National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Sapropterin for treating phenylketonuria

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	BioMarin	*[Would it be appropriate to refer this topic to NICE for appraisal?]* Yes	Comment noted. No action required
	The National Society for Phenylketonuria (NSPKU)	The health of patients with PKU should be a priority for NICE. The disease is chronic. The only treated currently funded in England is a low phenylalanine diet which involves removing almost all natural protein from the diet. In children, the dietary treatment has uneven outcomes which can permanently impact the life chances of the individual. The majority of adult patients are unable to adhere to dietary treatment. In adults, high phenylalanine levels can impair cognitive and neuropsychological functioning. In pregnancy, high phenylalanine levels can cause miscarriage, birth defects and developmental delay. Fear of Maternal PKU syndrome can impact the sexual and reproductive choices of women with PKU. The treatment burden for all ages is unacceptable, severely impacting quality of life for both the patient, parental carers and the wider family. The suboptimal outcomes and unacceptable treatment burden means alternative or adjunctive therapies are essential.	Comment noted. NICE has scheduled the appraisal of saproterin to start soon.

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	British Dietetic Association (BDA)	It is very important that this topic is referred to NICE and the health of patients with PKU should be considered a priority in the UK. It is crucial that any consideration of PKU is from a holistic perspective, rather than only considering its impact on neurological health. A low phenylalanine diet is the only treatment choice, and this has remained unchanged since treatment commencement in the early 1950‘s. The condition and its current treatment can have severe impact on mental and nutritional health, as well as severely limiting ‘normal’ socialisation which is an important aspect of life. It is accepted that dietary management is challenging, adds significant daily burden, and does not ease with advancing age. Maintaining a lifelong low phenylalanine diet is not a realistic option and it is particularly difficult for many adult patients. Some adults find dietary management complex and impractical and abandon treatment, with some withdrawing from medical care. Some adults were recommended to stop dietary treatment in childhood and the thought of diet recommencement is almost inconceivable, despite mental and physical health consequences. All these aspects should not be negated. Although stringent blood phenylalanine control is recommended throughout life (see European PKU Guidelines, 2017), it is well established that blood phenylalanine deteriorates from late adolescence and only one in four adults achieve satisfactory blood phenylalanine control. In the UK, despite European PKU Management Guidelines, the care of PKU patients is fragmented and disorderly and many patients are lost to follow up (potentially up to 2000). The NSPKU can only identify around 2200 patients from England in follow up care but around 4000 people with PKU should have been diagnosed (personal communication). There is evidence that co-morbidities are higher in the PKU community than the general population and according to a recent NSPKU survey, the use of anti-	Comments noted. NICE has scheduled the appraisal of saproterin to start soon.

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		depressants and anti-anxiety medication is high, their quality of life is poor with high levels of guilt and poor self-esteem (Ford et al 2018). Obesity is high in women and *disordered eating* is described in the literature. Women struggle throughout life, living in fear of pregnancy and potential harm to their infants and some do not participate in sexual relations (Ford et al 2018). Prior to pregnancy women must follow a very restrictive diet which some are unable to do so decide not to have children to avoid foetal damage. Others who manage diet in pregnancy, are unable to sustain dietary treatment post pregnancy as they cannot eat sufficient calories to sustain breast feeding. Many women say they are unable to take care of their infant and look after their own dietary needs (Ford et al 2018).	
	Royal College of Pathologists (RCP)	*[Would it be appropriate to refer this topic to NICE for appraisal?]* Yes	Comment noted. No action required.
	NHS England	NHS England considers that it is appropriate for NICE to consider the drug as a Single Technology Appraisal	Comment noted. No action required.
Wording	BioMarin	The remit stated as “To appraise the clinical and cost effectiveness of sapropterin within its marketing authorisation for treating phenylketonuria” is considered appropriate.	Comment noted. No action required.
	NSPKU	No comment.	Comment noted. No action required.
	BDA	*[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording]* Yes	Comment noted. No action required.

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	Genetic Alliance UK	The wording of the remit matches the standard format.	Comment noted. No action required.
	Royal College of Pathologists (RCP)	*[Would it be appropriate to refer this topic to NICE for appraisal?]* Yes	Comment noted. No action required.
Timing Issues	BioMarin	• PKU is a serious chronic life-long metabolic disorder with no effective treatment: Phenylketonuria affects the brain and other tissues and requires strict therapeutic control to avoid serious, lifelong consequences of elevated phenylalanine (Phe) levels. As a result of the seriousness of the disease, new-born screening is now commonplace across the UK. • Current management of PKU with low Phe restricted diet is near impossible to maintain for most patients. Even with Phe-restrictive dietary recommendations for all age groups, evidence suggests that PKU management with diet alone has resulted in sub-optimal outcomes, including deficits in neurocognitive and psychosocial metrics, quality of life measures, nutritional deficits, and brain pathology • Elevated blood Phe during childhood is the major determinant of irreversible negative cognitive outcomes and 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 • As such, given these issues, and that some patients with PKU are not being managed well on current treatment there is an urgency in having a policy that provides clarity on the benefit of Kuvan and its use within the NHS	Comments noted. NICE has scheduled the appraisal of saproterin to start soon.

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	NSPKU	The majority of developed nations already use sapropterin as an additional treatment option and have done so for a number of years. The NHS England policy E06/P/a was due for review in March 2017. The NHS England policy on the use of sapropterin in pregnancy was published in April 2013, and was due for review in 2014. The use of sapropterin has been under review by NHS England since summer 2017 and a parallel process is taking place at NHS England. NSPKU wishes there to be sensible and timely communication between NHS England, NICE and the Department of Health to ensure a fair and clear outcome for patients.	Comment noted. NICE has scheduled the appraisal of saproterin to start soon.
	BDA	Alternative treatments for the management of PKU are desperately needed. It is clear that many adults are unable to adhere to diet treatment, and children struggle with diet therapy particularly from the age of 5 years upwards. In the UK, there are children in social care because their parents are unable to cope with dietary treatment, other children with sub-optimal blood phenylalanine control (causing a lowering of IQ and behaviour problems), and children and adults have mental health issues associated with PKU and dietary management. For women, regular use of sapropterin would reduce the risk of foetal damage if a woman became pregnant and was not following a preconception diet. In England, ≥50% of women are not on pre-conception diet prior to pregnancy. Sapropterin has had a European licence for 10 years and is widely used by other European countries. It has a good safety profile and is effective in around 20 to 30% of the PKU population. In England, through Kuvan trials, IFR's, and personal funding, over 30 patients have been treated with Kuvan. For these patients, the impact of Kuvan has been life changing. Kuvan has led to significant relaxation of diet therapy, reduction in protein substitute intake and a significant improvement in their ability to socialise. Patients who are responsive to Kuvan report that they are happier on Kuvan, and for adult patients who had	Comment noted. NICE has scheduled the appraisal of saproterin to start soon.

