National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation

Afamelanotide for treating erythropoietic protoporphyria

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

Comment 1: the draft remit

Section	Consultees	Comments [sic]	Action
Wording	British Association of Dermatologists	Yes.	Comment noted.
	Clinuvel (UK) Ltd	The remit should acknowledge that the product would only be available in expert EPP centres, accredited to prescribe the treatment. SCENESSE® will only be administered under an approved post-authorisation safety study protocol. Suggested wording: "To evaluate the benefits and costs of afamelanotide within its licensed indication for treating erythropoietic protoporphyria in accredited expert porphyria centres for national commissioning by NHS England."	Comment noted. The remit is intended to state the technology and its indication. It is anticipated that service delivery will be discussed over the course of the evaluation.
	Genetic Alliance UK	Yes, though we note that the email notifying us of this scoping exercise referred to congenital erythropoietic porphyria as well as EPP. CEP is a different condition which does not currently form part of the licensed indication for this medicine.	Comment noted. The remit for this evaluation is to consider afamelanotide for treating erthropoietic protoporphyria only.
	Royal College of Pathologists	p1 ln : "Ultraviolet light therapy" should be amended to "Specialised ultra violet light therapy (Narrow band UV-B)".	Comment noted. The background section of the scope has been updated.
	Royal College of Physicians	Wording is fine	Comment noted.

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	British Porphyria Association/International Porphyria Patient Network	Yes	Comment noted.
Timing Issues	British Association of Dermatologists	URGENT; progress needs to be made as rapidly as possible to alleviate the considerable suffering of EPP patients.	Comment noted.
	Clinuvel (UK) Ltd	SCENESSE® has been approved by the EMA for erythropoietic protoporphyria (EPP) and could be made available by the company to UK patients as early as April 2016. Patients with EPP are most severely affected during the spring and summer months. Following delays from the European Medicines Agency in releasing the post-authorisation safety study protocol, these patients are now at risk of being deprived a much needed treatment for yet another season of severe symptoms. NHS's review must be expedited to ensure treatment can be facilitated for the months of greatest light intensity in 2016.	Comment noted.
	Royal College of Pathologists	From the patient's perspective this evaluation is urgent as they have been aware of the innovative treatment for several years. Given that for most EPP patients there is currently no effective treatment option at present, they are concerned that there is no further delay in making this decision.	Comment noted.
	Royal College of Physicians	Urgency is medium - the aim of the treatment is to improve quality of life but it is not a life-saving treatment.	Comment noted.

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	British Porphyria Association/International Porphyria Patient Network	Until now, no effective therapy for EPP has been available (see Minder EI, Schneider-Yin X, Steuer J, Bachmann LM: A systematic review of treatment options for dermal photosensitivity in erythropoietic protoporphyria. Cell Mol Biol (Noisy-le-grand) 2009;55:84-97). EPP should be considered a serious disease. The related light intolerance causes severly painful phototoxic skin reactions, which impair or make impossible normal schooling, training and education, and a full ability to work. As a result, it significantly impacts familiy life and its related activities/duties. Consequently, the QoL of those affected is severely reduced. The proposed treatment is very important to the QoL of those affected, as it aims to improve working capability, social, mental, physical and family wellbeing by reducing light intolerance, frequency and intensity of painful skin events, as well as the overall social isolation. Furthermore, it will reduce other medical complications such as low vitamin D and iron deficiency.	Comment noted.
Additional comments on the draft remit	Royal College of Physicians	treatment	-
	British Porphyria Association/International Porphyria Patient Network	We are assuming that XLDPP is included within the remit as it is a variant of EPP.	Comment noted. It was agreed at the scoping workshop that XLDPP is included as part of the remit.

