National Institute for Health and Care Excellence

Highly Specialised Technology (HST)

Givosiran for treating acute hepatic porphyria

Response to consultee and commentator comments on the draft remit and draft scope

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Alnylam	We believe that evaluation of givosiran by NICE as a Highly Specialised Technology is entirely appropriate.	Thank you for your comment. This topic will be evaluated through the Highly Specialised Technologies Programme.
	The British Porphyria Association	Yes, it is appropriate to be referred to NICE for evaluation. It is essential. For some patients with acute porphyria there are very few treatment options available and those that are don't work well and can cause significant complications.	Thank you for your comment. No changes to the scope are needed.
	British Society of Gastroenterology	Yes the evidence base is sufficient for a rare condition	Thank you for your comment. No changes to the scope are needed.
	Global Porphyria Advocacy Coalition	Yes, an evaluation is appropriate and essential by NICE. Acute porphyria can be very severe and debilitating for some patients. For these patients, the existing treatment options have	Thank you for your comment. No changes to the scope are needed.

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		various problems and for some they do not manage the condition well.	
	NHS England and Improvement	It is the opinion of NHS England that it is appropriate that NICE appraise this technology.	Thank you for your comment. No changes to the scope are needed.
	British Association for the Study of the Liver	Yes the evidence base is sufficient for a rare condition	Thank you for your comment. No changes to the scope are needed.
	National Acute Porphyria Service and British and Irish Porphyria Network	Givosiran is an important new treatment option for patients with severe recurrent acute attacks of porphyria that has recently been licensed by the EMA. The results of the phase III study have now been published in NEJM and are extremely positive.	Thank you for your comment. No changes to the scope are needed.
	International Porphyria Patient Network	Yes, the topic is appropriate for a NICE evaluation	Thank you for your comment. No changes to the scope are needed.
Wording ***Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that***	Alnylam	We agree that the wording in the remit appropriately reflects the issues NICE should consider.	Thank you for your comment. No changes to the scope are needed.
	The British Porphyria Association	Yes	Thank you for your comment. No changes to the scope are needed.

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NICE should consider? If not, please suggest alternative wording.	British Society of Gastroenterology	Yes	Thank you for your comment. No changes to the scope are needed.
	Global Porphyria Advocacy Coalition	Yes	Thank you for your comment. No changes to the scope are needed.
	NHS England and Improvement	This is relatively urgent given the delay between authorisation and appraisal with new patients (not currently on trials) potentially requiring treatment.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted. In some circumstances, this timescale may not be possible. No changes to the scope are needed.
	British Association for the Study of the Liver	Yes	Thank you for your comment. No changes to the scope are needed.
	National Acute Porphyria Service and British and Irish Porphyria Network	Givosiran has undergone trials for its effectiveness and safety as a treatment for recurrent attacks of acute hepatic porphyria. In the UK we are not expecting to use this drug to treat sporadic attacks, chronic symptoms, or skin problems. The remit should reflect this.	Thank you for your comment. The remit aims to describe the objective of the appraisal with a short statement. The scope outlines further detail on the population in whom givosiran

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			will be evaluated in. No changes to the scope are needed.
	International Porphyria Patient Network	Yes	Thank you for your comment. No changes to the scope are needed.
Timing Issues ***What is the relative urgency of this proposed evaluation to national commissioning by NHS England?***	Alnylam	A timely HST evaluation would be aligned with NICE's published procedural and methodological guidelines regarding the completion of appraisals as close to marketing authorisation as possible.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted. In some circumstances, this timescale may not be possible. No changes to the scope are needed.
	The British Porphyria Association	A timely and prompt response is of high importance as for a certain cohort of severely affected patients, there is clinical need for access to new treatments. There are currently no licensed drugs to prevent attacks of acute porphyria.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted. In some circumstances, this timescale may not be possible. No changes to the scope are needed.

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	British Society of Gastroenterology	Reasonable	Thank you for your comment. No changes to the scope are needed.
	Global Porphyria Advocacy Coalition	There is a clinical need for new treatments to better manage the most severely affected acute patients. Thus, a prompt response is needed.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted. In some circumstances, this timescale may not be possible. No changes to the scope are needed.
	British Association for the Study of the Liver	Reasonable	Thank you for your comment. No changes to the scope are needed.
	National Acute Porphyria Service and British and Irish Porphyria Network	There is an urgent need to use givosiran in a small number of patients with uncontrolled acute porphyria. In particular, a few of our patients can no longer be managed with prophylactic haem arginate, and unless givosiran can be made available very soon, their only treatment option is liver transplantation, a high risk procedure with long-term risks of immunosuppression for these young patients.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted. In some circumstances, this timescale may not be possible. No changes to the scope are needed.