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		Kuvan withdrawn at the end of longitudinal trials, they have found it very difficult with many failing to adhere to long term dietary treatment.	
	RCP	Relatively urgent and this medication may be transformative for people with PKU and have an impact on intellectual capacity, mental and physical health.	Comment noted. NICE has scheduled the appraisal of saproterin to start soon.
	NHS England	It would be helpful if NICE could prioritise this piece of work; the patient community are keen for a resolution of the commissioning arrangements.	Comment noted. NICE has scheduled the appraisal of saproterin to start soon.
Any additional comments on the draft remit	BioMarin	BioMarin believes the appropriate method of evaluation of Kuvan is via the HST route. The criteria for an assessment under an HST programme considers: • The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS; ***(we believe there are an estimated 300 patients within the licensed indication who are considered eligible for Kuvan in England)*** • The target patient group is distinct for clinical reasons; ***(Kuvan is licensed for use only in those who are responsive to Kuvan)*** • The condition is chronic and severely disabling; ***(this is true for PKU)*** • The technology is expected to be used exclusively in the context of a highly specialised service; ***(this is applicable for PKU)*** • The technology is likely to have a very high acquisition cost; ***(this is applicable for Kuvan)***	Stakeholder comments on the suitability of the HST programme have been noted. Sapropterin does not fulfil the criteria for Highly Specialised Technologies as described in the Interim Process and Methods of the Highly Specialised Technologies and will be appraised as a Single Technology Appraisal. Specifically the target population is estimated to be larger and the condition is chronic but the extent of its impact especially in children can be managed with a controlled diet – however this is very challenging.

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		• The technology has the potential for life long use; ***(this is applicable for Kuvan in PKU)*** • The need for national commissioning of the technology is significant. ***(this is true for Kuvan in PKU)*** Given these criteria, BioMarin believes Kuvan should be evaluated under the HST programme	
	NSPKU	Consideration should be given to conducting this appraisal through the HST programme. Having regard to the criteria in the HST methods guide: • The target patient group is clinically distinct – diagnosed PKU patients with residual enzyme activity. • The number of patients who are likely to be treated with sapropterin is small according to work conducted by NHS England. • It is expected that the treatment would be used exclusively in the context of specialist metabolic clinics. • The other factors relating to the disease and the treatment are also indicative that HST is an appropriate appraisal route.	Stakeholder comments on the suitability of the HST programme have been noted. Sapropterin does not fulfil the criteria for Highly Specialised Technologies as described in the Interim Process and Methods of the Highly Specialised Technologies and will be appraised as a Single Technology Appraisal. Specifically the target population is estimated to be larger and the condition is chronic but the extent of its impact especially in children can be managed with a controlled diet – however this is very challenging.

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	NSPKU (reporting BDA comments)	I have reviewed the comments of Professor Anita MacDonald on behalf of BDA in draft format and support them. Her comments include detailed references to the research papers Ford et al, 2018 (abstracts published) which analyses a survey conducted by NSPKU in both the general patient cohort and in women with PKU.	Comment noted. No actions required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	BioMarin	The following revised version is proposed (changes are underlined): Phenylketonuria is a <u>rare</u> autosomal recessive <u>genetic</u> disorder caused by the deficiency of an enzyme called phenylalanine hydroxylase (PAH). PAH breaks down phenylalanine into tyrosine and in the absence of this, phenylalanine accumulates in the blood <u>which is toxic to the central nervous system and can cause microcephaly (decreased brain and skull size) in paediatrics and defects in the myelin sheath which in turn leads to abnormalities to the speed of neural transmission. Uncontrolled PKU is also characterised by: irreversible cognitive deficits and intellectual impairment including for example loss of IQ (particularly in children); impaired executive function (which interferes with the ability to perform basic cognitive tasks such as focusing, memory, planning and impulse control); neurological complications; psychiatric disorders including anxiety and depression, phobias, low self-esteem; attention deficit hyperactivity disorder (ADHD); motor deficits such as tremors and ataxia; autism, seizures and psychological, social and behavioural problems</u>. <u>The recently published European Guidelines on phenylketonuria: diagnosis and treatment *(van Wegberg et al. Orphanet Journal of Rare Diseases (2017)*</u>	Comment noted. The background section is intended to give a brief overview of the condition; epidemiology data in the scope were updated. Further details of the condition and its treatment will be explored during the appraisal.

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		12;162) recommend that treatment of PKU should be started as early as possible to prevent neurological damage. Children with elevated Phe who have not been controlled under a Phe-restricted diet, exhibit from the age of about 6 months, developmental problems, which may be accompanied by aberrant behaviours including self-harm, aggression, impulsivity, and psychosis(7). All of these have an impact on day to day functioning and leads to a reduced quality of life for patients and their families. Given the severity of disease, new-born screening is now commonplace in the UK since 1969(1). As a result, children born in the UK since 1969 with phenylketonuria (PKU) have been diagnosed at birth. The introduction of new-born screening has meant all babies born in the UK are routinely screened for blood phenylalanine levels and neurological damage can therefore potentially be prevented by following a strict diet that is limited in the amount of phenylalanine that is present. Phenylalanine is an essential amino acid and cannot be synthesised de novo in the body and needs to be provided through food. Managing PKU therefore involves limiting the intake of phe through dietary restriction of foods containing natural protein (and as such phe). The phe-restricted diet excludes foods such as meat, fish, eggs, cheese, pulses, seeds, flour, bread and pasta.(1) The majority of patients cannot adhere to dietary treatment because it is very challenging and difficult to manage while living a normal life. When patients are treated with the phe-restricted diet alone, it has been shown to lead to sub-optimal outcomes (Enns, 2010)(2) in all age groups across a wide range of neurological and quality of life outcomes, as well as causing issues with bone pathology, growth and other nutritional deficiencies. Because of the consequences of elevated blood phe, recently developed European PKU guideline *(van Wegberg et al. 2017)* recommends that all PKU patients with untreated blood Phe levels >360 µmol/L should be treated. Patients with untreated phe levels between 360-600 µmol/L should be treated until the	