Comment 2: the draft scope

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Background information	British Association of Dermatologists	Inaccurate - understates severity of condition: 'when the face or hands of a person with EPP are exposed to sun, the porphyrin mediated damage causes necrosis of skin small blood vessel endothelium resulting invariably in 2-3 days of severe and intense burning pain during which the patient experiences burning pain usually described as 'like having burning oil poured on the skin'. The pain is unresponsive to all analgesia apart from opioids.'	Comment noted. The background section has been updated. Please note that the scope is intended to provide a brief summary of the disease and is not designed to be exhaustive; consultees are encouraged to expand on the condition, its symptoms and the impact on quality of life in their evidence submissions.
	Clinuvel (UK) Ltd	The proposed background mischaracterises the disease as a sensitivity disorder. EPP is a genetic storage disorder involving a mutation of the ferrochelatase gene located on chromosome 18q21.3, which results in accumulation of protoporphyrin IX (PPIX) in tissue, such as liver and skin. PPIX leads to destruction of the hepatobiliary system and in skin affecting the endothelial wall of the vasculature. The PPIX molecule is excited by light along the visible part of the electromagnetic spectrum at 408, 550 and 600 plus nanometers. This results in full thickness second degree burns, ulcerations (wounds), and ultimately scarring of exposed skin. EPP patients are starved and deprived of light lifelong and often lead a nocturnal and sheltered existence. The patients understand the risk of exposure to light, UV and sun and have an ingrained fear for an episode of anaphylactoid reaction, burns, edema and scarring causing an unspeakable internal ordeal often poorly – and by lack of a better word - expressed as “pain”	Comment noted. The background section of the scope has been updated. Please note that the scope is intended to provide a brief summary of the disease and is not designed to be exhaustive; consultees are encouraged to expand on the condition, its symptoms and the impact on quality of life in their evidence submissions.

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		(phototoxicity). During an attack patients are largely incapacitated for several days, with anxiety that further light exposure will compound existing symptoms. An isoalted life results in light deprivation. The biological effects of longer term light starvation in man are poorly understood and not well researched, except for the area of vitamin D. Thus far the only disorder known from a percentage of people living in Nordic countries suffering from Seasonal Affective Disorder (SAD), this makes them prone to depressive mood disorders. EPP has certain traits resembling SAD. Due to the fact that EPP symptoms are often invisible, adult patients are generally incapable of explaining the depth of their pain and suffering resulting from their immediate environment. This is a further handicap.	
	Royal College of Pathologists	Background para 1: Suggest amend "is caused by" to "is usually caused by" and add after the word "ferrochelatase": "A recently described variant, X-linked EPP, is due to gain of function mutations in the gene for the erythroid specific enzyme, Amino-laevulinic acid synthase- 2 (ALAS-2, which gives a similar clinical phenotype". Para 2. The statement on symptoms does not fully describe the severity and debilitating nature of this condition. Patients with EPP typically experience severe burning pain on exposure to sunlight, which leads to avoidance behaviour and results in a serious reduction in their quality of life (reference 2) Para 2: The frequency of liver dysfunction is estimated to be <5% but a considerably higher percentage of patients (~15-20%) develop gallstones and importantly, this may occur in children.	Comment noted. The background section of the scope has been updated. It was agreed at the scoping workshop that XLDPP is included as part of the remit.
	Royal College of Physicians	The estimate of 325 EPP patients in England derived from a 2006 study is a significant underestimate. More recent literature	Comment noted. Stakeholders support an estimate of around

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		(Elder et al, JIMD 36: 849-85, 2013) calculated the prevalence of EPP in the UK as 25.4 cases per million, which would suggest over 1000 cases in England. It should be noted that the clinical phenotype varies and some patients are more severely affected than others.	390 patients with EPP in England (which may increase to 500-600 if underdiagnoses are accounted for).
	British Porphyria Association/ International Porphyria Patient Network	The BPA and IPPN feel that the disease severity and the consequences of suffering from EPP are not adequately reflected. In brief, to improve the accuracy and completeness of information, the following should be noted: - The term phototoxicity should be included, this is a chemical reaction under the skin which is extremely painful due to damage within the blood vessels themselves. - The main symptom is pain (which can included burning and itching) and sometimes swelling and reddening, but many have nothing visibly wrong despite severe discomfort. In severe episodes 'crusting' can occur which can lead to thickening of the skin. A definition from William Weston and Joseph Morelli (2013: S24, 160), in their book: Pediatric Dermatology DDX Deck (Elsevier Health Science) provides a definition of symptoms in children: "EPP presents in the preschool child as stinging, burning and itching, often within minutes of sun exposure. Despite the symptoms, skin changes are frequently not seen. Intense sun exposure may result in facial oedema, erythema, urticaria, vesiculation and crusting". These symptoms are the same in adults as in children. - The symptoms in response to sunlight may not only last for 2-3 days, this can vary according to various other contributing factors, such as temperature, further exposure to all visible light and the individual's severity of EPP. If a person with EPP is exposed to sunlight, the skin can become painful within a few minutes. If light exposure is prolonged the pain becomes incapacitating. Wheals, redness, edema, erosions and blisters may appear [3]	Comment noted. The background section of the scope has been updated. Please note that the scope is intended to provide a brief summary of the disease and is not designed to be exhaustive; consultees are able to expand on the condition, its symptoms and the impact on quality of life in their evidence submissions.

