c. Yes, Sapropterin does address the disadvantages. It is easy to use, aids Phe control, improves overall nutrition (and financial impact) by enabling the eating of more natural protein, it reduces the stress of the burden of treatment and increases the quality of life for patients and their carers. Jahja, R., Huijbregts, S. C. J., De Sonneville, L. M. J., Van Der Meere, J. J., and Van Spronsen, F. J. (2014). Neurocognitive evidence for revision of treatment targets and guidelines for phenylketonuria. *Journal of Pediatrics.*164:895–899.
Disadvantages of this treatment	
10. If there are disadvantages of sapropterin over current treatments on the NHS please describe these? For example, are there any risks with sapropterin? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	I'm not aware of any potential side effects that I'd be concerned about. Sapropterin appears to be a safe treatment that is already in wide use in other countries.

Patient population	
11. Are there any groups of patients who might benefit more from sapropterin or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	All patients that would respond to Sapropterin would benefit from this technology. I also do not consider it to be appropriate to commence a patient on Sapropterin and if they are found to be responsive to the treatment, to then take it away (as in the example of PKU mothers to be).
Equality	
12. Are there any potential equality issues that should be taken into account when considering phenylketonuria and sapropterin? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race,	Some patients with low IQ and executive dysfunction/communication skills could be unaware, fail to understand or be unable to articulate why they need this treatment. Indeed, it has been found that some patients are only able to report the improvement in functioning and have insight about their deficits after receiving treatment to control their blood Phe, (Simon, 2008).

religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	There are considerable difficulties in instituting a phenylalanine-restricted diet in people with learning and behavioural difficulties. Thus, people with learning difficulties will be less able to cope and manage with the phenylalanine controlled diet. https://jnnp.bmj.com/content/80/6/631 People such as migrants (whose first language is not English) are disadvantaged in terms of possibly not being able to adequately read food labelling. There are gender inequalities as the greatest caring role falls heaviest on women. People with socio-economic disadvantages will face greater and more complex struggles. Supporting a varied and sufficient protein restricted diet has financial implications – a kitchen needs to be well equipped with various implements for cooking; I have a cooker, bread-maker, waffle maker, toaster, airfryer, 2 fridges, 2 freezers, food mixer, blender, soup maker, baking trays and mixing bowl to name but a few). A computer, phone and internet source are becoming an increasingly essential tool in the management of PKU and not everyone has the finances to one acquire and sustain the cost. There needs to be housing that is suitable, stable, a supportive family, the ability to work be it flexible or not all. There's also the problem that co-vid presents, many consultations are taking place via telephone or computer. This is something that not all patients have equal access to.

Other issues	
13. Are there any other issues that you would like the committee to consider?	That the treatment be made equally available to all patients that are responders. There is some concern amongst the PKU community that adults are not considered as equal importance as compared to children.

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

ERG report key issues	
Key issue 1: Limited relevance of the registry data to the decision problem	
Key issue 2: Outcomes not addressed in the company submission	Stability of blood phenylalanine concentrations – the 2018 NHSE clinical evidence review found evidence that Sapropterin improves blood phenylalanine stability but did not review evidence on the significance of stable blood phenylalanine levels. The variability of blood Phe levels is more closely related to cognitive outcome than the mean lifetime blood Phe level in early and

	continuously treated children with PKU. There are also studies showing correlations between Phe fluctuations and deficits in executive functioning, cognition, and intelligence. V. Anastasoaie, L. Kurzius, P. Forbes, S. Waisbren**Stability of blood phenylalanine levels and IQ in children with phenylketonuria** Mol. Genet. Metab., 95 (1–2) (Sep 2008), pp. 17-20
Key issue 3: Blood phenylalanine concentration level as a measure of efficacy	According to The European Guidelines, blood Phe concentrations are the best surrogate measure for the treatment goal of normal neurocognitive and psychosocial functioning. However, metabolic control can not be characterized solely on blood Phe levels since tyrosine levels and tyrosine:Phe ratios are also important There is an agreement that increased dietary phenylalanine intake is important for quality of life, nutrition, the health benefits of a better diet and reduction in burden of care for patients and carers.
Key issue 4: Limited randomised controlled trial data available	
Key issue 5: Unrealistic company model pathway	

Key issue 6: Implausible time and age invariant health state transition probabilities	
Key issue 7: Methods used to calculate transition probabilities	
Key issue 8: Annual rate that patients stop taking sapropterin (attrition rate)	
Key issue 9: Utility values used in the model are highly unlikely to reflect the experience of NHS patients with phenylketonuria	
Key issue 10: Effect of sapropterin on protein-restricted diet	From my observations of what parents have reported in the PKU support group about their child using Sapropterin; one parent has spoken about how their child has gone from being allowed 8 grams of protein a day to now having 50 grams of protein daily. Thus, this increase of Phe has enabled the child to eat a more normal diet, using less prescription food . An additional benefit is that the child has also reduced their intake of amino acid supplementation. Parents are keen to reduce the use of both protein substitutes and prescribed food as often this is the area that is often the source of prolonged daily difficulty.
Additional technical team questions	

14. Does damage to the brain and nervous system happen in children with phenylketonuria managed within the NHS?	It has been found that children who were able to maintain Phe levels below 400 µmol/l in early to middle childhood, had the best IQ outcomes. However, research depicts that 30% of children under 10 years of age routinely have Phe levels well above target range. Waisbren et al, (2007) found that each increase of 100 µmol/l in lifetime Phe for early-treated PKU patients was associated with a 1.9–4.1 reduction in IQ. It should also be noted that the use of IQ as a measure of neurocognitive outcome may not necessarily be the most sensitive measure in people with PKU. IQ-score is the result of scores deriving from various tasks that measure differing domains of cognition, and higher than average scores on some tasks can hide poor or below-average scores on other tasks. So, it could be hypothesised that neurocognitive function is actually lower than reported scores. It is stated in The European Guidelines that there is not a complete understanding as to which consequences during adulthood are due to Phe levels before adulthood. So, it should not be presumed that damage to the brain does not occur in children managed by the NHS. (Crossley, L. H., & Anderson, P. J. (2010). Neuropsychological Functioning in Early-Treated Phenylketonuria – A Review. *Annales Nestlé (English Ed.), 68*(2), 78-88. doi:10.1159/000312815 https://www.karger.com/Article/PDF/312815).
15a. What proportion of children go on to develop neurological damage because of uncontrolled phenylalanine levels despite being prescribed a protein restricted diet?	

15b. For those children who do develop neurological damage, what other treatments and care (health and social) will these children require?	
16. Does a 71.2% reduction in protein-restricted diet due to treatment with sapropterin reflect the level expected in clinical practice? (see ERG report page 77) If no, what approximate percentage reduction in protein-restricted die do you anticipate in clinical practice with sapropterin?	
17. Is a utility level of 0.095 appropriate or realistic for a patient with severe PKU symptoms and on a protein-restricted diet? (see ERG report pages 75 and 76) If no, what level reflects this state in clinical practice?	

Technical engagement questions	
18a. Are the comparators (the current treatment available in the NHS) in the company submission used in the NHS for treating phenylketonuria? 18b. Is the assessment tool used in the clinical trial appropriate for assessing the severity of phenylketonuria? 18c. What are the main benefits of sapropterin for patients? If there are several benefits please list them in order of importance. Are there any benefits of sapropterin that have not been captured? 18d. What are the benefits of sapropterin for carers?	18a. The comparator of established clinical management without Sapropterin is used. It should be noted, that not all patients with PKU have equal access to treatment due to confounding factors such as being lost to follow up; learning disabilities impairing their ability to adhere to treatment and or lack of a support network. It should not be assumed that patients with uncontrolled phenylalanine levels are exercising a free choice to not treat their PKU. 18b. The assessment tools used to measure the success of Sapropterin, i.e. the lowering of blood Phe does not capture the real life benefits. No effort has been made to measure the effect of Sapropterin on the carer, for example, should a patient be responsive to Sapropterin, the carer will experience a better quality of life as the dietary burden of PKU lifts. The ERG Report acknowledges that the company does not capture health related quality of life data. It is acknowledged that in rare diseases in general, there is a lack of conceptual clarity as to how to assess quality of life and this is further complicated by the lack of an assessment tool/scale by which to capture quality of life in PKU. The patients and carers voice, when it comes to the lived experienced of PKU should not be ignored (as written in answer to questions 6 and 7). 18c. See answer given at 9a above. Patients that can sustain Phe levels within target range see improvements in cognitive function, don’t report as having psychiatric problems and are thus able to be more productive with improved quality of life.

	18d. There is a lack of research when it comes to PKU and the caregivers lived experienced. The management of PKU places a significant burden on carers; there's the gravity of initial diagnosis and the administering of the diet, and it is acknowledged that patients with PKU can suffer from behavioural, mood, emotional, and social problems, psychiatric disorders, intellectual development delays, and neurological deficits. There is no break from a Phe restricted diet and Sapropterin would help in finding a break. Leaving a patient with PKU for a length of time is not something that carers routinely do due to worries that the patient will not receive the correct foods or that they would be given a forbidden food or that someone else would not adequately manage the diet (i.e. log, weigh and calculate all foods). From my own experience, I have lost my freedom. In losing freedom I have lost the opportunity to go on holidays when I wish, take nights out with friends, attend church, go to the gym and have hobbies - anything that is time bound. Carers would regain the opportunity to establish social relationships that had no doubt been lost in their isolation of being a carer. Loss of freedom is also related to having an ability or not to work. Sapropterin would increase a carers ability to do paid work. I stated in answer to question 6, that my ability to work has been dramatically restricted in being the caregiver to my children (in childhood and adulthood). When I had to stop work completely, it eventually led to my feeling that I had lost my identity and self-worth. With the care burden being taken away, I would be able to work and gain some self-esteem back. I think a lot about what will happen to my son when I am no longer able to care and provide for him. I would gain an overall feeling of peace if my son was to receive a treatment such as Sapropterin that would help him maintain optimum neurological function, keep Phe levels within range, and eat a diet of natural protein. The overall feeling of wellbeing that carers would gain from being relieved of the dietary burden would be tremendous. Carers often have little time to practice self-care as they often put their own needs last, this also has detrimental health implications. Thus, feeling less stressed and having more time would lead to carers being healthier.

	Overall, carers would gain a greater quality of life and would shift to managing PKU around their lives instead of their lives being managed around PKU.
19. Are there any important issues that have been missed in ERG report?	Though the statement on pg 20 of the ERG report outlines that, “a multidisciplinary team is involved in the clinical management of patients with PKU, including consultants, psychologists, specialist nurses and dieticians.” In reality, gaining access to the various elements of the ‘team’ is not achievable. Many patients and carers wait days for replies to emails and telephones calls with their dietician. When my son needed psychological intervention throughout his teenage years to help him be on diet, there was no access to psychologists. Eighteen months ago, my daughter told her metabolic consultant that she does not have visual imagery (not a new deficit) and the consultant thought it prudent that she should be seen for a neurocognitive assessment. She still has not been seen even though she has now been referred twice. I would like to reiterate the concern raised in the Company Submission that many people with PKU are likely to fail to articulate their health related quality of life, as I very much agree with that. My son would not be able to affectively put into words how dramatically his life has been negatively impacted by not having control of PKU. As I already stated, my son suffers from panic attacks, agoraphobia, an inability to see from another’s perspective, he’s impulsive, inattentive, he struggles to maintain friendships and is extremely fearful to be left on his own. Everything that he does in his daily life is about managing all of what he struggles with, consequently and subsequently he manages me to meet all of his needs. Thus, my son conversely, wouldn’t ever say that he has a reduced quality of life, he’s happy in not going out, he does not need to go to the shops, he does not need to go to work, because he has me. There is also the concern that research throughout the area of PKU is often distorted by failing to capture the experiences of people who are not in long term follow up or have functional

	impairments which are likely to inhibit their likelihood to volunteer for research. My son is not lost to follow-up because I am very much active in keeping him known at clinics. It shouldn't be accepted as part of the course, for a young man of 20 (at the time) to have an FMRI scan and for there to be significant white matter changes found in the frontal regions of his brain. The cumulative harm of Phe levels being above target range should not be ignored; research depicts that 30% of children under 10 years of age routinely have Phe levels well above target range. Waisbren et al, (2007) found that each increase of 100 µmol/l in lifetime Phe for early-treated PKU patients was associated with a 1.9–4.1 reduction in IQ. It should not be assumed that caring duties solely fall on parents towards children; from the account I have provided in answer to question 6, I am still very much involved in the care of my adult children. From my involvement in the support group, I am also aware of many partners that care for their PKU partners and indeed of adult children caring for their parent with PKU.