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		age of 12 years. The guideline also recommend treatment for life for any patient with PKU. PKU has also been associated with significantly higher prevalence for numerous neuropsychiatric conditions, like intellectual disability and autism spectrum disorder. PKU patients also have higher prevalence rates of fatigue/malaise, epilepsy/convulsions, sleep disturbance, personality disorders, phobias, psychosis, and migraines compared to matched general population (Bilder 2017).(3) In adults, elevated blood phe can have serious consequences including increased risk of lower IQ (Fonnesbeck et al.), intellectual disability, seriously impaired executive function, anxiety, depression and other medical and behavioural problems (Koch et al). Adults with phenylketonuria also may also develop comorbidities impacting cardio-vascular and metabolic functions. It is especially important to maintain low levels of phenylalanine during pregnancy and pre-conception to avoid its harmful effects on the foetus. The epidemiology of phenylketonuria in the UK is estimated as 1 in 14,300(4). In 2016-17, the incidence rate of positive screening tests for phenylketonuria was 0.0137% (107 babies screened positive and 779,688 babies were tested).[5] Highly restrictive diet that includes phe free foods with protein supplements is the mainstay of treatment in the UK. Sapropterin, the only pharmacological option available to PKU patients, is currently commissioned by NHS England for pregnant women only(6), with minimal utilisation within England. 1. *Downing and Pollitt 2008. Newborn bloodspot screening in the UK – past, present and future. Ann Clin Biochem 2008; 45: 11–17* 2. *Enns G et al. 2010. Suboptimal outcomes in patients with PKU treated early with diet alone: Revisiting the evidence. Molecular Genetics and Metabolism 2010. Molecular Genetics and Metabolism 101 (2010) 99–109*	

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		3. *Bilder et al, 2017. Neuropsychiatric comorbidities in adults with phenylketonuria: A retrospective cohort study. Mol Genet Metab. 2017 May;121(1):1-8.* 4. *Williams et al, 2008. Phenylketonuria: An Inborn Error of Phenylalanine Metabolism. Clin Biochem Rev Vol 29 February 2008 I 31.* 5. *Data Collection and Performance Analysis Report Newborn blood spot screening in the UK 2016/17 (Public Health England)*[i] 6. *https://www.england.nhs.uk/wp-content/uploads/2013/04/e12-p-a.pdf* 7. *Blau N, Shen N, Carducci C. Molecular genetics and diagnosis of phenylketonuria: state of the art. Expert Rev Mol Diagn 2014;14(6):655-71*	
	NSPKU	<u>Phe restricted diet:</u> The phenylalanine restricted diet is accurately described, however its complexity and burdensome nature are not fully conveyed. We suggest an additional sentence: "*Dietary management is burdensome to the individual or their caregiver. It requires detailed dietary knowledge, organisation and cooking skills, and extraordinary motivation to adhere to such a restrictive diet*." This issue is very relevant – an understanding of the burden of dietary treatment is required to appreciate health inequalities and discrimination. The family background of children with PKU and their ability to deliver the dietary treatment will permanently affect their outcome. In adults, a variety of personal and social issues will affect the ability to cope with dietary treatment. In addition, adhering to the diet is itself associated with problems in eating and feeding (see page 29 of The complete European Guidelines on phenylketonuria)	Comment noted. The background of the scope has been revised to include more details on the impact of phenylalanine restricted diet on carer and on the NHS criteria for commissioning.

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		and affects the quality of life of patients (Ford et al, from NSPKU survey of UK patients). We suggest the following addition: *"Dietary treatment can affect the quality of life of patients and is associated with eating disturbances and physical side effects, eg gastrointestinal symptoms across all age groups."* <u>Use in pregnancy:</u> The remit states that "Sapropterin is commissioned by NHS England for pregnant women." This does not accurately reflect the contents of the commissioning policy. The policy states that women who have "failed to establish metabolic control will be tested for sapropterin responsiveness." Therefore the policy is a "fail first" policy, in which the foetus will already be at risk before the use of sapropterin is considered, in a woman who typically has never had responsiveness testing and is already pregnant. NSPKU understands through it contact with patients and clinicians that sapropterin is rarely used in pregnancy, even in patients with poor metabolic control during their pregnancy. NSPKU has sought data on use and outcome in pregnancy and has been informed that NHS England has not reviewed the policy and holds no data on the use of sapropterin in pregnancy pursuant to the policy. NSPKU believes it is likely that the infrequent use of sapropterin in pregnancy in England is linked to the difficulties of having to fail dietary treatment first and then needing to undertake responsiveness testing in an already high risk pregnancy. NSPKU wishes the use of sapropterin in women to be fully reconsidered with outcome measures to include both healthy outcomes in pregnancy and improvements in the health related quality of life of women. We suggest the following replacement wording: "*NHS England has a policy dated 2013 allowing for the use of Sapropterin in pregnant women in restricted circumstances, which is due for review."* The serious nature of Maternal PKU should be referred to, for example:	