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	British Porphyria Association/ International Porphyria Patient Network	More appropriate wording here could be as follows: "The symptoms in response to sunlight last for 2 to 3 days and in more severe episodes up to 10 days or longer, leading to loss of sleep, severe irritability due to the intractable pain and consequent incapability to work or perform other daily activities. Pain is unresponsive to non-opiate analgesics. Quality of life is severely affected and a higher percentage of affected persons than the normal population is unemployed." - There is often extreme variation in the severity of EPP symptoms, even within the same family. - The BPA feel that it is difficult to comment on the number of adult patients in the UK. We have around 90 EPP members, however this is not likely to be a full representation of the true numbers and we would expect it to be higher than 325. Holme et al.'s (2006) study also indicates that they identified 389 patients in the UK. The background information also fails to consider in any way the real impact that living with EPP has on a person's life! - As such, various additional psycho-social and QoL factors need to be acknowledged to fully understand that EPP can lead to isolation, depression and other significant QoL complications. - This means that although the condition isn't life-threatening, it can be severely life-limiting as it affects all aspects of one's life from work/eduction, to family and social life and ultimately emotional and psychological well-being. It is also important to note, with regards to ultraviolet light therapy, that this is extremely dependent on various other factors for its success, for example patients need to maintain the protection acheived from light therapy, this is only possibly if the weather is suitable to maintain it. Also, there can be problems with access, medical supervision and knowledge of the machines and processes - meaning its success is as yet undetermined.	Comment noted. The background section of the scope has been updated. Please note that the scope is intended to provide a brief summary of the disease and is not designed to be exhaustive; consultees are encouraged to expand on the condition, its symptoms and the impact on quality of life in their evidence submissions. Stakeholders support an estimate of around 390 patients with EPP in England (which may increase to 500-600 if underdiagnoses are accounted for).

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The technology/ intervention	British Association of Dermatologists.	Yes.	Comment noted.
	Clinuvel (UK) Ltd	The description is inconsistent with the EMA approved Summary of Product Characteristics: *Afamelanotide is thought to mimic the endogenous compound's pharmacological activity by activating the synthesis of eumelanin mediated by the MC1R receptor.* *Eumelanin contributes to photoprotection through different mechanisms including:* • *strong broad band absorption of UV and visible light, where eumelanin acts as a filter* • *antioxidant activity through scavenging of free radicals; and* • *inactivation of the superoxide anion and increased availability of superoxide dismutase to reduce oxidative stress.* Further, it should be noted that, in the northern hemisphere, SCENESSE® is dosed up to a maximum of 4 injections per year between March and November. Patients will only receive treatment in Clinuvel trained and accredited European EPP expert centres.	Comment noted. The aim of the technology section of the scope has been updated to reflect the Summary of Product Characteristics.
	Royal College of Pathologists	Yes	Comment noted.
	Royal College of Physicians	Yes	Comment noted
	British Porphyria Association/ International Porphyria Patient Network	Yes. But, the outcomes are inappropriate. Afamelanotide has been approved under exceptional circumstances, because due to the life-long condition to light avoidance the patients increased their sunlight exposure only gradually. Thus, the testimonies of EPP patients and medical experts should have the highest weight.	Comment noted. Scoping workshop attendees agreed that the outcomes listed were appropriate, recognising that the committee can consider a broader range of outcomes