PART 3 -Key messages

20. In up to 5 sentences, please summarise the key messages of your statement:

- The current dietary treatment option available for all PKU patients on the NHS relies on dietary adherence and this is not sufficient in remedying neurological and psychosocial issues in patients with PKU..
- There are many patients with PKU that are currently not receiving treatment as there are no alternatives to a protein restricted diet, Sapropterin would help fill that gap.

- Not all patients with PKU have equal access to treatment due to confounding factors such as being lost to follow up; learning disabilities impairing their ability to adhere to treatment and or lack of a support network.
- People living with PKU have reduced quality of life due to the many unmet needs that the current diet only therapy does not address.
- Sapropterin could help carers to gain a greater quality of life and would promote a shift to managing PKU around their lives instead of their lives being managed around PKU.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Sapropterin for treating phenylketonuria [ID1475]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	**Claire Foreman**
2. Name of organisation	**NHS England and Improvement**

3. Job title or position	**Head of Acute Programmes, National Specialised Commissioning Team**
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? **x**☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are European Guidelines which are used by clinicians to treat and manage patients with PKU in order that Phe levels can be reduced or stabilised to recommended levels to protect brain function and development.
6. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	**Pathway for England** This is a lifelong condition and affects both adults and children. PKU is detected in the newborn bloodspot screening programme enabling affected children to be diagnosed and start treatment soon after birth. Most diagnosed patients are referred to metabolic services and receive specialist dietetic input to help them manage the prescribed diet. This prescribed diet is very restricted; patients are only able to eat very low

experience is from outside England.)	levels of natural protein without the risk of brain damage and must take synthetic protein supplements up to 3 times a day. Current recommendations are that this Phe-restricted diet is continued lifelong. People with PKU should regularly monitor their blood Phe levels using a fingerprick test. Recommendation of frequency of monitoring varies from multiple times per week to two-four times monthly depending on age and other patient specific factors. Therapeutic targets vary with age as per the European Guidelines. Patients with PKU are under regular follow up with specialist metabolic dieticians, to advise on dietary modification including supplements which are funded by CCGs. We understand patients can find it difficult to comply with the strict diet and to tolerate the supplements. This can be very difficult for young children and further reduces with age. Clinicians estimate about 50% of adults leave treatment. Patients therefore require significant support, including practical and psychosocial support. Sapropterin is a medicine that can reduce the Phe levels in some patients. Treatment aims to lower the blood Phe levels to close to or below the European Guideline levels. Only patients with a specific genetic mutation can respond to this treatment. Testing for the mutation and responsiveness to the drug is required. If recommended, it is envisaged that Sapropterin would be dispensed during routine outpatient appointments and delivered via homecare.
7. What impact would the technology have on the current pathway of care?	We understand that current recommendations are that a Phe-restricted diet is continued lifelong therefore the treatment would not replace the current pathway but will modify that pathway for some patients. The treatment can assist with management of Phe levels in responsive patients that may result in: • Reductions in the cost of synthetic protein supplements • Small reduction in dietetics / psychology appointments In relation to pregnancy, see question 8.
The use of the technology	

8. To what extent and in which population(s) is the technology being used in your local health economy?	NHS England already has in place a published clinical commissioning policy which covers the use of sapropterin in pregnant women: 'Sapropterin for Phenylketonuria: Use in Pregnancy' available at: https://www.england.nhs.uk/wp-content/uploads/2013/04/e12-p-a.pdf Following consideration at the Clinical Priorities Advsiory Group (CPAG) for the 3rd time, NHS England has also published a Not Routinely Commissioned policy for Sapropterin for PKU (all ages) https://www.england.nhs.uk/publication/sapropterin-for-phenylketonuria-all-ages/
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The treatment is in use in eligible pregnant women (see above). There may be some access for patients via compassionate use schemes. Final recommendations will need to clarify the approach to patient sub groups and starting / stopping criteria to ensure these can be operationalised into clinical practice.
• How does healthcare resource use differ between the technology and current care?	The main difference relates to • Synthetic protein supplements • Dietetics support (may reduce) • Access to genetic testing (increased) • Homecare dispensing of treatment (increased)
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care – there are around 20 metabolic services commissioned by specialised commissioning that treat patients with PKU. As the service is an outpatient service, the granularity of coding means that activity is funded by both specialised and CCGs commissioners.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	If recommended, the main investment relates to the cost of the treatment.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Response to the treatment is dependent on genetic mutations and response which involves additional testing.
10. What is the outcome of any evaluations or audits of the use of the technology?	See the published evidence review produced as part of the policy development process: https://www.england.nhs.uk/wp-content/uploads/2020/11/1840-Evidence-Review.pdf
Equality	
11a. Are there any potential equality issues that should be taken into account when considering this treatment?	We understand there are population groups that may be disproportionately affected by PKU. An Equalities and Health Inequalities impact assessment has been published on the NHS England website: https://www.england.nhs.uk/wp-content/uploads/2020/11/1840-Equality-Health-Inequalities-Impact-Assessment.pdf

	In the event that recommendations are made for specific subgroups, any criteria for continuation or discontinuation of treatment for those patients falling outside of those defined subgroups would need to be clarified to ensure these can be operationalised into clinical practice.
11b. Consider whether these issues are different from issues with current care and why.	A recommended treatment which is clinically effective and cost effective may assist in addressing the equality issues faced by certain population groups that may be disproportionately affected by PKU.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Sapropterin for treating phenylketonuria [ID1475]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: **5pm, Wednesday 16 December 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Dietetic Association/National Society for Phenylketonuria (NSPKU)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**I have no links to the tobacco industry**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Limited relevance of the registry data to the decision problem	**YES/NO**	No – I disagree that this evidence is limited. In fact, it is very relevant and 'real world' evidence. The results are consistent with the randomised controlled studies but provide longer term results. The drug company has presented the results of their drug registries. I understand that it was mandatory that they established a registry in Europe and USA, as part of the respective licencing agreements. The prospective registry study by Longo et al. (2015) followed 504 USA adults and children who had taken sapropterin continuously for up to 7 years (median dose 20 mg/kg/day for a median of 4 years) and 218 patients who took sapropterin for only ≤ 3 months. The patients who took sapropterin for ≤3 months had lower reduction in blood Phe levels when initially given sapropterin. The registry recruited patients from many centres and includes children and adults. This registry data clearly shows (including the latest data presented by the company) that when taking sapropterin long term, patients were able sustain a higher phenylalanine intake as well as maintain blood phenylalanine levels within target range. In contrast, in diet treated patients it is established from many cross sectional, observational studies only that blood phenylalanine control deteriorates with age.

		From the registry results, after 5 years (n=48), a statistically significant 199 micromol/litre improvement in mean blood phenylalanine concentrations was seen compared with baseline (392 micromol/litre compared with 591 micromol/litre, p=0.0009). There was a 1.7 increase in phenylalanine tolerance. This is real world evidence for large numbers of patients with PKU. Data also showed that BH4 responsive adult patients treated with sapropterin were able to improve blood phenylalanine control, although in contrast, adult patients on diet treatment only had deterioration of blood phenylalanine control. The primary objective of the European *'Kuvan® Adult Maternal Paediatric European Registry'* (KAMPER) was to provide information over 15 years on the long-term safety of sapropterin in patients with HPA, in accordance with a post-approval commitment with the European Medicines Agency. It was also designed to collect information on the use of sapropterin in maternal HPA and on the effects on childhood growth, diet, blood phenylalanine levels and neurocognitive outcomes. This is an ongoing, observational, multicentre registry. It has collected data on around 627 patients. It provides useful descriptive statistics. At the 10th interim analysis, patients had sustained blood phenylalanine control (numbers small) within target range. Blood phenylalanine tolerance increased by 1.5 to 2 times. 10.3% discontinued sapropterin.
Key issue 2: Outcomes not addressed in the company submission	**YES/NO**	Yes, there are omissions in the data presented by the company. • Impact on neurocognitive functioning and executive functioning (although cognitive functioning being addressed in 7 years Kognito study in children). • Impact on reducing burden of dietary care for carers and patients (particularly in patients/families who are socially vulnerable e.g., lone parents, poor health literacy, immigrants, travelling families, poor literacy skills).

		• Impact of sapropterin on enabling adults with PKU to recommence treatment if previously discontinued. • Outcome of sapropterin usage in patients late treated with sapropterin. Does sapropterin help reduce support needs? • Impact /role of sapropterin during pre-conception and in the postnatal period in maternal PKU.
Key issue 3: Blood phenylalanine concentration level as a measure of efficacy	**YES/NO**	Yes- blood phenylalanine levels should be used as a measure of efficacy. Phenylalanine accumulates in biological fluids and in brain tissue as consequence of phenylalanine hydroxylase deficiency. There is a clear relationship between higher blood phenylalanine levels and neurocognitive outcome (*Van Wegberg AMJ, MacDonald A, Ahring K, Belanger-Quintana A, Blau N, Bosch AM, et al. The complete European guidelines on phenylketonuria: Diagnosis and treatment. Orphanet Journal of Rare Diseases. 2017;12(1):162. 84*). Pilotto et al 2020 provided strong evidence for a correlation between phenylalanine levels and clinical, neuropsychological, neurophysiological, biochemical and imaging alterations in adult phenylketonuria patients. Nineteen phenylketonuria patients (median age 41 years) with different phenylalanine levels (median 873 µmol/L) entered the study. They showed higher prevalence of neurological symptoms, cognitive and behavioural abnormalities, autonomic dysfunction, alterations in neurophysiological measures and atrophy in putamen and right thalamus compared to controls. Plasma phenylalanine levels highly correlated with the number of failed neuropsychological tests, neuropsychiatric symptoms) motor evoked potential latency and parietal lobe atrophy (*Pilotto A, Zipser CM, Leks E, Haas D, Gramer G, Freisinger P, Schaeffer E, Liepelt-Scarfone I, Brockmann K, Maetzler W, Schulte C, Deuschle C, Hauser AK, Hoffmann GF, Scheffler K, van Spronsen FJ, Padovani A, Trefz F, Berg D. Phenylalanine effects on brain function in adult phenylketonuria. Neurology. 2020 Oct 22:10.1212/WNL.0000000000011088. doi: 10.1212/WNL.0000000000011088. Epub ahead of print. PMID: 33093221).*

		There have been 2 important meta-analysis in children and young adults that have showed a relationship between phenylalanine levels and neuropsychological outcomes. 1. Waisbren et al. (2007) performed a meta-analysis examining the correlation between IQ and Phe levels reported in 40 different publications. She concluded that a difference of 100 µmol/l between birth to 6-12 years predicted a difference in IQ between 1.3 to 3.1 points in patients whose blood Phe levels ranged from 423-750 µmol/l. Regarding lifetime Phe levels an increase of 100 µmol/l predicted an average 1.9 to 4.1-point reduction in IQ over a range of Phe from 394-666 µmol/l. For example, a patient with a Phe level of 500 µmol/l, on average had a 1.9 to 4.1-point lower score on an IQ-test compared to someone with a Phe level of 400 µmol/L (*Waisbren SE, Noel K, Fahrbach K, Cella C, Frame D, Dorenbaum A, Levy H. Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. Mol Genet Metab. 2007 Sep-Oct;92(1-2):63-70)*. 2. Fonnesbeck et al. (2013) performed a meta-analysis of 17 studies (432 individuals with PKU, aged 2-32 years) and addressed the relationship between the probability of an IQ less than 85 and Phe levels. The healthy population probability of an IQ less than 85 was approximately 15%. For PKU patients the probability was 14% when the mean blood Phe level during the time frame of ≥6 years of age was 400 µmol/L but increased to 20% when the mean Phe level was 600 µmol/L (*Lindegren ML, Krishnaswami S, Reimschisel T, Fonnesbeck C, Sathe NA, McPheeters ML. A Systematic Review of BH4 (Sapropterin) for the Adjuvant Treatment of Phenylketonuria. JIMD Rep. 2013;8:109-19).*