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		"High phenylalanine levels in pregnant women with PKU are toxic to the developing foetus and can cause birth defects, including congenital heart disease, microcephaly, developmental delay and miscarriage.	
	BDA	The severe restrictions and difficulties of dietary management are inadequately described. The diet excludes meat, fish, eggs, cheese, pulses, seeds, flour, bread, pasta and aspartame. Patients are prescribed a high volume of poor tasting protein replacement 3 times daily. Most of the diet is based on prescribed low protein foods which are generally high in carbohydrate and sugar. Unlike other diets, the PKU diet is unrelenting, time consuming, and complex to understand. There are few suitable foods that can be purchased from supermarkets; and the overall diet is not compatible with a normal life. The impact of PKU in childhood and adulthood is not adequately captured in the draft scope. Although the draft scope identifies some of the problems of PKU, it reads as though all issues are resolved if diet is followed. In addition, it suggests that PKU 'manifests in adulthood'. PKU does not manifest itself in adulthood; it is a lifelong condition. Complications are likely to increase with age. With children with PKU, European PKU Guidelines (2017) state that the aim is to ensure that the blood phenylalanine levels are maintained consistently below 360µmol/L. If levels are consistently above 360µmol/L there is a risk of long term cognitive impairment. 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. In fact, 2 meta-analysis have been conducted which should be included as part of the background. 1. Waisbren et al. (2007) performed a meta-analysis examining the correlation between IQ and Phenylalanine 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 phenylalanine	Comment noted. The background section is intended to give a brief overview of the condition; it has been revised to include more details on the impact of phenylalanine restricted diet on carers.

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		levels ranged from 423-750 µmol/l. With regard to lifetime phenylalanine levels an increase of 100 µmol/l predicted an average 1.9 to 4.1-point reduction in IQ over a range of phenylalanine from 394-666 µmol/l. For example, a patient with a phenylalanine 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 phenylalanine 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 phenylalanine levels. The healthy population probability of an IQ less than 85 was approximately 15%. For PKU patients the probability was 14% when the mean phenylalanine level during the time frame of ≥6 years of age was 400 µmol/L but increased to 20% when the mean phenylalanine level was 600 µmol/L. There are some children whose parents are unable to adhere to the severity of the dietary restrictions. They have poor blood phenylalanine control which results in low IQ. Other factors such as frequent illnesses, low energy intake or inability to take protein substitute all impact on blood phenylalanine control. 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. It is also recognised that many adults are unable to follow dietary management. PKU can lead to many issues: poor mental health, it impairs executive functioning e.g. inability to concentrate and handle complex tasks (which includes managing PKU diet), poor verbal memory, learning and problems with visuomotor co-ordination and poor social functioning. This also affects an	

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		individual's ability to work, their work performance, and ability to reach their academic and life potential. Tremor, spastic paresis, abnormal MRI scans, osteopenia, vitamin B12 deficiency are not uncommonly reported. Women, particularly those unable to follow dietary management have a higher incidence of obesity. In a recent large study from 4 million people on an insurance health care database, it was found in 377 adults with PKU patients that they had more intellectual disabilities, developmental disorders, psychosis/schizophrenia, and behavioural disorders. They had more major depressive disorders (recurrent), reaction to severe stress and adjustment disorders, other anxiety disorders, chronic ischemic heart disease, infectious gastroenteritis and colitis, and unspecified diabetes mellitus. The selected medications that were prescribed significantly more in the PKU vs control population were gastrointestinal agents, statins, analgesics and antipyretics, and antidepressants. In adulthood, the existing European treatment guidelines recommend that phenylalanine levels are maintained below 600 micromole/litre which is still double the USA guidelines, and it is 6 times greater than the normal level of blood phenylalanine. The life time consequences of this are not fully understood.	
	Genetic Alliance UK	We suggest the additional of a qualifying word such as 'largely' at the start of the fourth line of the second paragraph (ie. 'neurological damage can be largely prevented by following a strict phenylalanine restricted (low protein) diet'). This is because patients whose phenylalanine levels are well-controlled by diet tend to have IQs that are slightly lower than their unaffected siblings, although generally within the normal range, and may also have executive function difficulties (Van Zutphen K, et al, Executive functioning in children and adolescents with phenylketonuria. Clin Genet. 2007, 72: 13-8; Leuzzi V, et al. Executive function impairment in early-treated PKU subjects with normal mental development. J Inherit Metab Dis. 2004, 27: 115-25).	Comment noted. The background section of the scope has been revised.

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	RCP	No comment	Comment noted. No action required.
	NHS England	Greater detail regarding the number of children diagnosed each year would be helpful; is it constant, how many children with PKU are there in the country? In relation to adults, many are lost to follow up. This intervention is effective for only a subpopulation of patients who respond, the scope should reference this and give an estimate of potential patient numbers in England	Comment noted. The background section is intended to give a brief overview of the condition; further details of the population size will be explored during the appraisal.
The technology/ intervention	BioMarin	The document states that "The clinical trials defined hyperphenylalaninaemia as blood phenylalanine concentration≥400 µmol/L." This is incorrect. The normal range of Phe is normally between 60 -120 µmol/L. As such, suggest this sentence is amended or removed.	Comment noted. The clinical trial included people with hyperphenylalaninemia with past medical history with at least 2 blood phenylalanine level ≥400 µmol/L obtained in 2 separate occasions (or mean of 2 measurements blood phenylalanine level ≥450 µmol/L at screening). The scope was revised to reflect this.
	NSPKU	No comment	Comment noted. No action required.
	BDA	Sapropterin not only lowers blood phenylalanine, it leads to: 1. Increase in natural protein tolerance.	Comment noted. This section of the scope is intended to give a brief overview of the technology. The clinical trial

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		2. Lowering of phenylalanine-free protein substitute. 3. Lowering of use of low protein special foods. 4. In some patients it will lead to a normalisation of dietary treatment. It helps a subsection of the PKU population with mild or moderate PKU. This group of patients have some residual phenylalanine hydroxylase activity. It is only administered once daily. The dose of sapropterin has not been discussed. The European PKU Guidelines state that all patients with phenylalanine levels greater than 360 µmol/L should be treated for PKU and not ≥400 µmol/L. The safety profile of the drug has not been described. Also, it should be mentioned that sapropterin received a European licence in 2008. This section does not describe how sapropterin works. There is a body of references about sapropterin which are not included. None of the sapropterin trials have been discussed. *A separate list of references has been included in the appendix*. It is well accepted that a clinically effective response to sapropterin is a 30% reduction in blood phenylalanine levels from 7 to 30 days. This is assessed prior to sapropterin prescription/ commencement. Such a response rates results in a significant improvement in phenylalanine intake as well as maintenance of blood Phe control. Also sapropterin responsiveness could be assessed by mutation analysis. Many of the studies on sapropterin both aim to increase dietary phenylalanine intake and maintain blood Phe control. It is expected that	included people with hyperphenylalaninemia with past medical history with at least 2 blood phenylalanine level ≥400 µmol/L obtained in 2 separate occasions (or mean of 2 measurements blood phenylalanine level ≥450 µmol/L at screening). The scope was revised to reflect this.