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			during the evaluation. Consultees are encouraged to present evidence of the effectiveness of the technology in their submissions.
Population	British Association of Dermatologists	Yes it is defined accurately. No subgroups to consider separately.	Comment noted.
	Clinuvel (UK) Ltd	Agree with the population scope. There are no subsets of patients, each patient is at risk at variable times.	Comment noted.
	Royal College of Pathologists	The population is defined appropriately, though the total numbers are likely to be higher. The UK prevalence of EPP has more recently been estimated at 25.4 cases per million (Elder et al, 2013, JIMD 36:849-857) . The condition is lifelong and causes severe problems in children	Comment noted. Stakeholders support an estimate of around 390 patients with EPP in England (which may increase to 500-600 if underdiagnoses are accounted for).
	Royal College of Physicians	Children with EPP need special consideration	Comment noted. NICE can only issue recommendations that are within a technology's marketing authorisation; afamelanotide's marketing authorisation is for adults only.
	British Porphyria Association/ International Porphyria Patient Network	Yes. But, the term EPP needs to include the XLDPP population too. - Additionally, children with EPP will need special consideration, at some point.	Comment noted. The XLDPP population is included as part of the wider EPP population. NICE can only issue recommendations that are within a technology's marketing authorisation; afamelanotide's marketing

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			authorisation is for adults only.
Comparators	British Association of Dermatologists	Yes that is correct - i.e. there is no effective treatment currently	Comment noted.
	Clinuvel (UK) Ltd	There are no comparator treatments for the prevention of phototoxicity in adult patients with EPP. For reference, see Minder et al (2009) “A systematic review of treatment options for dermal photosensitivity in erythropoietic protoporphyria.” A copy of this paper has been appended to Clinuvel’s submission	Comment noted.
	Royal College of Pathologists	Definition of best alternative care requires agreement (see also response to Questions for Consultations below). It would be valuable to compare afamelanotide with courses of narrow band UV-B therapy. Although it is in theory possible to provide home-based phototherapy, in practice patients have to be able to commit to multiple hospital attendances within a short period of time to receive UV-B treatment. The safety of a lifetime of exposure to this treatment would need to assessed. The individual response to beta-carotene (more commonly used in practice than cholestyramine or activated charcoal) is highly variable, not least because of convenience and tolerability. Beta-carotene is marketed as a food supplement, rather than a pharmaceutical grade preparation. Effective doses for adults are in the range 150-300mg daily, necessitating the consumption of large numbers of 15mg capsules per day for approximately 6 months of the year.	Comment noted.
	Royal College of Physicians	The best alternative care is probably narrow band UV-B therapy, and it would be important to compare this with afamelanotide.	Comment noted.
	British Porphyria Association/ International Porphyria	Afamelanotide appears to be the only treatment to effectively work to prolong the time people can spend in the light. It is very difficult to compare Afamelanotide with any other treatment (including	Comment noted.

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	Patient Network	UVB light therapy), as there is no research to provide a comparison between the two treatments. -Ultraviolet light therapy is sometimes given in order to build up the skin's resistance to the effects of the sun, but induces painful skin reactions and increases the risk for skin cancer. -Non-pharmacological options include sunlight avoidance strategies, for example staying indoors, seeking shade during sunny periods (which is usually insufficiently protective), or wearing sunlight blocking clothing such as umbrellas, gloves and face masks. However, such protective measures are outside of Western norms and the social environment often reacts with deprecating comments, leading patients into psychological distress and social isolation. The photosensitivity results from light in the visible spectrum, meaning that sunscreens are of little use.	
Outcomes	British Association of Dermatologists	Meaningful outcome measures are a significant issue here. There is a consensus in the porphyria academic and clincial community that the outcomes measured in the trials (which are the ones listed here) have underestimated the therapeutic effects significantly (when compared to qualitative experience of patients).	Comment noted. Scoping workshop attendees agreed that the outcome measures listed were appropriate, recognising that the committee can consider a broader range of outcomes during the evaluation. Consultees are encouraged to present evidence of the effectiveness of the technology, which can come from other sources in addition to the clinical trial data, in their submissions.
	Clinuvel (UK) Ltd	The impact of lifelong light deprivation is yet poorly understood, but scientific progress is being made. Clinuvel is the first company to address this issue in EPP.	Comment noted. Consultees are encouraged to present evidence of the effectiveness of the technology, which can come from other sources in