		Routine monitoring of patients with PKU is based predominantly on phenylalanine levels, so measurement of phenylalanine is of crucial importance.
Key issue 4: Limited randomised controlled trial data available	**YES/NO**	I do not agree that the randomised controlled data is limited. The European PKU Guidelines statement state that PAH deficient patients proven to be BH4 responsive should benefit from an increase in their phenylalanine tolerance and /or better metabolic control by treatment with BH4. This was given a grade of B, which is a high score rating and indicates that evidence of evidence with sapropterin is strong. (*Van Wegberg AMJ, MacDonald A, Ahring K, Belanger-Quintana A, Blau N, Bosch AM, et al. The complete European guidelines on phenylketonuria: Diagnosis and treatment. Orphanet Journal of Rare Diseases. 2017;12(1):162. 84*). The evidence review 'sapropterin for phenylketonuria' conducted by the NICE Medicines and Technologies Programme on behalf of NHS England Specialised Commissioning, March 2020 concluded that the level of evidence was for: Impact on blood phenylalanine concentrations: Grade A Impact on phenylalanine tolerance: Grade A Stability of blood phenylalanine concentrations: Grade C • Thereby it is clear from the available trial data that sapropterin lowers blood phenylalanine levels and improves phenylalanine tolerance in the sub section of patients who are sapropterin responsive. • Phenylketonuria is a rare disease and the research/registry data available is more extensive and longer term with sapropterin usage than data for other

		drugs used to treat some rare disorders which are already funded by the NHS. Most of the available data has been sponsored by industry. The company have only collected data required by them for regulatory purposes. It would require 'huge' funding investment to conduct randomised controlled studies outside industry investment.
Key issue 5: Unrealistic company model pathway	**YES/NO**	Yes, it is a difficult model pathway to understand. However, there are likely to be considerable cost differences between patients with PKU in a controlled and uncontrolled state. Patients with PKU in an uncontrolled state will take up a significant amount of health/non health resources in order to support them. It is very difficult to bring patients into sustainable long-term metabolic control using conventional dietary treatment only.
Key issue 6: Implausible time and age invariant health state transition probabilities	**YES/NO**	Possibly. However, in my experience of using sapropterin in studies over the last 10 years with children, I have observed that children with long term use have maintained their blood phenylalanine control within target range without or limited deterioration. In contrast, almost all children on dietary treatment only have some deterioration of control. Children living in social disadvantage have more deterioration of their control throughout childhood years. Generally, if we observe very poor blood phenylalanine control by the age of 2 years, it is difficult to gain control again, without safeguarding intervention. Once *van Rijn M, Ahring K, Bélanger-Quintana A, Dokoupil K, Ozel HG, Lammardo AM, Robert M, Rocha JC, MacDonald A. When should social service referral be considered in phenylketonuria? Mol Genet Metab Rep. 2015 Feb 9;2:85-88.*

Key issue 7: Methods used to calculate transition probabilities	**YES/NO**	This is a difficult question to answer but my understanding from is that this information has been calculated from the USA registry data working between controlled and uncontrolled states with patients on sapropterin – which is similar to my clinical experience. If patients were proven to be sapropterin unresponsive at one stage in life (and I consider patients in the USA registry study on sapropterin for ≤3 months were not 'true' sapropterin responders); they would be unlikely to become sapropterin responsive later in life as responsiveness is dependent on their severity of PKU.
Key issue 8: Annual rate that patients stop taking sapropterin (attrition rate)	**YES/NO**	Yes. 10% is a reasonable suggestion and the percentage identified from the USA registry study. I currently have 11 patients on long term sapropterin (either performing studies, successful IFR's or self-funded) and there is no suggestion that any patient has any need/desire to stop using sapropterin. Adherence with the drug is excellent. Patients consider this is a very easy treatment to adhere to in comparison to the rigorousness of a low phenylalanine diet.
Key issue 9: Utility values used in the model are highly unlikely to reflect the experience of NHS patients with phenylketonuria	**YES/NO**	Yes. They do not appear to have captured the life cycle costs of all the full range and severity of all patients with PKU (including the needs of late treated patients with PKU). As acknowledged in the proposed policy, some parents will struggle with the demands of this relentless and harsh dietary treatment and children (cared for by the NHS) may have long term poor blood phenylalanine control starting early in life. Once a patient is poorly controlled in early childhood, it is likely that neurological damage occurs and it is very difficult for an individual to successfully manage dietary treatment later in life due to the executive, cognitive and psychological issues they experience. Much of the dietetic, social and community support into caring for this group of patients is probably underreported and thereby costs are

		likely to be underestimated. Much professional time is spent trying to help re-establish dietary treatment, commonly without success. Also, child safeguarding measures may be implemented. This is time consuming, commonly involving a wide team of professionals. Therefore, the economics of this group should be factored into the impact assessment costs.
Key issue 10: Effect of sapropterin on protein-restricted diet	**YES/NO**	Yes. I have new data from a systematic review which is due to be submitted for publication to the *Nutrients* Journal in early February 2021. It is expected to be published within 6 weeks of submission date if accepted by peer reviewers. **This information should be kept confidential. Academic information has been removed**

Additional technical team issues

Please use the table below to respond to questions raised by the NICE technical team related key issues presented in the ERG report. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key questions	**Does this response contain new evidence, data or analyses?**	Response
1. Does damage to the brain and nervous system happen in children with PKU managed within the NHS?	**YES/NO**	Yes, but this is information that is not routinely measured in the UK. Palermo and colleagues performed a cross-sectional study on the outcome of IQ and several neuropsychological skills of early and continuously treated UK (Birmingham) adult patients with classical PKU. With respect to age-matched

		controls, the authors found that only 38% of subjects attained a totally normal IQ and neuropsychological performances while in contrast 24% shows a definitively pathological score in one or both domains. Average IQ of ECTPKU patients was lower than that of controls and the number of impaired cognitive tasks was significantly higher in PKU as compared to controls. In the UK, Ford et al 2018 survey, it was reported that 28% (n= 67/236) of children had educational difficulties at school, with 19% (n= 51/272) receiving school intervention for educational or behavioural issues. Data from Birmingham PKU paediatric clinic about the number of children receiving an educational support through an Education, Health and Care (EHC) plan has been removed. In any UK paediatric clinic, there are children with PKU with persistent poor control, with less than 70% of their blood phenylalanine levels within target range. The higher the percentage of levels outside target range, the greater the risk of brain damage occurring due to PKU. Data published in 2002, showed that in UK children under 10 years had 20 – 30% of blood phenylalanine levels above target range. It is likely that some of the individual children would have had sustained poor blood phenylalanine control over time. *Walter JH, White FJ, Hall SK, MacDonald A, Rylance G, Boneh A, Francis DE, Shortland GJ, Schmidt M, Vail A. How practical are recommendations for dietary control in phenylketonuria? Lancet. 2002 Jul 6;360(9326):55-7.*

2. What proportion of children go on to develop neurological damage because of uncontrolled PHE levels despite being prescribed a protein restricted diet?	**YES/NO**	Yes Leuzzi et al 2020 concluded: • an undetermined, but relatively high, percentage of early and continuously treated phenylketonuria (ECTPKU) patients have an IQ score lower than expected (as compared to healthy controls or unaffected relatives) • a clinically relevant neuropsychological impairment is found in about 25% of ECTPKU subjects • about 90% of adult ECTPKU shows variable white matter alterations on brain MRI • 20-40 % of ECTPKU suffer from minor neurological symptoms (tremor, brisk lower limb reflexes, mild motor impairment) • about 0.4% of early treated PKU who have discontinued the diet experiences severe neurological deterioration that may be reversed by metabolic control restoration. • exceptional PKU cases suffer in adulthood from visual impairment after diet discontinuation that can be reversed by reinitiating the diet (Leuzzi, unpublished case). The cumulative results of several studies show that: a) blood levels of phenylalanine (≥400 µmol/l) during the first 12-14 years of life influence (predict) the IQ level at adult age b) after the age of 14-18 years IQ score is less affected by the levels of blood phenylalanine. *Leuzzi V, Chiarotti F, Nardecchia F, van Vliet D, van Spronsen FJ. Predictability and inconsistencies of cognitive outcome in patients with phenylketonuria and personalised therapy: the challenge for the future guidelines. J Med Genet. 2020 Mar;57(3):145-150. doi: 10.1136/jmedgenet-2019-106278.*

3. For those children who do develop brain damage, what other treatments and care (health and social) will these children require?	**YES/NO**	• School/college: Education, Health and Care (EHC) plans for learning needs • All children with PKU receive additional teacher/teaching assistant time to supervise protein substitute. • Additional blood phenylalanine monitoring • Use of home support workers • Additional hospital appointments and telephone contacts by health professionals • Possible hospital admission • Possible involvement of safeguarding and social services – in particular referral to early help services for patients with very poor phenylalanine control (as per recommendation by PKU European Guidelines 2017). Data on the number of children with PKU referred to 'early help services' and 'social services' is not been collected by the NHS. It is likely that all paediatric clinics will have vulnerable paediatric patient who have poor blood phenylalanine control. *van Rijn M, Ahring K, Bélanger-Quintana A, Dokoupil K, Ozel HG, Lammardo AM, Robert M, Rocha JC, MacDonald A. When should social service referral be considered in phenylketonuria? Mol Genet Metab Rep. 2015 Feb 9;2:85-88.*
4. Does a 71.2% reduction in protein-restricted diet due to treatment with sapropterin reflect the level expected in clinical practice? (ERG report page 77) If no, what approximate percentage reduction in protein-restricted	**YES/NO**	Yes – **please see key issue 10.** In patients with established BH4 responsiveness with PKU, protein equivalent intake from protein substitute intake significantly decreases with long-term BH4 treatment. This is seen as an important advantage by patients. Unpalatable synthetic amino acid mixtures are especially poorly tolerated. Factors that can hinder diet acceptance include the poor palatability, disagreeable smell, or textures of protein substitutes and SLPF. Food neophobia is common in both children and adults and disordered eating is reported in adults.

die do you anticipate in clinical practice with sapropterin?		There should be significant reduction in the use of 'Foods for Specialist Medical Purposes' with sapropterin. This includes both protein substitute and low protein special foods. Protein substitute is an essential part of a low phenylalanine diet and it is reported to provide anything from 52-80% of the total protein intake in patients with PKU on diet (van Wegberg et al 2017). However, acceptance and administration of Phe-free amino acid substitute is particularly challenging. They are bitter tasting, the volume required is high and they are given evenly throughout the day (at least 3 times) to avoid amino acid oxidation and minimize blood Phe fluctuation. In addition, the rigorous regimen of 3 times daily dosing is demanding, and dosages are commonly missed or partly given. They may also cause gastrointestinal upset, particularly if taken very concentrated or without extra fluid (Van Wegberg et al 2017). As it is well established that protein substitute supplementation is problematic for many patients, any change/reduction in dosage associated with sapropterin usage is advantageous
5. Is a utility level of 0.095 appropriate or realistic for a patient with severe PKU symptoms and on a protein-	**YES/NO**	About 0.4% of early treated PKU who have discontinued the diet experiences severe neurological deterioration that may be reversed by metabolic control restoration (Leuzzi 2020).

restricted diet? (ERG report pages 75 & 76) If no, what level reflects this state in clinical practice?		There are around 30 reported cases of adult patients with PKU with severe neurological symptoms including cerebellar ataxia and visual loss. These neurological complications were associated with leucopathy on brain magnetic resonance imaging (27/29). *Jaulent P, Charriere S, Feillet F, Douillard C, Fouilhoux A, Thobois S. Neurological manifestations in adults with phenylketonuria: new cases and review of the literature. J Neurol. 2020 Feb;267(2):531-542.*

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

NICE National Institute for Health and Care Excellence

Technical engagement response form

Sapropterin for treating phenylketonuria [ID1475]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: **5pm, Wednesday 16 December 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Dr Hugh Lemonde**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Inherited Metabolic Disease Group**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Limited relevance of the registry data to the decision problem	NO	There is a paucity of evidence that compares the efficacy of Sapropterin + Protein restricted diet and Protein restricted diet alone in the general literature. Whilst the registry data provides evidence for safety and efficacy (ability to reduce PHE levels/increase protein tolerance) of Sapropterin, they do not provide a direct comparison as per the scope specified by NICE.
Key issue 2: Outcomes not addressed in the company submission	NO	As in Key Issue 1, there is limited comparative data to support outcomes.
Key issue 3: Blood phenylalanine concentration level as a measure of efficacy	**No**	Blood phenylalanine levels in PKU are dependent on phenylalanine intake. Considering phenylalanine levels in the context of phenylalanine intake would be a better measure of efficacy. The longterm data in the registry trials show, for some groups, sustained reduction of phenylalanine levels and in others an increase. Phenylalanine intake generally increased across the groups. However, with a very significant dropout rate over time, it is not clear whether the baseline groups and long-term follow-up groups are comparable. There is clear and robust evidence that lowering maternal phenylalanine concentration during pregnancy protects the unborn child from neurological and cardiac damage. BIMDG strongly supports the availability of Sapropterin for any woman shown to be Sapropterin responsive and

		actively planning pregnancy. There are an average of 50 deliveries per year in the UK in women with PKU.
Key issue 4: Limited randomised controlled trial data available	**NO**	Not aware of any further data to support this. Longterm RCT data for rare conditions is very challenging/often not possible, especially when there is definite or very likely perceived benefit from the treatment in question.
Key issue 5: Unrealistic company model pathway	No	Unable to comment. Do not have expertise in health care modelling
Key issue 6: Implausible time and age invariant health state transition probabilities	**No**	Unable to comment. Do not have expertise in health care modelling
Key issue 7: Methods used to calculate transition probabilities	**No**	Unable to comment. Do not have expertise in health care modelling
Key issue 8: Annual rate that patients stop taking sapropterin (attrition rate)	**No**	Unable to comment
Key issue 9: Utility values used in the model are highly unlikely to reflect the experience of NHS patients with phenylketonuria	**No**	The utility values used in the company model seem very low – please see comment 5 below.
Key issue 10: Effect of sapropterin on protein-restricted diet	**No**	Please see comment 4 below – the effect of sapropterin on reducing protein-restricted diet will be variable depending on how you select sapropterin responsive patients. The stricter the criteria for selection, the greater proportion of patients who will have larger reduction in protein restricted diet. The methods of patient selection in the large registry data sets is not clear, and is likely to be significantly

		less stringent than the ESPKU recommendations that have been previously recommend for use in the NHSE policy working group.