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	International Porphyria Patient Network	For the subgroup of AHP patients for which givosiran is intended, access is urgently needed. Current treatment options are not sufficient in this group of patients	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months of the date when the marketing authorisation for a technology is granted. In some circumstances, this timescale may not be possible. No changes to the scope are needed.

Comment 2: the draft scope

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Background information ***Consider the accuracy and completeness of this information.***	Alnylam	We believe that the background information is mainly accurate and complete but would like to add clarifications on two points: 1) The statement 'liver transplantation is an option for some people with severe recurrent acute attacks' is somewhat misleading as it may imply this is a routinely used treatment modality. In the UK, liver transplantation is reserved for AHP patients who meet the very specific criteria of "recurrent refractory attacks or a severe attack with neurological deficit despite medical therapy." [NHS Blood and Transplant guidelines for referral of liver transplant assessment]. These stringent criteria, along with considerations regarding the appropriateness of transplant in individual patients due to the risks of the procedure, have resulted in only ten liver transplants being performed for AHP in the UK until 2011. [Dowman 2012] Additionally, fewer than one such transplant has been performed per year since 2012. Therefore, liver transplantation is not a routinely used treatment modality in the UK and this should be acknowledged in the background information.	Thank you for your comment. The background section has been amended to add clarity that liver transplantation may be an option for some people with severe recurrent acute attacks when other treatment options have not worked. The background section has also been amended to describe the number of people who are currently receiving treatment for severe recurrent acute attacks in the UK.

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		2) We believe the background information is not complete regarding the number of patients with AHP in the UK that should be considered in the scope. Due to the rarity of AHP, diagnosis and treatment is delivered through the nationally commissioned Highly Specialised Service, the National Acute Porphyria Service (NAPS). Patients are managed by three designated lead physicians based in two hospitals (Kings College, London and Cardiff), with additional satellite clinics. As outlined in the draft scope, around 560 patients in England have AHP. Approximately 50 patients have severe disease [Manual for Prescribed Specialised Services 2018/19]. However, only 20 to 30 patients from this total caseload of 50 patients with severe disease would be treated with givosiran due to the ongoing frequency of attacks and severity of disease. This small subset of AHP patients is the patient group that may be considered for givosiran, as discussed further in the population section of the scope. Dowman JK et al. Liver Transplantation for Acute Intermittent Porphyria is Complicated by a High Rate of Hepatic Artery Thrombosis. *Liver Transpl.* 2012;18(2):195–200. NHS Blood and Transplant guidelines for referral of liver transplant assessment. March 2012. http://odt.nhs.uk/pdf/advisory_group_papers/LAG/referral_for_transplantation.pdf **NHS England (2018/2019) Manual for prescribed specialised services, service 99: Severe acute porphyria service (adults and children). https://www.england.nhs.uk/publication/manual-for-prescribed-specialised-services/**	
	The British Porphyria Association	The background is generally accurate. However, we would like to draw attention to the following additional points: **Symptoms**: In addition to being life-threatening as it can lead to paralysis and respiratory arrest, AHP is immensely debilitating in the long term because of symptoms such as severe acute and chronic pain, nausea, vomiting, weight loss, constipation, seizures, weakness that can be progressive, fatigue, as well as long-term complications such as renal impairment, hypertension and dependence on analgesics. These symptoms and complications should be included in the scope.	Thank you for your comment. The background section includes information on the debilitating long-term symptoms of acute hepatic porphyria. However, this section aims to provide a summary of the symptoms and is not exhaustive.

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		Prevalence: Elder et al (2013) noted prevalence to potentially be as low as 5.4 per million in Europe for AIP with recurrent attacks in 3% (male) and 5% (female) of patients (suggesting around 10-15 patients in England). The BPA believe the number of patients suffering recurrent attacks of all acute porphyrias (AIP, VP and HCP) in England to lie somewhere in between the figure implied in the scoping documents (50-60) and the above calculated figure of 10-15 patients. This ties in with the figure of 20-30 patients quoted by Marsden et al. (2015). **Treatment** options in the background section include glucose – this is questionable as a treatment – see our note in the Comparators section.	The background section has also been amended to describe the number of people who are currently receiving treatment for severe recurrent acute attacks in the UK. The description of current treatment options has been clarified to describe that glucose is used as treatment of an acute attack, as it is understood that this is not used as a prophylactic treatment.
	British Society of Gastroenterology	Adequate	Thank you for your comment. No changes to the scope are needed.
	Global Porphyria Advocacy Coalition	Within the background certain elements have not been fully explored. It should be noted that for those with recurrent attacks (i.e. the cohort identified) the patient journey is complex and can be devastating to live with not only during but also between patient attacks (Simon et al. 2018). AHP can be life threatening, but the debilitating impact that some patients experience needs exploring fully by NICE. The following should be included within the background: significant weakness and nerve damage, not just paralysis; the psychological impact and	Thank you for your comment. The background section includes information on the debilitating long-term symptoms of acute hepatic porphyria. However, this section aims to provide a summary of the symptoms and is not exhaustive.