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		sapropterin should double dietary phenylalanine intake without deterioration of blood phenylalanine control. With sapropterin, it is likely that growth and IQ would be maintained. 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 20% of sapropterin responsive patients would be expected to stop dietary treatment.	
	RCP	*[Is the description of the technology or technologies accurate?]* Yes	Comment noted. No action required.
	NHS England	As referred to above the technology only works for a proportion of patients with PKU and this should be referenced in detail.	Comment noted. No action required.
Population	BioMarin	People with phenylketonuria should be amended to: Adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to sapropterin (as per licensed indication)	Comment noted. The population and economic section of the PICO table have been amended.
	NSPKU	The population should include patients of all ages, including pregnant women.	Comment noted. The population is defined as "people with phenylketonuria whose disease has been shown to be responsive to sapropterin therapy", which includes adults, paediatric patients of all ages and pregnant women.

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	BDA	Groups should not be considered separately. Sapropterin will only benefit a sub section (20 to 30%) of the PKU population anyway who have mild or moderate PKU (this is associated with residual phenylalanine hydroxylase activity).	Comment noted. No action required.
	Genetic Alliance UK	The scope mentions the incidence of PKU in babies. However, as the expected indication for the treatment is adults with inadequate blood phenylalanine control (defined as more than 600 umol/L), the birth incidence gives very little indication of the likely number of patients who would be eligible and wish to be treated with sapropterin. It likely be appropriate to consider subgroups such as children and young people (both because of the irreversible nature of damage in childhood and also the tendency for adherence to reduce as patients approach adulthood), pregnant women who do not meet eligibility criteria under the NHS England commissioning policy. It would also likely be appropriate to distinguish between those patients whose phenylalanine are not controlled within safe levels while fully adherent to the diet and those who are unwilling or unable (for example due to cognitive or behavioural problems) to maintain the strict diet.	Comment noted. The population is defined as "people with phenylketonuria whose disease has been shown to be responsive to sapropterin therapy", which includes adults, paediatric patients of all ages and pregnant women. Subgroups according to pregnancy, age and adherence to diet have been added to the scope and will be considered if evidence allows.
	RCP	Yes, medication already allowed to be used during pregnancy but this might be regarded as a population to be regarded separately.	Comment noted. Subgroups according to pregnancy, age and adherence to diet have been added to the scope and will be considered if evidence allows..
Comparators	BioMarin	Established clinical management without sapropterin should be amended to Current management in the NHS without sapropterin	Comment noted. No action required.
	NSPKU	Patients can experience uneven access to services for PKU across the UK. As an example, many CCGs or GPs restrict access to some or all products required	Comment noted. Details of the availability of treatments

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		for dietary treatment against the advice of metabolic clinical specialists. Similarly, many patients have need for psychology or other support to deal issues such as refusal of amino acid supplements, eating disorders and phobias but this is rarely available or accessible. The consensus document "Management of PKU" published by NSPKU dated July 2014 refers to a multidisciplinary approach across the hospital-community interface with full practical and emotional support given to patients at all life stages of dealing with this chronic condition; however this is not the experience of many patients in practice. When comparing the cost of dietary treatment to sapropterin, it should be a comparison between the high standard of care which should be experienced, not the cost of what is actually delivered in practice.	in the NHS may be considered, if appropriate, during the appraisal. No action required.
	BDA	Diet therapy is the only approved therapy for PKU, however many patients struggle to adhere to this treatment particularly from the age of 5 years. Many adults have no treatment due to their inability to adhere to the extreme dietary restrictions that they must follow. Sapropterin is the only alternative treatment available and licenced in Europe. It is safe and effective in 20 to 30% of patients with PKU.	Comment noted. No action required.
	RCP	Alternate / current care is low natural protein diet with phenylalanine free protein supplements.	Comment noted. No action required.
	NHS England	PKU Diet is the only clinical comparator	Comment noted. No action required.
Outcomes	BioMarin	Changes highlighted below (with underline) The outcome measures to be considered include: • phenylalanine concentration in the blood • Dietary phe and natural protein intake	Comment noted. The reference case defined in the NICE Guide to the methods of technology appraisal (sections 5.1.7 and 5.1.8) specifies that all direct health

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		• change in neuropsychological function • nutritional biochemistry (e.g., vitamin B12) • adverse effects of treatment • cognitive and mood symptoms • Health-related quality of life. • Caregiver burden • Work productivity	effects, including those for patients and for carers, should be considered. The NICE Guide to the methods of technology appraisal (section 5.1.10) specifies that productivity costs are not included in reference-case or non-reference-case analyses. No change was made to the scope.
	NSPKU	Other outcome measures: Bone health BMI Ataxia and tremor, motor –coordination, spastic paresis Changes to brain white matter Executive functioning Mental health improvements Reduction in treatment burden Pregnancy outcomes NSPKU supports the statement in the European guidelines that “the primary goal of treatment is normal neurocognitive and psychosocial functioning”: the outcome measures should reflect this aspiration.	Comment noted. More specific outcomes can be considered under the broad scope outcomes, as part of the appraisal. No change was made to the scope.
	BDA	I agree with most of the outcome measures described. My comments are as follows:	Comment noted. More specific outcomes can be