Additional technical team issues

Please use the table below to respond to questions raised by the NICE technical team related key issues presented in the ERG report. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key questions	Does this response contain new evidence, data or analyses?	Response
1. Does damage to the brain and nervous system happen in children with PKU managed within the NHS?	No	The severe clinical phenotype seen in untreated PKU (microcephaly, learning difficulties, seizures, severe behavioural difficulties) does not occur in children treated within the NHS. Effective newborn screening and healthcare and social support for children prevent this. Children within the NHS that have the effects of untreated PKU have generally been born in regions without newborn screening or without access to dietary treatment. The outcomes of early treated PKU are covered elsewhere in this report.
2. What proportion of children go on to develop neurological damage because of uncontrolled PHE levels despite being prescribed a protein restricted diet?	**No**	As with question one, the neurological damage associated with untreated PKU is not seen in the NHS. Adverse outcomes in early treated PKU include neurocognitive, neuropsychological and psychosocial and have been covered in the STA report [refs 16-20]. Evidence to quantitate the proportion of early-treated children in the NHS that develop such symptoms is lacking. Evidence to quantify the level of phenylalanine control in the UK has been previously collected (Macdonald A *et al.* Retrospective, observational data collection of the treatment of phenylketonuria in the UK, and associated clinical and health outcomes. Curr Med Res Opin. 2011 Jun;27(6):1211-22)

3. For those children who do develop brain damage, what other treatments and care (health and social) will these children require?	**No**	See above
4. Does a 71.2% reduction in protein-restricted diet due to treatment with sapropterin reflect the level expected in clinical practice? (ERG report page 77) If no, what approximate percentage reduction in protein-restricted die do you anticipate in clinical practice with sapropterin?	**No**	Clinical experience of managing diet on Sapropterin in the UK is limited. The answer to this question also depends on the group of patients being considered. A practical and robust definition of sapropterin “responder” is a 30% reduction in phenylalanine levels and a doubling of natural protein intake (ESPKU guidelines). The % reduction in protein restricted diet in these “responders” is likely to be much higher [71.2% may be a reasonable reduction rate in this patient group], as they will generally be on a higher baseline protein intake compared with the patient groups in the longterm register data, whose inclusion criteria is not entirely clear, but likely to contain significantly more patients with a more limited or no response to sapropterin.
5. Is a utility level of 0.095 appropriate or realistic for a patient with severe PKU symptoms and on a protein-restricted diet? (ERG report pages 75 & 76) If no, what level reflects this state in clinical practice?	No	Considering children and adults with early-treated PKU, a utility level of 0.095 does not reflect what is seen in clinical practice (considering 0=Death, 1= full health and further examples of utility level include adults stroke survivors scoring 0.41 [major stroke] and 0.72 [minor stroke]). I am not aware of any other literature to accurately quantitate. A utility value nearer 1 might be expected.

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

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Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

Technical engagement response form

Sapropterin for treating phenylketonuria [ID1475]

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Deadline for comments: **30 November 2020**

Thank you for your time.

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Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**BioMarin International Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
ERG comments	**Liverpool Reviews and Implementation Group (LRiG)**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Limited relevance of the registry data to the decision problem	**NO**	The Phenylketonuria Demographics, Outcomes and Safety (PKUDOS) registry is a phase 4 voluntary observational study designed to provide up to 15 years of data from adult and maternal[1] subjects with Phenylketonuria (PKU) who are (or have been) treated with sapropterin. We maintain that the PKUDOS registry is a relevant dataset to use to support the assessment of long-term comparative benefit of sapropterin and as such is relevant for the decision problem. To be eligible to enter the PKUDOS registry, subjects must have a diagnosis of PKU and have previously received sapropterin, are currently receiving sapropterin, or intend to receive sapropterin therapy within 90 days of enrolment. The PKUDOS dataset is available with comparable data in a population of approximately 1922 patients with some patients' data available since 2008. The data has been published by Longo et al, 2015 (Molecular Genetics and Metabolism 114 (2015) 557–563) and numerous posters all of which are referenced in the company submission. PKU is a rare disease and as such it is difficult and impractical to collect long term data as an RCT from a small limited patient population. The ability to capture long- term evidence from the PKUDOS registry by the manufacturer (9 years in some cases) is testament to the commitment of the manufacturer to continue to expand the evidence base supporting PKU. On the one hand, the ERG has recognised the value of the registry data. The ERG states on page 32, table 6, last row that "The registries provide long-term data that are more representative of usual clinical practice than trial data. The ERG agrees that the registries are the most

[1] *D.K. Grange, R.E. Hillman, B.K. Burton, S. Yano, J. Vockley, C. Fong, J. Hunt, J.J. Mahoney, J.L. Cohen-Pfeffer, Sapropterin dihydrochloride use in pregnant women with phenylketonuria: an interim report of the PKU MOMS sub-registry, Mol. Genet. Metab. 112 (2014) 9–16.*

		appropriate data sources to inform conclusions relating to long-term efficacy and safety outcomes" but then paradoxically, the point is made that there is insufficient data available. **Given the patient numbers, the length of available data, and the comparable evidence, the dataset represents a substantial body of evidence for patients with PKU who have previously received sapropterin, are currently receiving sapropterin, or intend to receive sapropterin therapy within 90 days of enrolment.**
ERG comment		As stated within the Section 3.5 Conclusions of the clinical effectiveness section of the ERG report: "The PKUDOS and KAMPER registry studies are well-designed and well-reported and are of good methodological quality. However, the objectives of the PKUDOS and KAMPER studies are to provide long-term efficacy and safety data for patients treated with sapropterin+PRD, rather than to provide a comparison between sapropterin+PRD and PRD, as specified in the final scope issued by NICE." Even though the PKUDOS and KAMPER registry studies are of good quality and are the most appropriate data sources available to inform conclusions relating to long-term efficacy and safety outcomes, the PKUDOS and KAMPER registry studies are relevant only to patients who have a history of treatment with sapropterin+PRD. There are no data available for patients who have been treated with PRD only (the main comparator in the final scope issued by NICE).
Key issue 2: Outcomes not addressed in the company submission	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
ERG comment		No comment required
Key issue 3: Blood phenylalanine concentration level as a measure of efficacy	**YES**	• **We would argue that blood Phe concentration level is a validated measure of efficacy and is the most widely used measure of efficacy in clinical practice.** We do not therefore accept the proposal of a composite endpoint (as suggested by the ERG). There is no scientific or clinical basis to support this composite endpoint nor is there clinical support for such an approach. • **In addition to blood Phe being the most widely used measure of efficacy in clinical practice, it is also the dominant measure widely referenced across literally hundreds of publications and referred to in national and international guidelines.** **Blood Phe is used across the globe as a target measure to reach to demonstrate improvement in disease outcomes.** o For example, the European guidelines recommend target blood Phe levels between 120 and 600 µmol/l for patients older than 12 years – clearly an endorsement of the importance of blood Phe.

		○ The American College of Medical Genetics and Genomics (ACMG) guidelines in the US (Vockley et al, 2014) state a goal of maintaining blood phenylalanine in the range of 120–360 µmol/l, again recognition of the importance of using blood Phe as a measure to assess disease outcome. **The body of literature is substantial in relation to the use of blood Phe and indeed, it's impact on other outcomes.** ○ For example, ten Hoedt et al, 2011 highlights the findings from a randomised double-blind placebo-controlled trial showing that "high plasma Phe levels have a direct negative effect on both sustained attention and on mood in adult patients with PKU." ○ Waisbren et al, 2007 states in her systematic literature review and meta-analysis that "Blood phenylalanine (Phe) levels provide a practical and reliable method for the diagnosis and monitoring of metabolic status in patients with phenylketonuria (PKU)." ○ This is further reinforced by Lindegren 2012 in her Comparative Effectiveness review 2012 which states "Increasing Phe is clearly associated with decreased IQ, with a probability of IQ less than 85 exceeding the population probability (approximately 15 percent) at blood Phe over 400 µmol/L and levelling off at about 80 percent at 2,000µmol/L. This finding supports the typical target goal for blood Phe levels in individuals" ○ The reliance on the use of blood Phe can be found in publications regarding co-morbidities (Bilder, Rutsch), cognition (Lindegren, Romani, Jahja) and neuropsychological deficit (Bik-Multanowski) to name just a few. This list is by no means exhaustive. The clinical papers are extensive and too numerous to list here. • **Whilst emphasising the criticality of blood Phe, we do also recognise the importance of Phe intake which is why this was captured in our clinical trials (e.g. in the SPARK study); however they cannot be used as a composite endpoint as suggested by the ERG.** ○ The outcome of poor nutrition results in elevated Phe, which reinforces the use of blood Phe as the dominant outcome measure. ○ In addition, Phe intake influences blood Phe levels which therefore invalidates their use as a composite outcome measure (notwithstanding the lack of clinical rationale for such a measure). This was also recognised by the ERG which states on page 41 that "Clinical advice to the ERG is that a known confounder of sapropterin treatment on clinical outcomes is dietary adherence" ○ The majority of UK clinical opinion is also aligned to the manufacturer position. Maintenance of blood Phe levels in, for example, paediatrics is very clear that blood Phe levels below 360 micromol/L is linked to good neuropsychological outcomes. The EU guidelines have a threshold of 600 micromol/L for patients over the age of 12 years and maintaining Phe levels below 600 micromol/L will help prevent IQ loss, with implications on education, speed of processing and executive function. This will in turn also affect patients' quality of life, their ability to maintain relationships, engage in social interactions, operate effectively in a work environment etc. ○ The other huge advantage of Phe being the primary outcome measure is that it is readily measurable and consistent. All patients can measure it and can measure it frequently.

		• The evidence above had been presented during the review of the ERG report by the manufacturer. The clinical advice to the ERG must be considered and weighed in conjunction with the robust body of literature and clinical opinions of experts consulted by the manufacturer (including three specialist adult metabolic physicians (collectively experienced in the care of approximately 50% of the UK adult PKU population), two-specialist paediatric metabolic physicians (collectively experienced in the care of approximately 20% of the UK paediatric PKU population),and an advanced practitioner in metabolic disease and experienced metabolic dietitian) which express a view that blood Phe concentration level is a validated measure of efficacy.
ERG comment		Clinical advice to the ERG is that whole blood or plasma Phe concentration is a product of individual Phe tolerance (amount of dietary Phe tolerated without exceeding target Phe concentrations) and dietary Phe intake. Blood Phe concentration is the most important outcome marker in the treatment of PKU besides neurocognitive outcomes. Sapropterin works by increasing Phe tolerance and if effective, either (i) decreases blood Phe levels with unchanged dietary intake or (ii) maintains blood Phe concentration while allowing increased dietary Phe intake. The efficacy of sapropterin should therefore be measured using both factors simultaneously, Phe concentrations and Phe intake. Using only one of the factors can produce misleading results. In clinical practice, blood Phe concentration as a measure of efficacy of sapropterin needs to be used in conjunction with dietary Phe intake.