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		Per the EMA CHMP review of SCENESSE®, the clinical benefit expressed by patients receiving the drug is substantially larger than that captured in statistical analyses of clinical data.	addition to the clinical trial data, in their submissions.
	Genetic Alliance UK	A rare long term effect of EPP is liver failure. Though this occurs in less than 5% of patients, this is an extremely serious and potentially fatal outcome, and should be included We would like to emphasis that in addition to health related quality of life, it is important to consider the health related and psychological benefits of being able to go outside for a few minutes more. Avoidance of the sun prevents many of the activities that are regarded as part of a health lifestyle, as well as preventing normal social activities. A patient with EPP can be very socially isolated, and even a small improvement in light tolerance could substantially improve their ability to participate in society more fully, with all the psychosocial benefits that entails	Comment noted. Scoping workshop attendees agreed that the outcome measures listed were appropriate, recognising that the committee can consider a broader range of outcomes during the evaluation. Consultees are encouraged to present evidence of the effectiveness of the technology, and its impact on quality of life, in their submissions. Please note that social functioning should be captured as part of health-related quality of life.
	Royal College of Pathologists	Yes, provided the quality fo life issues are fully explored. Wider social effects require evaluation since the severe photosensitivity suffered by EPP patients imposes considerable restrictions on their employment, personal and family life.	Comment noted. Wider social effects are captured in the scope, under 'impact of the technology beyond direct health benefits'.
	Royal College of Physicians	It is concerning that the key outcome measure, duration of sunlight tolerance, is not sufficiently objective.	Comment noted. Consultees should define outcome measures in their submissions.
	British Porphyria Association/ International Porphyria Patient Network	Further outcome measures should be considered to capture these aspects. Afamelanotide was approved under exceptional circumstances, because it was agreed by the representatives of EMA that	Comment noted. Scoping workshop attendees agreed that the outcome measures listed were appropriate,

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		measurement of efficacy is not possible in EPP. Instead approval was given based on testimonies of patients and medical experts. Sunlight tolerance has never been measured, rather, the measurements included spontaneous sunlight exposure time. Comments have been directly inserted in the draft.	recognising that the committee can consider a broader range of outcomes during the evaluation. Consultees are encouraged to present evidence of the effectiveness of the technology, which can come from other sources in addition to the clinical trial data, in their submissions.
Equality and Diversity	British Association of Dermatologists	It seems unfair to exclude teenage patients for whom there is no biological or scientific reason to assume that the drug is any less effective or more dangerous than in adults. Teenage patients have a paticularly high impact on quality of life from this disease	Comment noted. NICE can only issue recommendations that are within a technology's marketing authorisation; afamelanotide's marketing authorisation is for adults only.
	Clinuvel (UK) Ltd	Patients, human subjects have a right to minimum light.	Comment noted.
	Royal College of Pathologists	Children and patients>70y are excluded	Comment noted. NICE can only issue recommendations that are within a technology's marketing authorisation; afamelanotide's marketing authorisation is for adults only. The summary of product characteristics states that afamelanotide should not be used in people aged over 70 years.
	Royal College of Physicians	Children need special consideration.	Comment noted. NICE can only issue recommendations that are within a technology's marketing authorisation; afamelanotide's marketing

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			authorisation is for adults only.
	British Porphyria Association/ International Porphyria Patient Network	There is no impact on equality, as neither gender nor ethnicity nor sexual orientation is particular involved. Also, it is imperative that children are considered, at some stage, in the future.	Comment noted. NICE can only issue recommendations that are within a technology's marketing authorisation; afamelanotide's marketing authorisation is for adults only.
Innovation	British Association of Dermatologists	Yes it is a step change - it is the first effective treatment in EPP.	Comment noted.
	Clinuvel (UK) Ltd	SCENESSE® (afamelanotide 16mg) is the first ever treatment for EPP patients. It is a proprietary and highly innovative first-in-class product. The drug is prescribed by specialist physicians and falls within the category of High Specialty Technology.	Comment noted.
	Genetic Alliance UK	This is the first medicine specifically available to treat EPP.	Comment noted.
	Royal College of Pathologists	Yes.	Comment noted.
	Royal College of Physicians	Probably	Comment noted.
	British Porphyria Association/ International Porphyria Patient Network	Yes, it is a step change in the management of EPP, as patients on Scenesse report that this drug has changed their life in a significantly positive direction and they are able to do things they never thougth they would ever have been able to. It is therefore likely to have signicant impact on their overall QoL, including family, work, social, emotional, and physical impacts	Comment noted.
Other considerations	British Association of Dermatologists	None.	Comment noted.
	Clinuvel (UK) Ltd	N/A	Comment noted.
	Royal College of Physicians	It would be useful to examine the individual raw patient data from the trials referred to in the key publication (NEJM 373: 48-59, 2015) and to repeat the statistical evaluation. Concerns include	Comment noted. It is anticipated that a full critical appraisal of the clinical