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		• Usual quality of life questionnaires are ineffective in collecting issues about the day to day problems experienced in patients with PKU. It is better to conduct qualitative interviews with patients/caregivers to understand the day to day impact of PKU and dietary management. • Data on MRI scans should be collected • Protein intake should be divided into: natural protein intake and protein equivalent from protein substitute intake.	considered under the broad scope outcomes, as part of the full appraisal. The NICE Guide to the methods of technology appraisal (section 5.3.1) specifies that the EQ-5D is the preferred measure of health related quality of life in adults in the reference-case analyses. However, the merits of different measures of quality of life may be considered during the appraisal.
	Genetic Alliance UK	In addition to nutritional biochemistry it may be worth including more clinical indicators of poor nutrition such as weight, height, BMI, and features of micronutrient and phenylalanine deficiency (such as anorexia, listlessness, alopecia, and perineal rash).	Comment noted. More specific outcomes can be considered under the broad scope outcomes, as part of the full appraisal. No change was made to the scope.
	RCP	Yes, I would say “increase in natural protein intake” and have this as the second outcome listed.	Comment noted. The outcomes were revised accordingly.
	NHS England	The outcomes are comprehensive; carers have reported that they consider that managing the diet is an excessive burden and this is not recognised currently	Comment noted. The reference case defined in the NICE Guide to the methods of technology appraisal (sections 5.1.7 and 5.1.8)

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			specifies that all direct health effects, including those for patients and for carers, should be considered. No change was made to the scope.
Economic analysis	BioMarin	No changes proposed "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."	Comment noted. No action required.
	NSPKU	See comments above in relation to "comparators" This analysis is being conducted a year prior to the expiry of the orphan drug market exclusivity for sapropterin. The cost of this drug may significantly reduce with generic competition. Social services costs: NSPKU is aware through its contact with families that children with PKU appear to have a much higher prevalence of social services intervention. European guidelines require consideration of child safeguarding measures linked to the family's inability to control blood phe through dietary management.	Comment noted. The appraisal will take into account the cost of sapropterin at the time of the appraisal. The reference case defined in the NICE Guide to the methods of technology appraisal (sections 5.1.7 and 5.1.8) specifies that all direct health effects, including those for patients and for carers, should be considered. The reference case also includes

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		Individuals with learning disabilities or other issues frequently cannot cope with PKU dietary management unless they have significant family or social services support. In practice, due to the poor understanding of PKU in the community this support may not be available and the individuals either do not have any treatment option available to them or alternatively rely on informal family support to cope. Further, as this is a rare disease which is not well understood in a social services context, the appropriate social service provision will not be well defined and costs information will not be easily assessable. Informal caring costs should be included. Interventions in education and other social costs should be considered. As the burden of care of PKU falls squarely on family caregivers or individuals themselves, the NHS and Personal Social Services perspective is an inadequate measure of the cost of PKU. The wider perspective this is available in the HST would be more appropriate	cost from the NHS and PSS perspective, as stated in the NICE Guide to the methods of technology appraisal (sections 5.5.11 to 5.5.13). No change was made to the scope.
	BDA	Patient numbers likely to respond to sapropterin is likely to be small and no more than 350 patients with PKU in England. Patients who are treated with sapropterin are less dependent on specialist dietary/medical foods. Special low protein usage is small when patients tolerate more than 20g/day protein (exception low protein milk) and requirement for synthetic protein/protein substitute is likely to reduce by 50%. These cost savings should be considered in the economic analysis. Patient/caregiver inability to follow diet results in increased health professional time. This should be considered. Individuals who are either unable to adhere to diet therapy or suffer from mental health issues (because of poor blood Phe control) are more likely to require extra dietetic, psychology/ counselling support,	Comment noted. The cost savings in reduced established care should be included. The reference case defined in the NICE Guide to the methods of technology appraisal (sections 5.1.7 and 5.1.8) specifies that all direct health effects, including those for patients and for carers, should be considered. The reference case also includes cost from the NHS

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		hospital admissions, medications for depression or anxiety and additional blood Phe samples/monitoring. If children are removed from their home as a consequence of safe guarding concerns due to poor dietary management, resulting legal, foster care and social services costs are high. Although most children with PKU will attend mainstream school, some children with sub-optimal control need additional teaching support in school/adult education. Also, extra school supervision must be provided at mealtime due to the extreme severity of the diet. It is establishing that a proportion of caregivers (predominantly mothers) are unable to work or reduce their working hours so they can care for their child with PKU. They lose income.	and PSS perspective, as stated in the NICE Guide to the methods of technology appraisal (sections 5.5.11 to 5.5.13). No change was made to the scope.
	RCP	6-12 months	Comment noted. No action required.
	NHS England	Patients are most likely to need to continue with the PKU diet, there is evidence that a small number of patients can eat normally on this drug. The impact on families, given time taken to manage the diet could be considered as part of the economic analysis	Comment noted. The reference case defined in the NICE Guide to the methods of technology appraisal (sections 5.1.7 and 5.1.8) specifies that all direct health effects, including those for patients and for carers, should be considered. No change was made to the scope.

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Equality and Diversity	BioMarin	No equality issues to highlight.	Comment noted. No action required.
	NSPKU	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	Comment noted. The scope has been revised in light of the issues raised, please see the accompanying EIA for further details.

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		to ease the burden of care will have a greater impact fon women, due to the higher number of women who are primary carers. NSPKU notes that women with PKU reported that PKU could adversely affect their sexual and reproductive choices and their experience of mothering. This appraisal should be conducted to ensure that these female focused issues are fully considered. (refer to Ford et al, 2018 abstract published)	
	BDA	• 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 are lost to follow up and no 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 – need a national register of patients	Comment noted. The scope has been revised in light of the issues raised, please see the accompanying EIA for further details.