Key issue 4: Limited randomised controlled trial data available	**NO**	There are significant challenges in undertaking long term RCTs in a rare disease such as PKU. Kuvan has been granted orphan designation on the basis of this rarity. However, notwithstanding this, the manufacturer has undertaken an extensive clinical development programme that includes studies across phases II, III and IV and undertaken across a range of patient groups (such as those below the age of 4 years, maternal PKU for example) and includes a range of patient relevant endpoints (such as reduction in Phe levels, Phe tolerance and neurological outcomes for example). **As such, the data exists despite the rarity of PKU and the challenges of undertaking long term RCTs in a rare disease.** The studies are captured below: **Phase II studies:** PKU-001 (screening study) **Phase III studies**: PKU-003 (Pivotal Phase III); PKU-004 (Ph III extension); PKU-006 (Diet study); PKU-016 (Neurocognitive study); PKU-008 (Phase III OLE from PKU004 and PKU006); SPARK (<4 age group); PKU-015 (young children) **Phase IV studies:** ENDURE; PKUDOS; PKUMOMS; KAMPER; KOGNITO The clinical trial and registry evidence thus capture strong evidence across a range of endpoints and populations. Given the backdrop of a rare disease, it is therefore incorrect and unfair to state there is limited evidence available. In regard to long term evidence, a paper by Longo et al, 2015[2] states that: "Sapropterin has been assessed in long-term clinical studies. Burton et al. reported the safety of sapropterin and maintenance of blood Phe reduction in a population with PKU (N = 111, age range: 4 to 50 years) **for up to 2.6 years** at doses of 5 to 20 mg/kg/day" Furthermore, the PKUDOS registry (reported by Longo et al, 2015) captures data for 5 years (as stated in the publication) and >9 years today.
ERG comment		As noted in Section 3.5 of the ERG report, the evidence from the three RCTs (PKU-006=10 weeks, PKU-016=13 weeks, SPARK=13 weeks) that are relevant to the NICE appraisal of sapropterin is limited due to the short duration of the trials. The company considered that the data from these RCTs are of too short a duration to be included in the company economic model (CS, p42) and that the data from these phase III trials (and also data from the phase II trials) are 'largely historical'.
Key issue 5: Unrealistic	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

[2] *Molecular Genetics and Metabolism 114 (2015) 557–563*

company model pathway		
ERG comment		No comment required
Key issue 6: Implausible time and age invariant health state transition probabilities	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
ERG comment		No comment required
Key issue 7: Methods used to calculate transition probabilities	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
ERG comment		No comment required
Key issue 8: Annual rate that patients stop taking sapropterin (attrition rate)	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
ERG comment		No comment required
Key issue 9: Utility values used in the model are highly unlikely to reflect	**NO**	The utility figures used in the model have been derived by a Time Trade Off (TTO) study undertaken in Sweden based on a sample size of over 1000 respondents from the general population. These figures were subsequently validated by UK KOLs and as such reflects the experience of NHS patients with phenylketonuria.

the experience of NHS patients with phenylketonuria		In terms of methodology, the Swedish TTO study is based on a robust sample size of over 1000 respondents from the general population. The health state vignettes were developed based on a Delphi panel of PKU experts in the US, a targeted review of the literature and feedback from internal medical expertise from the manufacturer. The draft vignettes were then reviewed by three European health care professionals (HCPs) with experience of treating PKU patients. A revised version based on their comments were constructed after the review, presented, and discussed with the HCPs during a follow-up interview. After the follow-up interview, a final version of the vignettes was constructed (the TTO study report was provided in the CS). Uncontrolled PKU is characterised by symptoms that have a profound impact on daily living and patients' quality of life. Caregivers/ partners of these patients with sustained high level of blood Phe often report severe symptoms. These patients also suffer from what has been termed as hidden disabilities (Gentile 2010) and end up in a vicious downward spiral where patients need to resume therapy (such as the Phe-restricted diet) but are hindered from doing so due to neurological and neurocognitive impairment caused by elevated blood Phe levels. These levels continue to rise if sapropterin and / or the Phe-restricted diet is not initiated. If not initiated, the blood Phe levels rise further leading to worsening neurological and neurocognitive impairment. A degree of executive functioning ability is required for the planning and organising the highly restrictive Phe-free diet. The utility data was validated by UK clinical experts in July 2020 which involved three specialist adult metabolic physicians (collectively experienced in the care of approximately 50% of the UK adult PKU population), two-specialist paediatric metabolic physicians (collectively experienced in the care of approximately 20% of the UK paediatric PKU population), and an advanced practitioner in metabolic disease and experienced metabolic dietitian. This combined experience represents a significant portion of UK PKU clinical care and as such provides strong and confirmatory support for the applicability of these utility results from the TTO study to a UK perspective. Patients with PKU suffer from a range of neurological and neurocognitive impairments including but not limited to for example tremors, anxiety, depression, impaired executive function, and cognitive impairment. The manufacturer notes that utility values of 0.30 are observed in other disorders such as severe depression.[3] **As such, the manufacturer does not accept the statement that the utility figures are highly unlikely to reflect the experience of NHS patients with PKU. It remains unclear what scientific evidence was reviewed, or clinical rationale gained, or indeed systematic literature search was applied/undertaken by the ERG to then state these utility values do not reflect UK patients' experience. Greater clarity on this point would be appreciated.**
ERG comment		As stated in Table 31 and explained fully in Section 5.2.3 of the ERG report, the ERG has the following concerns: • the methods used by the company to elicit health state values are not in line with the NICE Reference Case

[3] *Fitzgibbon et al, 2019; Can J Psychiatry,2019 Jul 1; ():706743719890167*

		• health state descriptions valued by the company in the TTO study do not match the health states used in the company model • the utility values for patients with uncontrolled blood Phe concentration levels are too low • the method used to map health state utility values from the company TTO study to the company model health states is overly simplistic.
Key issue 10: Effect of sapropterin on protein-restricted diet	**YES**	The manufacturer does not accept the view of the ERG regarding protein supplement intake. The ERG report states: "It may, therefore, be the case that use of sapropterin in the UK may lead to no reduction in patient intake of protein supplements." UK clinical experts aim to meet protein requirements by a combination of natural protein and PKU phe free amino acid mixtures/protein substitutes. If phe tolerance increases, then a greater proportion of the daily protein requirements can be met by dietary natural protein. The requirement for protein substitutes is then reduced. **Clinical experts state that they would expect to see a 50% reduction in protein supplement use, and with good responders potentially going even further.** Indeed, this is one of the major incentivising factors for many children is that they are able to take less amino acid mixture which is perceived by a child, for example, as a far greater benefit than having to consume additional protein substitute. Protein substitutes tend not to be removed entirely to allow for some buffer for illness (even if it's only 10g) and to ensure patients do not forget the taste or technique associated with protein substitute intake should they need additional protein particularly in times of illness. A poster by Yilmaz et al, presented at ESPKU, reports the following: *"8 centers from 8 countries reported the dietary management of 291 sapropterin responsive patients. More than half (n=163, 56.0%) of the sapropterin treated patients achieved WHO/FAO/UNU safe levels of protein intake. Of 291 sapropterin responsive patients, 82 (28%) did not require a L-AA supplements and in the remaining patients L-AA dosage reduced by 60%. Only 26% (n=75) patients used low protein milk, and 6% (n=33) low protein foods like bread. Only 30% were prescribed vitamin/mineral supplements."* **It is clear that some patients were able to remove their Phe-free protein supplements entirely and others reduced their intake by 60%.** There are further publications that highlight the reduction in amino acid (AA) supplements as a result of sapropterin (Scala, 2015[4], Thiele, 2012[5], Singh, 2010[6], Burlina 2009[7]) which all highlight the reductions observed in AA mixture. The table below captures the range of studies that have explored the impact of sapropterin on phe-tolerance and the studies also highlight the reduction in protein supplement intake (see appendix 1 for fuller details). **Phe tolerance**

[4] *Scala et al. Orphanet Journal of Rare Diseases (2015) 10:14*
[5] *JIMD Rep. 2013;9:31-40*
[6] *J Inherit Metab Dis (2010) 33:689–695*
[7] *J Inherit Metab Dis (2009) 32:40–45*

Reference and centre	n	Age	Mean Dose	Pre-sapropterin(g)	Post-sapropterin(g)	% increase
Belanger 2007, Spain	7	0-18 years	12.5	32.5	104	220%
Burlina 2009, Italy	12	0-7 years	10	52.5	175	233%
Hennerman 2005, Switzerland	5	0-3 years	10	9.5	75	689%
Singh 2010, Atlanta	6	5-12 years	20	42.1	147	249%
Thiele 2012, Germany	8	5-16 years	20	62.9	213.1	239%
Vilaseca 2010, Spain	13	4-14 years	10		64.15	
Muntau 2002, Germany	5	4-14 years	8.9	18.7	61.4	228%
Muntau 2017, Germany	25	0-4 years	15			
Thiele 2015, Germany	8	6-17 years	14.5	49.3	220.8	348%
Tansek 2016, Slovenia	9	2-10 years	13.05	55	150	173%
Scala 2015, Italy	17	14 years	10	58.3	279.8	380%
Mean			13.09	42.31	149.03	307%

ERG comment		Thank you for providing the new information (presented in the table above). The ERG notes that the studies include small numbers of patients who are all aged under 18 years and are not from the UK. The ERG also has concerns that some of this information may not be accurate; for example, information about Phe tolerance from two of the studies (Vilaseca 2010 and Muntau 2017) listed in the table are not provided and, for the Burlina 2009 study, the patient age (and length of treatment) appears incorrect. Clinical advice to the ERG is that for most patients, significant reductions in the intake of protein substitute would not be expected, the exceptions would be individuals with an already high Phe tolerance prior to the intervention who in exceptional cases might be able to discontinue taking a protein substitute. On the background of current dietary recommendations and looking at the whole population of patients receiving sapropterin, only minor reductions in the amount of prescribed protein substitutes would be expected. The ERG has presented cost effectiveness results for a range of assumptions relating to the reduction in PRD (diet and supplements) experienced by patients taking sapropterin. The values used by the ERG range from 71.2% (company base case value) to 0% (extreme ERG value).
Additional Issue: 11 The challenges in obtaining quality of life	**NO**	Capturing quality of life (QoL) data in PKU patients is extremely challenging due to the small patient population and range of disease states. Patients with PKU are less able to report their own quality of life due to reduced executive function and neurological and neurocognitive impairment which contributes significantly to hidden disabilities in these patient groups. This manifests as difficulties in planning, organizing and reduced processing speed for example. As a result, patients are less able to undertake a subjective evaluation of his or her own functioning and

data in PKU patients and recognition of the evidence provided		emotional well-being. These challenges are also observed in other diseases areas such as psychiatry. Reliability and validity of reporting QoL in psychiatric disorders has been questioned because of the cognitive impairments and distortions that characterize several mental health conditions.[8] As such, there are no quality of life tools successfully validated in PKU. Attempts have been made in the past to try and address this with, for example, the PKU-QoL tool (a PKU disease specific tool). However, this has been unsuccessful. Initial psychometric validation of the tool shows poor content and construct validity. There has been further psychometric evaluation of this instrument but no clinically important difference (CID) estimates have been derived. Furthermore, generic tools such as SF36 or EQ5D have been unsuccessful in capturing the impact of PKU. The limited data on the use of the SF-36 in PKU has shown the tool to be insensitive. Attempts to map PKU-QoL to SF36 have also been unsuccessful and has been shown to have poor correlation between PKU-QoL and SF36. It is clear therefore that capturing QoL in PKU presents significant challenges. The manufacturer has captured data from a Swedish time trade-off (TTO) study in over 1000 members of the general population and PKU patients across a range of clinically validated disease states. Whilst this was undertaken in Sweden, UK clinical experts have confirmed that it is transferable to the UK. The TTO study is based on a robust sample size of over 1000 respondents from the general population. The health state vignettes were developed based on a Delphi panel of PKU experts in the US, a targeted review of the literature and feedback from internal medical expertise from the manufacturer. The draft vignettes were then reviewed by three European health care professionals (HCPs) with experience of treating PKU patients. A revised version based on their comments were constructed after the review, presented, and discussed with the HCPs during a follow-up interview. After the follow-up interview, a final version of the vignettes was constructed (the TTO study report was provided in the CS). Uncontrolled PKU is characterised by symptoms that have a profound impact on daily living and patients' quality of life. Caregivers/ partners of these patients with sustained high level of blood Phe often report severe symptoms. These patients also suffer from what has been termed as hidden disabilities (Gentile 2010) and end up in a vicious downward spiral where patients need to resume therapy (such as the Phe-restricted diet) but are hindered from doing so due to neurological and neurocognitive impairment caused by elevated blood Phe levels. These levels continue to rise if sapropterin and / or the Phe-restricted diet is not initiated. If not initiated, the blood Phe levels rise further leading to worsening neurological and neurocognitive impairment. A degree of executive functioning ability is required for the planning and organising the highly restrictive Phe-free diet. The utility data was validated by UK clinical experts in July 2020 which involved three specialist adult metabolic physicians (collectively experienced in the care of approximately 50% of the UK adult PKU population), two-specialist paediatric metabolic physicians (collectively experienced in the care of approximately 20% of the UK paediatric PKU population),and an advanced practitioner in metabolic disease and