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		the unblinding of many partcipants in the trial and the subjective primary end point	effectiveness data will be performed over the course of the evaluation.
Questions for consultation	British Association of Dermatologists	1) There are no relevant comparators - the treatments we currently have are not effective. Best supportive care should include 'visible light photoprotection'. 2) There are seven Photodermatology tertiary Departments in the UK, all of which see EPP patients. 85 patients followed up in Cutaneous Porphyrias Clinic at Guy's Hospital. National highly Specialist centrally commissioned Acute Porphyria Service does not treat EPP. Diagnostic labs for EPP are the same porphyrin labs as for Acute Porphyria National Service.	Comments noted..
	Clinuvel (UK) Ltd	**Have all relevant comparators for afamelanotide been included in the scope?** There are no current comparators. **Which treatments are considered to be established practice for treating EPP?** There is no currently agreed standard of care for EPP patients. Under the post-authorisation safety study with SCENESSE® a standard of clinical care is being established. No other treatment has been evaluated under placebo-controlled clinical trials for the prevention of phototoxicity, however narrowband UVB phototherapy has been used by select expert centres to limited effect in the UK. **How should best supportive care be defined?** N/A **Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?** Clinuvel believes SCENESSE® may provide clinical benefit to	Comments noted. Regarding congenital erythropoietic porphyria (CEP) - NICE can only issue recommendations that are within a technology's marketing authorisation, which does not currently include CEP. The remit for this evaluation is to consider afamelanotide for treating erythropoietic protoporphyria only.

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		patients with congenital erythropoietic porphyria (CEP) for whom a more regular dosing regimen is appropriate. Given the known number of CEP patients (only 1-2 in the UK), clinical trials in this indication are not possible at this time. **Please describe any existing services in England for the diagnosis and management of this condition.** Photodermatology units at the Royal Salford NHS Trust and Guy's and St Thomas' NHS Trust in the UK are seen as the first two (of the total four) expert centres where SCENESSE® would be made available to patients. These units work closely with the British and Irish Porphyria Network (BIPNET) and the European Porphyria Network (EPNET) in the management and diagnosis of EPP across England. Due to the rarity of EPP, however, few EPP patients currently receive comprehensive care for their condition through the NHS, even after a successful diagnosis. **Do you consider the technology 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)?** SCENESSE® is highly innovative in its molecule, formulation, mode of action and rare disease it targets. Protocolised treatment with SCENESSE® will ensure adult EPP patients receive regular multidisciplinary care for their condition at expert treatment centres.	
	Genetic Alliance UK	On the question of how best supportive care should be defined, we understand best supportive care to consist of light avoidance strategies and pain relief. Although beta-carotene, activated charcoal, cholestyramine and UV light therapy are commonly used to treat EPP, they it is not clear whether they have any effect.	Comment noted.

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	Royal College of Pathologists	Q5. There are no formally commissioned specialist services for patients with EPP. The clinical diagnosis of EPP is typically made by dermatologists. Confirmation is critically dependent on the availability of specialist biochemical analysis. Essential specialised tests are plasma spectrofluorimetric scanning, quantitation of free and zinc bound protoporphyrin levels in red blood cells. Faecal porphyrin analysis may be required in selected cases. Mutation analysis may also occasionally be required to confirm a biochemical diagnosis, particularly in X-linked EPP. Specialist UK porphyrin laboratories (recognised by the European Porphyria Network) are University Hospital of Wales, Cardiff, King's College Hospital London, St James' Hospital, Leeds and Salford Royal NHS Foundation Trust, Salford. Specialist Porphyria Clinics are provided for EPP patients in each of the above centres. The King's College Hospital service supports a specialist photodermatology clinic at St John's Institute of Dermatology (Dr R Sarkany). The Salford Royal Porphyria Clinic is linked to the Salford Academic Photobiology Unit, (Director Prof Lesley Rhodes) through which specialised photodermatology assessment and UV-B treatment is provided. The Cardiff Porphyria clinic sees patients from the West of England. Q6 The remit and scope excludes children and patients over the age of 70, but does not otherwise exclude or discriminate against people with protected characteristics. Q7 The technology is innovative and potentially offers significant symptomatic benefits in a condition where exisitng options are extremely limited.	Comments noted. NICE can only issue recommendations that are within a technology's marketing authorisation; afamelanotide's marketing authorisation is for adults only and states that afamelanotide should not be used in people aged over 70 years.
	Royal College of Physicians	Q1. Have all relevant comparators for afamelanotide been included in the scope? Relevant comparators for afamelanotide are included but it is	Comments noted. NICE can only issue recommendations that are within a technology's marketing authorisation; afamelanotide's marketing