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		anxiety levels in patients also needs consideration; as does fatigue (Gouya et al. 2020). Prevalence: GPAC believe that prevalence in the UK (for recurrent acute attacks) would be more in line with 20-30 patients as quoted by Marsden et al. (2015). In terms of the current treatment options – we feel it is important to note that none of the treatments listed are wholly effective in managing recurrent acute attacks and there is still a significant unmet need for this cohort of patients. Further, glucose would not be considered a successful treatment option for this group. Liver transplant is mentioned, but this would only be considered as a last resort and it is often too late for patients by the time a donor is found. Further, even if successful, the patient would then be left with another host of issues that would be costly and impactful on the patient and the NHS.	The background section has also been amended to describe the number of people who are currently receiving treatment for severe recurrent acute attacks in the UK. The background section describes the current treatment options available for people with acute hepatic porphyria but does not describe how effective these treatments are. The description of current treatment options has been clarified to describe that glucose is used as treatment of an acute attack, as it is understood that this is not used as a prophylactic treatment. The background section has also been amended to add clarity that liver transplantation may be an option for some people with severe recurrent acute attacks when other treatment options have not worked.

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	NHS England and Improvement	The background is comprehensive. It does not address the financial impact on patients with severe forms of the disease as they have challenges in maintaining employment.	Thank you for your comment. The background section aims to provide a summary of the impact of the disease but is not exhaustive. No changes to the scope are needed.
	British Association for the Study of the Liver	Adequate	Thank you for your comment. No changes to the scope are needed.
	National Acute Porphyria Service and British and Irish Porphyria Network	The background is broadly accurate but we would like to clarify a few points: • *"AHP is life-threatening as it can lead to paralysis and respiratory arrest during acute attacks.*" Life-threatening complications of porphyria attacks include severe hyponatraemia, seizures, and arrhythmias, as well as neuropathy leading to paralysis and respiratory arrest. • "*…it is debilitating in the long term because of symptoms such as pain, nausea and seizures."* Seizures are a complication of a severe acute attack, not a long term problem. As well as pain and nausea, other long term debilitating problems include fatigue, neuropathy, anxiety and depression and complications of treatment (such as iron overload, loss of venous access). • *"HCP and VP are associated with damage to the skin through sun exposure."*	Thank you for your comment. The background section includes information on the life-threatening and long-term debilitating symptoms of acute hepatic porphyria. This includes the skin problems associated with VP and HCP, as these groups are included in the scope. However, this section aims to provide a summary of the symptoms and is not exhaustive. The background section has been updated to include seizures as a complication of a

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		Skin problems in VP and HCP are not relevant to this intervention which is a treatment to prevent recurrent acute attacks. • *"The prevalence of AHP is estimated to be 0.1 in 10,000 people[3] in the general European population which is equivalent to around 560 patients in England"* This is correct for symptomatic acute porphyria (all types). However clinical penetrance is very low and the prevalence of pathogenic mutations may be up to 100 fold higher (Chen *et al.* Acute intermittent porphyria: predicted pathogenicity of HMBS variants indicates extremely low penetrance of the autosomal dominant disease. Hum Mutat. 2016 37:1215-1222). • *"In around 10% of cases, acute attacks are recurrent"* Almost all patients with recurrent attacks have AIP, and it is extremely rare to have recurrent attacks of VP or HCP. Prevalence of symptomatic AIP in Europe (excluding Sweden) is estimated as 5.4 per million (Elder *et al.* The incidence of inherited porphyrias in Europe. JIMD. 2013 36:849-57), equivalent to 300 cases in England, so the estimated number of patients with recurrent attacks is about 30. This is consistent with the experience of NAPS which currently has 35 patients receiving treatment for recurrent attacks.	severe acute attack and not a long-term problem. The background section has also been amended to describe the number of people who are currently receiving treatment for severe recurrent acute attacks in the UK.