[8] *Bullinger M, Quitmann J. Quality of life as patient-reported outcomes: principles of assessment. Dialogues in clinical neuroscience 2014;16(2):137*

		experienced metabolic dietitian. This combined experience represents a significant portion of UK PKU clinical care and as such provides strong and confirmatory support for the applicability of these utility results from the TTO study to a UK perspective. It remains unclear what scientific evidence was reviewed, or clinical rationale gained, or indeed systematic literature search was applied/undertaken by the ERG to state that patients with low utility values would not modify their diet and/or start or return to take sapropterin. Patients with this level of disease severity have significant cognitive and executive function impairment. It is not possible for them to rationalise the cause of their 'fogginess' and impaired quality of life, and to then make an informed judgement about the best course of action to take that will best address the source of their impairment.
ERG comment		The ERG agrees with the company that capturing quality of life data in patients with PKU is extremely challenging due to the small patient population and range of disease states. The ERG considers that data from the company's TTO study are the best available source of utility values for different modelled PKU states (with the caveat that 'best available' is not the same as 'robust').
Additional Issue: 12 Mean dose recommendation from experts deemed as not robust	**NO**	The dosages come directly from NHS England's Clinical experts sitting on the Clinical Reference Group (CRG) and published in NHS England's Integrated impact Assessment report. The manufacturer has merely cited the view of NHS England's clinical experts. With regard to the second statement from the ERG which states "This suggests that the values used in the company model may be underestimates of real-world dosages" the manufacturer would highlight that the dosages observed in KAMPER reflect the countries that are part of the registry which consist of 8 countries including Austria, France, Germany, Italy, the Netherlands, Slovakia, Spain, and Sweden. The UK is not part of this registry.
ERG comment		The mean adult dose published in NHS England's Integrated Impact Assessment report is very similar to the mean dose received by KAMPER registry study participants ([redacted] are <18 years of age). As the company has pointed out, the ERG considers that the values used in the company model (and published in the NHS England Integrated Impact Assessment report) may be underestimates of real-world dosages.
Additional Issue: 13 Long term benefits of sapropterin treatment have not been accepted	**YES**	There are longer term benefits of sapropterin that continue even if the treatment is stopped. Treatment with sapropterin lays down foundations that prevent future complications and as such the benefits do accrue over time. For example, treatment with sapropterin will help children achieve better metabolic control and as such there will be benefits that are maintained and carried forward into adult life even if treatment is subsequently stopped. Elevated blood Phe leads to neurological and neurocognitive disorders. It can also lead to neurotransmitter imbalance and structural deformities of the brain. If left untreated, PKU can result in severe intellectual impairment

		It is therefore clear that by preventing these neurological and neurocognitive disorders one can prevent intellectual impairment, IQ loss and intellectual disability that could inhibit educational attainment in school and university. This can then impact work prospects and other life chances, job opportunities. Clinical experts state that brain development continues into mid-20s for many individuals and brain remodelling occurs throughout life. From a neurotransmitter imbalance perspective, the role of dopamine changes over time and insufficient dopamine will have a different impact at a young age compared to a young adult for example. With elevated blood Phe levels, this can lead to a reduction in other neurotransmitters including dopamine. The pre-frontal cortex develops in later life which is dependent on dopamine hence a lack of dopamine at 5 years of age is vastly different to lack of dopamine at 15 years or 20 years of age for example. Dopamine has a fundamental role to play in critical thinking, decision making, higher orders of thinking for example which rely on dopamine. As the pre-frontal cortex develops as a young adult, the ability to undertake more complex and higher order thing increases. A lack of dopamine at this stage (due to elevated blood Phe) can then lead to executive function impairment, reduced speed of processing, poorer working memory etc. This could then manifest as poorer exam results for example, poor decision making in the workplace, inability to retain information thus limiting one's true potential and reduced lifetime earning capability. Given the risk of intellectual disability associated with elevated blood Phe levels, the company economic model has been refined into a decision tree model that better captures this impact. Please see appendix 2 for a report on this revised model structure and justification
ERG comment		Thank you. However, this response does not reference any published study or provide evidence on the specific likelihood of long-term neurological disability due to elevated blood Phe levels in children, or the costs or utility loss associated with long-term neurological disability.
ERG comment on new cost effectiveness calculation		The ERG notes that the company has presented a new cost effectiveness calculation that attempts to take into account long-term neurological disability. The company calculation is the same as the ERG calculation presented in the ERG report, except that it includes three revisions: **Revision 1. The company has added an assumed utility decrement for intellectual disability based on a reduction in IQ if patients have moderate or severe symptoms. This is applied to both children and adults**. The ERG is concerned about the way in which the disutility for neurological disability related to IQ has been applied in the new calculation for four reasons. (1) The company has applied the disutility to patients of all ages when the danger of elevated blood Phe levels on neurological development is only a risk for children. (2) As the calculation only has a 1 year time horizon, it is unclear if an added disutility for neurological

		disability is double-counting the disutility already applied in the calculation for symptomatic PKU. (3) For adults with severe symptoms adhering to a PRD, the calculation assumes a utility of [redacted]. Whilst [redacted] utility values are possible, they are unusual and no discussion or justification for use of such a [redacted] value has been provided by the company. (4) As the calculation only has a 1 year time horizon, it is not possible for the calculation to have captured the long-term impact of neurological disability from uncontrolled blood Phe levels. **Revision 2. For patients who take sapropterin, the company has added a [redacted] QALY gain for all patients with moderate symptoms and a [redacted] QALY gain for all patients with mild or severe symptoms** No justification for these values has been provided by the company and the ERG therefore considers that these values should not have been included in the calculation. **Revision 3. The company has added a [redacted] QALY gain for women of child-bearing age who take sapropterin** This value is arbitrary and whilst elevated blood Phe levels in pregnant women can harm the unborn child, the extent of that QALY loss is unclear, as is the effect of sapropterin on that QALY loss. In summary, the ERG considers that the results provided by the company's new cost effectiveness calculation are less informative than the calculations undertaken by the ERG that were proposed as 'alternative cost effectiveness results' in the ERG report. Sapropterin may generate QALY gains and reduce healthcare costs by reducing the risk of long-term neurological disability in children with PKU and the ERG acknowledges that these benefits are not captured in the ERG's cost effectiveness calculation. This uncertainty means that, all other things being equal, the ERG's calculation will overestimate the size of the ICER per QALY gained for sapropterin if sapropterin does reduce the risk of long-term neurological disability.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	**Company's base case before technical engagement**	**Change(s) made in response to technical engagement**	**Impact on the company's base-case ICER**
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
			[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Subgroups** / **Incremental QALY gain** 0-3 years-Mild [redacted] Moderate [redacted] Severe [redacted] 0-17 years-Mild [redacted] Moderate [redacted] Severe [redacted] ≥18 years-Mild [redacted] Moderate [redacted] Severe [redacted] Woman of child-bearing age-Mild [redacted] Moderate [redacted] Severe [redacted]	**Subgroups** / **Incremental cost gain** 0-3 years-Mild [redacted] Moderate [redacted] Severe [redacted] 0-17 years-Mild [redacted] Moderate [redacted] Severe [redacted] ≥18 years-Mild [redacted] Moderate [redacted] Severe [redacted] Woman of child-bearing age-Mild [redacted] Moderate [redacted] Severe [redacted]	**Subgroups** / **ICER** 0-3 years-Mild [redacted] Moderate [redacted] Severe [redacted] 0-17 years-Mild [redacted] Moderate [redacted] Severe [redacted] ≥18 years-Mild [redacted] Moderate [redacted] Severe [redacted] Woman of child-bearing age-Mild [redacted] Moderate [redacted] Severe [redacted]

Appendix 1

Review of evidence - impact of sapropterin on phe-tolerance and low protein foods

				Phe tolerance		
Reference and centre	**n**	**Age**	**Mean Dose**	**Pre-sapropterin(g)**	**Post-sapropterin(g)**	**% increase**
Belanger 2007, Spain	7	0-18 years	12.5	32.5	104	220%
Burlina 2009, Italy	12	0-7 years	10	52.5	175	233%
Hennerman 2005, Switzerland	5	0-3 years	10	9.5	75	689%
Singh 2010, Atlanta	6	5-12 years	20	42.1	147	249%
Thiele 2012, Germany	8	5-16 years	20	62.9	213.1	239%
Vilaseca 2010, Spain	13	4-14 years	10		64.15	
Muntau 2002, Germany	5	4-14 years	8.9	18.7	61.4	228%
Muntau 2017, Germany	25	0-4 years	15	50.1	80.6	61%
Thiele 2015, Germany	8	6-17 years	14.5	49.3	220.8	348%
Tansek 2016, Slovenia	9	2-10 years	13.05	55	150	173%
Scala 2015, Italy	17	14 years	10	58.3	279.8	380%
Mean			13.09	423.09	142.8	282%

Reference & Name of centre	Number of the patients on BH4	Age of patients at the beginning of BH4 treatment	Duration of BH4 treatment	Dose of BH4 and dosing time	Phe tolerance		Use and dose of protein substitute & low protein foods +notes	Phe levels	
					pre BH4 (mg/kg/d)	*post BH4 (mg/kg/d)*		*Before BH4 (µm/L)*	*With BH4 (µm/L)*
Belanger,2007, Spain	7	8 months-18 years	5-18 months	5-20 mg/kg/d 1-3 doses	20-45	75-133	?	200-520	145-530
Burlina, 2009, Italy	12	2-16 years	6 months-7 years	10 mg/kg/d Twice a day	350-700 mg/d	800-2700 mg/d	7 of them free diet 5 of them combined (low phe-100 mg/kg-no amino acid mixture)	433-12115	Drop below defined threshold levels
Hennermann, 2005, Switzerland	5	0,5-42 months	5.5-29 months	10 mg/kg Twice a day	?-19	30-120		77-208	190-314
Singh, 2010, Atlanta	6	5-12 yrs	24 months	20 mg/kg/d	421±128 mg/d	1470±455 mg/d	3 out of 6 no longer required any medical food No patient required SLPF	120-360	120-360
Thiele, 2012, Germany	8	5-16 yrs (11.13±4.4)	<3 months	20 mg/kg/d	629±476 mg/d	2131±1084 mg/d	Decreased consumption of SLPF Increased consumption of high protein foods. 6 out of 8 patients no longer take AAM, remaining 2 of them reduced	283±145	304±136
Ziesh, 2012, Germany	*Looks like the same results and method with Thiele, 2014.*								
Vilaseca, 2010, Spain	13		1-6 yrs	5-15 mg/kg/d	No inf	34.8-93.5			
Muntau, 2002, Germany*	5	4-14 yrs	166-263 days	7.1-10.7 mg/kg/d	18.7±8.6 mg/kg	61.4±27.9	*This study consists of 2 different part. I just took long term results of BH4 therapy which was briefly mentioned.	366±120	378±173
Muntau, 2017, Germany/ SPARK Study	25	<4 yrs	26 week	10-20 mg/kg/d	Mean change: 36.9±27.3 mg/kg/d		Significantly improved dietary phe tolerance		300.1±115.2

Thiele, 2015, Germany	8	6.0-16.6 yrs (10.5±3.8)	3 yrs	10-19 mg/kg	493.2±161.8	After 3 months: 2208.9 ±1336.4 After 2 yrs: 2021.9 ± 897.4	*4 out of 8 patients entirely stopped AAM. Remaining 4 reduced AAM dosage *Markedly increased intake of normal, protein rich food, primarily bread, potatoes, pasta and rice during short-term follow-up over a three month period *The mean consumption of special low protein products significantly declined further in long-term follow up. No changes detected regarding the consumption of edible fats as well as sweets and snacks	262.2±129.4	1st yr: 337.1±129.6 2nd yr: 382.7±148.1 3rd yr: 371.7 ±119.8
Tansek, 2016, Slovenia	9	2-10 yrs	Min 2 yrs	15.5 (starting dose) 10.6 (after 2 yrs follow up)	400-700 mg	1000-2000 mg	No significant change on blood Se, Zn and B12 levels. Improves quality of life. Cost effective.	191-302	135-285
Scala, 2015, Italy	17	14.4±4.5	60-84 month*1 patient discontinued after 12 months	10 mg/kg/d	583±443	2798±1568	9 out of 17 patients don't need AA and vitamin supplements. 2 of the patients need them only small amounts.	468 (204-570)	432 (210-600)

Ref & Name of centre	How many patients on BH4	Age of patients at the beginning of BH4 treatment	Duration of BH4 treatment	Dose of BH4 (mg/kg/d) and dosing time	Phe tolerance		Use and dose of protein substitute & low protein foods	Phe levels		Results
					pre BH4 (mg/kg/d)	*post BH4 (mg/kg/d)*		*Before BH4 (µm/L)*	*With BH4 (µm/L)*	
Belanger 2007 Spain, Hospital Ramon y Cajal,	7	18 yrs	18 months	10-2 doses	20	100 (free)		520	530	Oral BH4 is well tolerated and no side effects Normal weight gain and growth of the patients Normal psychomotor Development Great improvement in the quality of life
		12 yrs	18 months	5-1 doses	44	111 (free)		420	470	
		12 yrs	5 months	10-2 doses	44	120 (free)		300	245	
		8 yrs	18 months	15-2 doses	20	133 (free)		330	230	
		3 yrs	10 months	10-2 doses	30	75		300	280	
		8 months	5 months	20-3 doses	45	133		200	300	
		8 months	5 months	15-3 doses	45	90		200	145	