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		especially important to compare narrow band UV-B therapy. Q2 and 3. Which treatments are considered to be established practice for treating EPP? How should best supportive care be defined? There are no published best practice guidelines for EPP, but there is general agreement by members of the British and Irish Porphyria Network (BIPNET) that supportive care should include strict photoprotection, use of reflectant sunscreens (such as Dundee suncream), and oral beta-carotene. Courses of narrow band UV-B treatment are usually offered in spring. Patients need regular monitoring (including full blood count, iron stores, liver function, vitamin D and red cell protoporphyrin). Q4 Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately? Children should be examined separately Q5. Please describe any existing services in England for the diagnosis and management of this condition. EPP is usually diagnosed clinically by dermatologists and confirmed biochemically in one of the specialist porphyria laboratories (University Hospital of Wales, King's College Hospital in London, St James' Hospital in Leeds and Salford Royal NHS Foundation Trust are all accredited by the European Porphyria Network). Specialist Porphyria Clinics are provided at each of the above	authorisation is for adults only.

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		centres and also in the Photodermatology unit at Guy's and St Thomas' Hospital. Q6 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 afamelanotide is 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. The remit and scope excludes children but does not otherwise exclude any groups with protected characteristics. Q8 Do you consider the technology 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)? The technology is innovative and if effectiveness is proven, it could significantly improve quality of life in patients with this rare condition.	

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	British Porphyria Association/ International Porphyria Patient Network	Supportive care for EPP patients should be defined as involving all of their physical, emotional, psychological and social needs. BIPNET (British and Irish Porphyria Network) is an establish porphyria network and there are specialist centres for the cutaneous porphyrias in London, Leeds, Salford and Cardiff. Clinuvel are also involved in establishing further expert centres which should help to improve patient care, including diagnosis and the management of EPP. As with all of the porphyrias, initial diagnosis can often take time, until seen by the right people. See - Holme et al. (2006) for more information on symptoms and QoL affecting those with EPP - as EPP is a very hidden disease.	Comments noted.
Additional comments on the draft scope	Clinuvel (UK) Ltd	A short powerpoint presentation has been submitted alongside this response.	Submission noted. NICE are only able to respond to comments presented by Clinuvel in its response table. However, Clinuvel's additional comments were discussed afamelanotide at the scoping workshop.
	Genetic Alliance UK	In the section on related national policy, we note that one is missing: NHS England (2013) 2013/14 NHS STANDARD CONTRACT FOR SPECIALISED DERMATOLOGY SERVICES (ALL AGES) PARTICULARS, SCHEDULE 2- THE SERVICES, A-SERVICE SPECIFICATIONS A12/S/a	Comment noted. This policy has been added to the scope.
	British Porphyria Association/ International Porphyria Patient Network	Because Afamelanotide was approved under exceptional circumstances and because it was agreed that measurement of efficacy is complicated by life-long conditioning to avoid daylight, the testimonies of patients and experts are to be weighed more than the net study results, i.e., clinical benefit is a more relevant measure than statstical benefit. Thus, the BPA and IPPN feel that it is vital multiple patient perspectives are taken into account during the full evaluation	Comments noted. Consultees are encouraged to present evidence of the effectiveness of the technology, which can come from other sources in addition to the clinical trial data, in their submissions.

Section	Consultees	Comments [sic]	Action
		stage in order to truly understand the complex nature and severity of the condition	

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

Department of Health