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	NHS England	Currently only pregnant women have routine access to this drug	Comment noted. No action required.
Innovation	BioMarin	It has been found that 20-56% of patients respond to sapropterin therapy (based on the EMA licence). For these responsive patients, sapropterin brings significant benefits including a reduction in blood phe, an increase in natural protein intake and improvement in neurological function. The efficacy of sapropterin treatment has been thoroughly examined in a robust clinical programme and is supported by real life evidence, through the registries. 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).(1) 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 difference between the two treatment groups (sapropterin + diet group versus diet only group) was 30.5 mg/kg/day (95% CI: 18.7; 42.3) and was found to be statistically significant (p< 0.001)(2). 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.(3,4) This is clearly a step change in the management of PKU as current management (with low Phe restricted diet) is impossible to maintain for most patients. Total and lifelong adherence to such a restrictive, Phe-free diet is impossible to achieve in practice for most patients and can lead to suboptimal outcomes in all age groups across a wide range of neurological and quality of life outcomes, as	Comment noted. Innovation will be considered in more detail as part of the appraisal.

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		well as causing issues with bone pathology, growth and other nutritional deficiencies[5]. Amino acid supplements (that do not contain phenylalanine) have very poor palatability and in addition maintaining metabolic control becomes significantly more difficult with age[4,5]. Furthermore, dietary management alone is inadequate for most patients and extremely difficult to achieve in practice [3,6,7] The benefits of Kuvan extend beyond those relating directly to the health of the patient. For example, patients with PKU have severe restrictions across a range of settings and as a result places a significant burden on them and their carers. This has an impact on their ability to have personal relationships, affects their educational, academic and work performance, ability to hold down a job and function in society. In addition, PKU patients cannot eat a normal diet, which impacts on their social life, and their ability to interact with friends, colleagues, partners in a social setting. This is distressing, causes unhappiness, leads to feelings of social isolation and ultimately reduces the quality of life of these patients. Patients with PKU can suffer from neuropsychological, psychosocial, academic, and/or neuropsychiatric impairments[8] which manifests as mood swings, fatigue, frustration, anger and depression for example. As the diet is so challenging to maintain, patients really struggle and despite trying to adhere, they suffer from guilt for not being able to achieve this. In addition, the regimen involved in preparing meals, measuring and taking appropriate amounts of protein supplements is lengthy and requires a certain level of cognition and focus which many patients with PKU struggle with. As the blood phe levels rise due to being unable to adhere to the diet, this task becomes more challenging, and further guilt can result. The impact on carers is significant. Mothers of PKU patients had significantly higher depression (13.6±8.6 versus 5.7±4.6) and state trait and anxiety scores (STAI-S) of 39.8±8.5 versus 32.6±7.7; STAI-T of 44.4±6.7 versus 32.1±7.1) compared with the other parental groups[9]. A subset of parents of PKU patients also demonstrate anxiety or depressive disorder. From a time burden perspective, carers report a significant amount of time is spent on preparing	

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		meals - approx. 19 hours per week)[10]. Caring for a child with PKU can have a negative impact on the carer's professional life with over half of all caregivers in one study reporting an impact on their jobs from having a child with PKU. Changes to employment included changed job (4.7%); reduced working hours (20.8%) or stopped work altogether (23.6%). 1. Levy et al. 2007; Lancet;370(9586):504-10. 2. Muntau et al. 2014; SSIEM Annual Symposium; 2–5 September 2014; Innsbruck, Austria 2014:1 3. Longo 2015; Mol Genet Metab;114(4):557-63. 4. Muntau et al. 2017; Society for Inherited Metabolic Disorders Annual Meeting: March 11-14, 2018, San Diego, CA 5. Enns G. M; Koch R. Suboptimal outcomes in patients with PKU treated early with diet alone: Revisiting the evidence. Molecular Genetics and Metabolism 2010. 6. Walter JH, White FJ, Hall SK, et al. How practical are recommendations for dietary control in phenylketonuria? Lancet 2002;360(9326):55-7 doi: S0140673602093340 [pii][published Online First: Epub Date]|; 7. Brown C.S., U. Lichter-Konecki, Phenylketonuria (PKU): a problem solved? Mol. Genet. Metab. R. 6 (2016) 8–12, http://dx.doi.org/10.1016/j.ymgmr.2015.12.004. 8. D.A. Bilder, et al., Neuropsychiatric comorbidities in adults with phenylketonuria: A retrospective cohort study, Mol. Genet. Metab. (2017), http://dx.doi.org/10.1016/j.ymgme.2017.03.002 9. Gunduz M, Arslan N, Unal O, et al. Depression and anxiety among parents of phenylketonuria children. Neurosciences 2015;**20**(4):350-6 10. MacDonald A, Smith TA, de Silva S, et al. The personal burden for caregivers of children with phenylketonuria: a cross-sectional study investigating time burden and costs in the UK: Birmingham Children's Hospital, 2016.	
	NSPKU	The care of PKU in England has largely remained the same since the invention of the phenylalanine restricted diet in the 1950s. The majority of developed	Comments noted. Innovation will be considered in more detail as part of the appraisal.

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		nations have already adopted this therapy but it would be a step change for patients in England. The use of this treatment would have substantial health related benefits: - increase of treatment adherence and reduction of poor outcomes, - reduction in burden of dietary treatment, both in the patient and wider family, - increase in natural protein improves nutrition, reduces physical side effects - diet is more normal, reducing social isolation and harmful effects of a restricted and abnormal diet, - better pregnancy outcomes, reduction in the fear and anxiety of Maternal PKU and improving the health related quality of life for women with PKU - reduction in reliance on social or informal carers. - improvements in executive functioning and mental health, the life chances of children and adults and functioning in daily life - reduction in access to other health services (eg psychology/psychiatry, primary health care) and other pharmacological interventions. 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. In particular, the following issues are well known to the NSPKU through its contact with the patient community but are inadequately reflected in published data: - pregnancy outcomes, for example a poster presentation from the West of Scotland Maternal Phenylketonuria clinic (Sarah Adam, 2017) showed	

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		that only 11/20 pregnancies were planned and 4/17 infants presented with congenital abnormalities. Other conference data (Cook J et al, 2018) show unplanned conception in off diet patients was 23% of pregnancies in last 6 years and at Phe of >800 umol patients and in patients on diet (also 23%) ~500umol - The cost of dietary treatment has increased with changes in dietary management but this is not reflected in published data. - The prevalence of social services involvement in families affected by PKU is little researched - PKU and the dietary treatment has a complex and multi-factoral impact on patients which is hard to capture by conventional health related quality of life questionnaires. Thus, for example, in NSPKU's own research open ended questions to the patient community found issues such as the impact of PKU on reproductive choices. The wider qualitative approach utilised in HST would be more appropriate. Please refer to the papers Ford et al, 2018 (abstracts published) for the results of NSPKU's survey work.	
	BDA	Yes – it is very innovative. Any treatment that is safe and alleviates some of the burdensome and intolerable diet therapy in some patients is important. Kuvan therapy is effective, substantially improves natural protein intake. Is very safe and easy for patients to manage. Its drawback is that it is only efficacious in 20% to 30% of patients. It will lessen the burden on caregiver time. It is likely to lower days lost working due to issues such as anxiety and depression.	Comments noted. Innovation will be considered in more detail as part of the appraisal.