Ref & Name of centre	**How many patients on BH4**	**Age of patients at the beginning of BH4 treatment**	**Duration of BH4 treatment**	**Dose of BH4 (mg/kg/d) and dosing time**	**Phe tolerance**		**Low phe diet**	**Phe levels**		**Results**
					pre BH4 (mg/d)	*post BH4 (mg/d)*		*Before BH4 (µm/L)*	*With BH4 (µm/L)*	
Burlina, 2010 University Childrens Hospital Padua, Italy	12	3 yrs	3 yrs	10 mg/kg/d Twice a day	400	1000	Combined*	561	Phe drop below defined threshold levels (e.g. 360 mmol/L during the first 12 years of life and 600 mmol/L up to 17 years	-BH4 therapy allowed the introduction of high-protein foods such as meat -Their psychomotor development was normal and it has been adequate for each patient`s age -All patients and their families indicate great improvement in their quality of life.
		3 yrs	6 yrs		650	2700	No	502		
		2 yrs	3 yrs		350	1400	Combined*	564		
		10 yrs	2 yrs		600	2000	No	490		
		11 yrs	3 yrs		350	1400	No	564		
		2 yrs	6 mo		370	1600	No	433		
		3 yrs	3 yrs		400	1000	Combined*	605		
		2 yrs	2 yrs		550	800	Combined*	1215		
		9 yrs	7 yrs		700	2000	No	684		
		2 yrs	5 yrs		500	1200	No	649		
		16 yrs	4 yrs		500	1400	No	961		
		4 yrs	4 yrs		350	1200	Combined*	716		

- *Low-Phe (100 mg/kg, without amino acid mixture) and BH4 (10 mg/kg) treatment

Ref & Name of centre	How many patients on BH4	Age of patients at the beginning of BH4 treatment	Duration of BH4 treatment	Dose of BH4 (mg/kg/d) and dosing time	Phe tolerance		Use and dose of protein substitute & low protein foods	Phe levels		Results
					pre BH4 (mg/kg/d)	*on BH4 (mg/kg/d)*		*Before BH4 (µm/L)*	*With BH4 (µm/L)*	
Hennermann, 2005 Switzerland	5	18 months	24 months	10mg/kg bw twice a day	19	35		143 (18–557) n= 65	299** (61–1065) n=78	-No side effects during BH4 short- and long-term treatment - Growth, length, and head circumference were within the percentiles for age and sex. - Normal mental and motor development -Increase in quality of life
		1.2 months	29 months		19	80		77 (30–157) *n*=6	314 (36–726) n=52	
		0.5 months	8 months		-*	40		-*	293 (30–720) n=49	
		0.5 months	5.5 months		-*	30		-*	190 (30–490) *n*=21	
		42 months	24 months		18	120		208 (18–775) n=75	249** (54–799) *n*=51	

*In patients 3 and 4, BH4 treatment was started already at the age of 2 weeks. Therefore data on treatment before BH4-treatment do not exist.
** The slight increase of median phe serum concentrations on long-term BH4 treatment is associated with commencement of kindergarten and subsequent recurrent febrile infections.

Ref & Name of centre	How many patients on BH4	Age of patients at the beginning of BH4 treatment	Duration of BH4 treatment	Dose of BH4 (mg/kg/d) and dosing time	Phe tolerance		Use and dose of protein substitute & low protein foods	Phe levels		Results
					pre BH4 (mg/d)	*post BH4 (mg/d)*		*Before BH4 (µm/L)*	*With BH4 (µm/L)*	
Singh, 2010 Atlanta	6	5-12 yrs	24 months	20 mg/kg/d	421±128	1470±455	-3 of the 6 patients no longer required any medical food# in the remaining medical food prescribed but less than baseline -No patient required special low protein food	120-360	120-360	Dramatic increase in phenylalanine tolerance and the ability to consume intact protein Improved quality of life
Results	-By the third month of BH4 therapy, three patients were consuming a reduced proportion of their original medical food prescription (50%, 20%, and 38%, respectively). The other three patients no longer required medical food. -Total protein intake, the sum of intact protein and medical food, remained at approximately 1.0±0.08 g/kg per day (43.7±4.2 g/day) throughout the 24 months of the study. -Consumption of intact protein over 24 months increased significantly (p=0.0006), with a corresponding significant decline in medical-food intake (p=0.0002). -Mean dietary phenylalanine prescription (mg/kg per day) increased 3.3-fold within the 24-month study period, whereas patients' blood phenylalanine concentrations remained between 120 and 360 µmol/L -By month 3, the phenylalanine prescription had increased from a baseline average of 11.9±4.1 mg/kg to 39.9±11.5 mg/kg (p=0.001), and phenylalanine intake from food increased from 15.9±5.3 mg/kg to 34.2±13.8 mg/kg (p=0.007). -There were no significant changes in mean plasma tyrosine concentration over the 2-year study period -Serum albumin and total serum protein were within reference range -Hemoglobin and hematocrit concentrations began to improve after 9 months of BH4 treatment (p<0.001), stabilizing after 12 months -Total serum cholesterol increased slightly during the first 6 months on BH4, from 131±9.9 to 138±15.0 mg, without reaching statistical significance -Mean height-for-age Z score of study participants increased significantly over the 24-month follow-up									

Ref & Name of centre	How many patients on BH4	Age of patients at the beginning of BH4 treatment	Duration of BH4 treatment	Dose of BH4 (mg/kg/d) and dosing time	Phe tolerance		Phe levels	
					pre BH4 (mg/d)	*post BH4 (mg/d)*	*Before BH4 (µm/L)*	*With BH4 (µm/L)*
Thiele 2014 Germany	8	5-16 yrs	<3 months	20 mg/kg/d	629±476	2131±1084	283±145	304±136
Results	-Decreased consumption of special low protein products and fruit while increased consumption of high protein foods such as processed meat, milk and dairy products. - Intake of vitamin D (P ¼ 0.016), iron (P ¼ 0.002), calcium (P ¼ 0.017), iodine (P ¼ 0.005) and zinc (p=0.046) significantly declined during BH4 treatment while no differences in energy and macronutrient supply occurred. - During follow-up six of the eight BH4- sensitive patients could end any AAM supply. In the other two BH4-sensitive patients the dosage could be reduced. - Under classical dietary treatment, the BH4- sensitive PKU patients showed a higher mean intake of vitamin D, iron, calcium and iodine, but a lower mean intake of vitamin C and vitamin B12. Under BH4 treatment the supply of almost all micronutrients proved to be markedly lower compared to the healthy German children.							

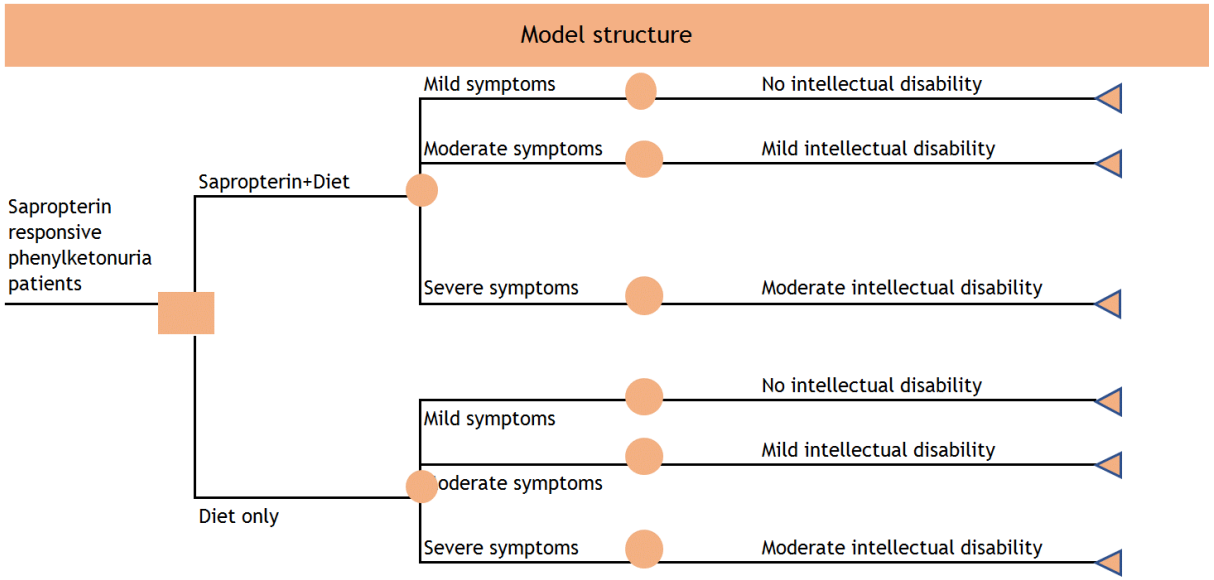
****Ziesch,2012 is looks like the same.

Ref & Name of centre	How many patients on BH4	Age of patients at the beginning of BH4 treatment	Duration of BH4 treatment	Dose of BH4 (mg/kg/d) and dosing time	Phe tolerance	
					pre BH4 (mg/kg/d)	*post BH4 (mg/kg/d)*
Vilaseca, 2010 Spain	13		5.7	5-15	No information	59.7
			5.7			53.5
			5.6			43.9
			5.8			39.3
			5.3			34.8
			6.0			35.4
			5.6			81.2
			5.6			49.1
			5.8			84.1
			6.0			93.5
			2.2			85.0
			1.0			80.2
			1.0			71.1
Results	*LCPUFA status is within the reference values in PKU patients treated with BH4. This translates to a further advantage of BH4 therapy. *Phe tolerance significantly increased after BH4 therapy (Wilcoxon test; p= 0.004; data in baseline conditions not shown).					

Appendix 2 – technical report to support revised company decision tree model

1. **Objective:** What is the incremental cost-effectiveness ratio (ICER) of 'sapropterin+diet' against 'diet only' for different age groups, namely 0-3 years, 0-17 years, 18+ years and 'woman of child bearing age'

2. **Model structure:** A one year decision tree was developed following discussion with NICE and the ERG. Structure of the model is shown below:



Phenylketonuria (PKU) is one of the several rare autosomal recessive condition that is diagnosed at birth through new-born screening programme (heel prick test). As per the SmPC (summary of product characteristics https://www.ema.europa.eu/en/documents/product-information/kuvan-epar-product-information_en.pdf accessed on 01/12/2020), a child born with PKU, after a four week response testing, sapropterin responsive PKU patients are put on treatment of sapropterin. Sapropterin non-responsive patents are put on 'diet only' (standard of care).

3. **Model health states**

Based on blood phenylalanine (Phe) reduction, Phe tolerance and symptoms level achieved, patients are categorised to be in either mild, moderate or severe health states (Okhuoya et al. 2020). Definition of these health states are detailed below:

Mild health state

European PKU guidelines recommend blood Phe between 120-360 µmol/L for children up to 12 years of age and maternal PKUs. The guideline recommends blood Phe between 120-600 µmol/L for >12 years of age (Van Wegberg et al. 2017). The mild symptomatic PKU health state have blood Phe between 600-900 µmol/L. The utility for this health state was derived from a general population in Sweden using TTO methodology (Swedish health utility report 2020 in original submission). The vignette for this state was defined as

You experience the following symptoms associated with PKU:

Emotional symptoms

- You experience **mild** feelings of unhappiness, anxiety, moodiness, irritability and worthlessness.

Cognitive symptoms

- You **occasionally** experience mild concentration issues, slowness of thinking and Forgetfulness.
- This **mildly** affects performance at work/school/home and ability to complete complex tasks (e.g. less productive while at work).

Physical symptoms

- You **occasionally** experience **mild** headaches, **mild** nausea and trembling hands.

In order to control your disease, you need to follow a **restricted, low-protein diet** as it was described in the first health state. [A question mark was included that led to a pop-up box with the diet description].

Moderate health state

The moderate symptomatic PKU health state have blood Phe between 900-1,200 µmol/L. The utility for this health state was derived from a general population in Sweden using TTO methodology (Swedish health utility report 2020 in original submission). The vignette for this state was defined as

You experience the following symptoms associated with PKU:

Emotional symptoms

- You experience **moderate** feelings of unhappiness, anxiety, moodiness, irritability and worthlessness.

Cognitive symptoms

- You **often** experience, **moderate** concentration issues, slowness of thinking and Forgetfulness.
- This **moderately** affects performance at work/school/home and ability to complete complex tasks (e.g. days missed of work).

Physical symptoms

- You **often** experience **moderate** headaches, **moderate** nausea and trembling hands.

In order to control your disease, you need to follow a **restricted, low-protein diet** as it was described in the first health state. [A question mark was included that led to a pop-up box with the diet description].

Severe health state

The moderate symptomatic PKU health state have blood Phe between 900-1,200 µmol/L. The utility for this health state was derived from a general population in Sweden using TTO methodology (Swedish health utility report 2020 in original submission). The vignette for this state was defined as

You experience the following symptoms associated with PKU:

Emotional symptoms

- You experience **severe** feelings of unhappiness, anxiety, moodiness, irritability and worthlessness.

Cognitive symptoms

- You **often** experience **severe** concentration issues, slowness of thinking and forgetfulness.
- This **severely** affects performance at work/school/home and ability to complete complex tasks (e.g. days missed of work and likelihood of unemployment).

Physical symptoms

- You **often** experience **severe** headaches, **severe** nausea and trembling hands.

In order to control your disease, you need to follow a **restricted, low-protein diet** as it was described in the first health state. [A question mark was included that led to a pop-up box with the diet description].

Patients with mild symptoms have lower risk of developing downstream neurological, psychiatric and neuro-cognitive complications. Whereas, moderate and severely symptomatic patients are at relatively higher risk of developing downstream neurological, psychiatric and neuro-cognitive complications. If left untreated, PKU can lead to irreversible intellectual disability (approximately 98% of individuals with untreated PKU fall within the range of global intellectual disability (Christ et al. 2010), as well as microcephaly, motor deficits, eczematous rash, autism, seizures, developmental problems, aberrant behaviour and psychiatric symptoms (Van Wegberg et al. 2017).

4. Key features of the cost-effectiveness model

The key features are summarised in the table below:

Current appraisal	**Chosen values**	**Justification**
Model structure	Decision tree model	The model structure was developed following discussion with NICE and ERG on 12/11/2020. It captures the impact of distinct resource use and patient HRQoL associated with each health state and allows for a cost-utility analysis over one year for a range of age groups. It incorporates a number of consequences of uncontrolled disease that were not accounted for in the ERG model.
Time horizon	One year	Initial manufacturer submission had life-time horizon. Based on the discussion with NICE and ERG on 12/11/2020, this alternative decision tree model has one year time horizon for a range of age groups.
Source of utilities	Elicitation of values from a sample of the overall Swedish population using a TTO exercise	Sample size and scope of work as well as a paucity of published information meant that both the manufacturer and ERG concluded that this was the best available source.
Source of costs	NHS reference costs, BNF, MacDonald	Consistent with the NICE reference case.
Treatment-related adverse events (TRAE)	Not included	The rate of adverse reactions in the clinical development programme for sapropterin was low (see Section B.2.10 of the original company submission). Therefore, adverse events are not a key driver of cost-effectiveness.
Mortality	Not included	Not enough evidence to support the hypothesis that there is an impact of the underlying condition on overall survival.

Abbreviations: BNF: British National Formulary; HRQoL: health-related quality-of-life; NICE: National Institute for Health and Care Excellence; TRAE: treatment-related adverse events.

Model also has checkboxes for selection of PAS (patient access scheme) price of sapropterin, intellectual disability and extra utility for woman of ‘child-bearing age’. The base case is based on PAS and intellectual disability. Scenario analysis is presented with including extra utility for woman of ‘child-bearing age’.

5. Model inputs

A separate model input worksheet captures all the key inputs to the model. These model inputs are presented in the table below:

Parameters	User input	Default value	Reference
Sapropterin Price per 100mg tablet	£19.91	£19.91	British National Formulary. 2019. £597.22 for 30 tablets. Available from: https://bnf.nice.org.uk/medicinal-forms/sapropterin-dihydrochloride.html
PAS	[redacted]	[redacted]	
Price after PAS	[redacted]	[redacted]	
Number of days in a year	365.25	365.25	
Sapropterin Dose (mg/kg) for 0-12 years	10	10	Integrated Impact Assessment Report for Clinical Commissioning Policies, Policy reference number: 1840, Title: Sapropterin for phenylketonuria all ages, interim pending NICE guidance, Proposal for routine commissioning (ref A3.1)
Sapropterin Dose (mg/kg) for 13-17 years	10	10	Integrated Impact Assessment Report for Clinical Commissioning Policies, Policy reference number: 1840, Title: Sapropterin for phenylketonuria all ages, interim pending NICE guidance, Proposal for routine commissioning (ref A3.1)
Sapropterin Dose (mg/kg) for 18+ years	12.5	12.5	Integrated Impact Assessment Report for Clinical Commissioning Policies, Policy reference number: 1840, Title: Sapropterin for phenylketonuria all ages, interim pending NICE guidance, Proposal for routine commissioning (ref A3.1)
Cost of diet (£) for 0-3 years	[redacted]	[redacted]	Anita MacDonald. Protein supplement based the average cost of 3 brands
Cost of diet (£) for 4-17 years	[redacted]	[redacted]	Anita MacDonald. Protein supplement based the average cost of 3 brands
Cost of diet (£) for ≥18 years	[redacted]	[redacted]	Anita MacDonald. Protein supplement based the average cost of 3 brands
Mean reduction in diet cost for patient on sapropterin	71.20%	71.20%	Yilmaz et al. 2018
Baseline utilities- no symptoms, no diet restrictions			
0-17 Years	0.829	0.829	Swedish health utility study in general population 2020
18+	0.816	0.816	Swedish health utility study in general population 2020
Woman of child-bearing age	0.817	0.817	Swedish health utility study in general population 2020
Health state utility values for intellectual disability (lower IQ and its impact over lifetime)			
Mild intellectual disability	0.787	0.787	Phe difference above the threshold (van Wegberg et al. 2017); IQ translation (based on Waisbren et. Al 2007, mid-value of 1.9 to 4.1=3); IQ reduction compared to normative (based on van Vliet et al. 2018, 102); Utility values from

			http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/weight0.aspx accessed in December 2020
Moderate intellectual disability	0.578	0.578	Phe difference above the threshold (van Wegberg et al. 2017); IQ translation (based on Waisbren et. Al 2007, mid-value of 1.9 to 4.1=3); IQ reduction compared to normative (based on van Vliet et al. 2018, 102); Utility values from http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/weight0.aspx accessed in December 2020
Health state utility decrement	0		
0-17 years with mild symptoms	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
0-17 years with moderate symptoms	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
0-17 years with severe symptoms	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
≥18 years with mild symptoms	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
≥18 years with moderate symptoms	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
≥18 years with severe symptoms	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
0-17 years on diet compared to sapropterin	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
≥18 years on diet compared to sapropterin	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
% of patients symptom-free on sapropterin compared to diet	0		Swedish health utility study in general population 2020, ERG Model 2020
0-17 years	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
≥18 years	[redacted]	[redacted]	Swedish health utility study in general population 2020, ERG Model 2020
Utility gain associated with sapropterin treatment in women of child bearing age	[redacted]	[redacted]	Maternal PKU syndrome refers to the teratogenic effects of elevated maternal blood Phe on the developing foetus. These high blood Phe levels during pregnancy can lead to growth retardation, microcephaly, intellectual disabilities and birth defects, including congenital heart defects (CHD) (Van Wegberg et al. 2017). The estimated utility gain is based on sapropterin as a treatment option that can bring to mothers and the effect on child over the lifetime

The disease pathophysiology and its manifestations in different subgroups, i.e. children of 0-17 years, adults of 18+ years and woman of 'child-bearing age' are summarised below:

Elevated Phe in children and adolescents

Children 0-11 years old

Blood Phe concentration during childhood is the major determinant of cognitive outcome. If blood Phe levels remain uncontrolled, children with PKU can suffer severe mental retardation and loss of IQ, microcephaly, seizures and tremors, psychological, behavioural and social problems, stunted growth, delayed speech and difficulties with executive thought processes (Kaufman et al. 1989, Huttenlocher et al. 2000).

Children 12-17 years old

Early dietary management to control blood Phe levels is effective in the prevention of severe and irreversible damage to the grey matter of the brain and the resulting mental disabilities caused by high Phe concentrations during brain development in childhood. However, high Phe concentrations in adolescence and adulthood can lead to a number of reversible complications. Good Phe control during childhood thus allows for patients with PKU to have normal/near normal intellectual ability but, with progressive loss of Phe control, patients develop the following complications (Blau et al. 2010, Enns et al. 2010):

- Neurocognitive deficits, largely related to poor executive function (EF), including attention deficits, reduced inhibitory control and reduced speed of response over multiple domains (Bilder et al. 2016, Romani e al. 2017)
- Neuropsychiatric symptoms, including high levels of depression, anxiety and inattention (Bilder et al. 2016, Bilder et al. 2017)
- Psychosocial impairments, including lack of autonomy, social maturity deficits and difficulties forming relationships (Enns et al. 2010, Gentile et al. 2010).

Elevated Phe in adults

The effect of high blood Phe is also detrimental to adults; higher Phe is associated with an increased prevalence of neuropsychiatric symptoms and EF deficits (Bilder et al. 2016). European PKU guidelines state that deficits in EF, attention problems, decreased verbal memory and social and emotional difficulties are observed in adults with PKU, even when treated early (Van Spronsen et al. 2017).

EF refers to higher order cognitive abilities, which encompasses planning, organisation, cognitive flexibility, inhibitory control and working memory. These are considered as EF because they require the integration and processing of information across a range of cognitive domains, sensory modalities and response modalities (Christ et al. 2010).

Poor EF may also impact treatment adherence and, therefore, lead to psychosocial deficits that

are not always visible. These psychosocial aspects include social difficulties and psychosocial problems, such as forming interpersonal relationships, achieving autonomy, attaining educational goals, maintaining steady employment and having healthy emotional development. The key to reducing the risks associated with PKU is improved metabolic control throughout life (Gentile et al. 2010).

The neurological complications observed due to elevated Phe are well documented (Blau et al. 2010, Van Spronsen et al. 2017). Untreated PKU can lead to irreversible intellectual disability (approximately 98% of individuals with untreated PKU fall in the range of global intellectual disability (Christ et al. 2010) as well as microcephaly, motor deficits, eczematous rash, autism, seizures, developmental problems, aberrant behaviour and psychiatric symptoms (Van Wegberg et al. 2017). Furthermore, neuropsychiatric symptoms such as depression, anxiety and attention deficit disorder are higher in PKU patients than the general population (Bilder et al. 2017).

Elevated Phe in women of childbearing age

Maternal PKU syndrome refers to the teratogenic effects of elevated maternal blood Phe on the developing foetus. These high blood Phe levels during pregnancy can lead to growth retardation, microcephaly, intellectual disabilities and birth defects, including congenital heart defects (CHD) (Van Wegberg et al. 2017).

Signs of maternal PKU may be evident at birth, but other signs can be delayed and only observed over the course of an individual's growth and development.

Tight Phe control before conception and continually throughout pregnancy is therefore critically important. Cognitive outcomes in children whose mothers had good Phe control pre-conception are better than in children whose mothers began or resumed dietary Phe restriction after conception (Grange et al. 2014).

The European PKU guidelines (Van Wegberg et al. 2017) recommend the following for maternal PKU:

- Women with untreated Phe level >360 micromol/L must be treated to bring Phe level to 120-360 micromol/L;
- Blood Phe levels before and during pregnancy should be maintained at 120-360 micromol/L;
- Significant effort should be taken to avoid any unplanned pregnancies in PKU women; and
- Education and effective contraceptive methods are key elements.

6. Results

ICER for the base case, based on ERG model, including PAS and intellectual disability is presented in the table below:

Subgroups	Mean sapropterin dosage(mg/kg/day)	Mean sapropterin cost per day	Reduction in daily PRD cost with sapropterin	Incremental daily cost with sapropterin	Annual incremental cost with sapropterin	Symptom severity level	QALY incremental gain with sapropterin	ICER per QALY gained with sapropterin
0-3 years	10mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]
0-17 years	10mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]
≥18 years	12.5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]
Woman of child-bearing age	12.5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]

Scenario analysis: Scenario analysis including extra utility gain that sapropterin will bring to woman of 'child-bearing age' is presented in the table below:

Subgroups	Mean sapropterin dosage(mg/kg/day)	Mean sapropterin cost per day	Reduction in daily PRD cost with sapropterin	Incremental daily cost with sapropterin	Annual incremental cost with sapropterin	Symptom severity level	QALY incremental gain with sapropterin	ICER per QALY gained with sapropterin
0-3 years	10mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]
0-17 years	10mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]
≥18 years	12.5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]
Woman of child-bearing age	12.5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	Mild	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Moderate	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	Severe	[redacted]	[redacted]

7. Summary and conclusions

Treatment of children and adolescents with sapropterin plus diet compared with diet alone is a cost-effective use of NHS resources based on this one-year decision tree model.

Treatment with sapropterin in the 0-3 age group is dominant (more effective and less costly) at PAS price across all disease severity levels, while treatment with sapropterin in the 0-17 age group has an ICER of less than £20,000 per QALY across all disease severity levels (i.e. it is more effective and associated with a modest incremental cost). The use of sapropterin in adults is associated with higher ICERs, however, there may be groups such as women of childbearing age that accrue additional benefits from sapropterin treatment where this ICER is substantially lowered.