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		Unfortunately, PKU clinics do not use the same monitoring policies. Most clinics only routinely collect data on the following: • Blood phenylalanine • Blood tyrosine • Weight • Height	
	Genetic Alliance	This treatment represents a step change in the management of the condition, as it can reportedly treat all patients with PKU (not only those with residual enzyme activity as is the case for sapropterin) and would allow patients to manage their condition much more easily and without the constraints of the very restrictive diet.	Comments noted. Innovation will be considered in more detail as part of the full appraisal.
	RCP	none	Comments noted. No action required
Questions for consultation	BioMarin	One additional point to note relates to capturing impacts of neuro-psychiatric and neuro-cognitive impacts and capturing health related quality of life: There are several published literature that shows improvements in neuro-psychiatric and neuro-cognitive outcomes with sapropterin treatment, however, the benefits in neurocognitive, neuro-psychiatric outcomes are difficult to capture and patients often struggle with the instruments that are used to measure these outcomes. As such a number of tools have been used but no single tool captures these domains adequately. This is a similar perspective to measurement of quality of life (QoL), PKU patients have a well acknowledged 'disability paradox' due to their executive function challenges where they are poorly able to assess QoL. There have been attempts to develop disease specific quality of life instruments such as the	Comments noted. No action required. The NICE Guide to the methods of technology appraisal (section 5.3.1) specifies that the EQ-5D is the preferred measure of health related quality of life in adults in the reference-case analyses. However, the merits of different measures of quality of life may be considered during the

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		PKUQOL tool (Regnault 2014, Bosch 2015), but this has been little researched and not shown convincing psychometric properties. It is well acknowledged by all publications related to measuring quality of life in PKU patients using generic tools that these poorly capture QoL. PKU is often considered to be hidden disease; health related quality of life is difficult to capture in these patient groups who have potentially impaired cognition (Demirdas 2013). As such there is no PKU specific instrument available from which health state utility values can be elicited, previous attempts have focused on proxy reported measures from clinicians or public.	appraisal. No change was made to the scope.
	NSPKU	The questions for consultation asks about established clinical practice for "adults with phenylketonuria" – this does not relate to the scope which is for people with PKU of all ages. Pregnancy related questions would be beneficial.	Comments noted. No action required.
	BDA	Barriers to adoption • NHS budgets • Lack of experience/exposure by some clinics with sapropterin. • Lack of mutation analysis to 'gauge' severity of PKU	Comments noted. No action required.
	NHS England	**Which treatments are considered to be established clinical practice in the NHS for adults with phenylketonuria**? Dietary protein restriction and phenylalanine-free amino acid and other nutritional supplements. **How should established clinical management be defined?** European guidelines are helpful although some clinicians regard these as unrealistic **Are the outcomes listed appropriate?** Yes **Are there any subgroups of people in whom sapropterin is expected to be more clinically effective and cost effective or other groups that should be**	Comments noted. No action required.

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		examined separately? One could consider a higher threshold for responsiveness, e.g. 50% **Will patients receiving sapropterin continue following a protein restricted diet regimen**? Depending on individual response, a partial relaxation may be considered. **How is hyperphenylalaninaemia defined in clinical practice?** The trial definition is reasonable as a definition of hyperphenylalaninaemia, but this is not the same as a definition of PKU. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which sapropterin will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. • None Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.	

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		Do you consider sapropterin to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes, it is innovative. Whether the impact is substantial is a matter for discussion. **Do you consider that the use of sapropterin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Benefits to carer quality of life	
Any additional comments on the draft scope	BDA	Very few references have been included and also not the more important references related to PKU. A separate list of references has been included. In clinical terms, hyphenylalaninaemia is defined as blood Phe levels >360 µmol/l; dietary treatment should be commenced when blood Phe is >360 µmol/l. **Definition of established dietary treatment** The current treatment for phenylketonuria is a very strict low phenylalanine diet which contains controlled and limited amounts of natural protein (often less than 10g/day of natural protein and this is only 10 to 20% of the amount contained in a normal diet). The diet excludes many sources of natural protein (e.g. meat, fish, eggs, cheese, nuts, bread, pasta and soya), with nutrient requirements being met by synthetic sources. It requires supplementation with artificial protein, vitamin and mineral supplements and special prescribable low protein food, based on food starch. Except for fruit and vegetables, there are few foods that can be eaten without severe limitation. Monitoring is conducted by routine home blood spot monitoring of blood Phe levels. Continual dietary supervision and modification is essential to attain good Phe control and avoid nutritional deficiencies.	Comment noted. A systematic review will be conducted as part of the appraisal. The definitions of hyperphenylalaninaemia and established dietary treatment may be considered if appropriate during the appraisal.
	NHS England	Any additional comments on the draft scope	Comment noted. The background of the scope has

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		The background text would better reflect the clinical scenario if the following version is adopted '*This is a severely restrictive diet excluding all most natural proteins (such as meat, fish, eggs, cheese, pulses, seeds, flour, bread and pasta). Many patients struggle to adhere to dietary treatment because it is very challenging and difficult to manage while living a normal life. Poor metabolic control in adulthood can sometimes manifest as a decline in in executive function, depression, anxiety disorders, phobias and low self-esteem.'*	been revised to include more details on the impact of phenylalanine restricted diet on carer.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health and Social Care