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	International Porphyria Patient Network	P.1: “Acute hepatic porphyria (AHP) is a rare inherited metabolic disorder which is caused by the deficiency of one of the enzymes needed to create haem (a component of haemoglobin).” Proposed wording: Acute hepatic porphyrias (AHPs) are a group of rare inherited metabolic disorders which are caused by the deficiency of one of the enzymes needed to create haem (a component of haemoglobin and haemoproteins). > AHPs is a group of disorders, not just one condition > In the liver, haem is not produced as a component of haemoglobin, but for haemoproteins like Cytochrome P 450, which is involved in drug metabolism. P1: “In AHP, these precursors to porphyrin accumulate in the liver and other tissues.” Proposed wording: In AHPs, these precursors to porphyrin are produced in excess in the liver during an acute attack. P.1: “The prevalence of AHP is estimated to be 0.1 in 10,000 people3 in the general European population which is equivalent to around 560 patients in England.4” Please add: Based on studies in blood donors in France and Finland, the number of asymptomatic AIP mutation carriers was estimated to be around 1:1800 to 1: 500. (Nordmann et al. 1997; Mustajoki et al., 1992). Currently unknown genetic or environmental factors determine the susceptibility for acute attacks after exposure to trigger factors. Because of lack of awareness, AHPs frequently	Thank you for your comment. The background section of the scope has been amended to make clear that acute hepatic porphyrias are a group of disorders and detail on haem has been removed. The background section has also been amended to describe the number of people who are currently receiving treatment for severe recurrent acute attacks in the UK.

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		remain undiagnosed. Switzerland, with a population of around 8 million, is a country with relatively high porphyria diagnosis rates, and 145 families with AHPs have been detected until 2009, encompassing approximately 400 AHP patients. (Schneider-Yin et al. 2009). Therefore, the number of AHP patients in England is likely higher than the number of patients with a confirmed AHP diagnosis. Nordmann, Y., Puy, H., Da Silva, V., Simonin, S., Robreau, A. M., Bonaiti, C., ... & Deybach, J. C. (1997). Acute intermittent porphyria: prevalence of mutations in the porphobilinogen deaminase gene in blood donors in France. Journal of internal medicine, 242(3), 213-217. Mustajoki, P., Kauppinen, R., Lannfelt, L., Lilius, L., & Koistinen, J. (1992). Frequency of low erythrocyte porphobilinogen deaminase activity in Finland. Journal of internal medicine, 231(4), 389-395.	
The technology/ intervention ***Is the description of the technology or technologies accurate?***	Alnylam	We believe that the description of givosiran is generally accurate. We would however note that givosiran does now have a marketing authorisation following EMA approval in March 2020. Additionally, it should be added that givosiran represents a step change in the treatment of patients severely affected by AHP. It is only the second licensed RNAi therapeutic and the first utilising N-acetylgalactosamine (GalNAc) conjugation, thereby allowing monthly subcutaneous dosing.	Thank you for your comment. The technology section of the scope has been amended in line with the marketing authorisation. The innovative nature of this technology will be considered by the committee during the appraisal. No changes to the scope are needed on this point.

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	The British Porphyria Association	Generally accurate, although Givosiran does now have marketing authorisation in the EU.	Thank you for your comment. The technology section of the scope has been amended in line with the marketing authorisation.
	British Society of Gastroenterology	Yes	Thank you for your comment. No changes to the scope are needed.
	Global Porphyria Advocacy Coalition	Givosiran received Market Authorisation from the EMA/EC in March 2020.	Thank you for your comment. The technology section of the scope has been amended in line with the marketing authorisation.
	NHS England and Improvement	The description of the technology is accurate	Thank you for your comment. No changes to the scope are needed.
	British Association for the Study of the Liver	Yes	Thank you for your comment. No changes to the scope are needed.
	National Acute Porphyria Service and British and Irish Porphyria Network	• The EMA granted marketing authorisation in March 2020 • Givosiran works by blocking translation of liver ALAS1 mRNA which is greatly increased in patients with recurrent attacks. This reduces the rate of haem synthesis and reduces the production of neurotoxic haem precursors particularly ALA.	Thank you for your comment. The technology section of the scope has been amended in line with the marketing authorisation. The mechanism of action of givosiran is described in the technology section and no

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			further detail is required in the scope.
	International Porphyria Patient Network	P.2: “Givirosan …” ff Please correct: Givosiran …	Thank you for your comment. This error has been amended.
Population ***Is the population defined appropriately? Are there groups within this population that should be considered separately?***	Alnylam	We believe that the population is defined appropriately, in line with the indication statement detailed in the SmPC. However, use of givosiran by the NAPS will be limited to the subset of patients most severely affected by porphyria, defined as those experiencing ≥4 attacks in a year. This population is broadly aligned with the ENVISION trial population where patients who experienced 2 or more attacks within the past 6 months could be enrolled. This usage restriction significantly reduces the population eligible to receive givosiran from the 560 patients with AHP in the UK estimated in the scope, and equates to approximately half of the 50 patients with recurrent severe disease managed by NAPS i.e. only 20 to 30 patients in total would be considered for givosiran.	Thank you for your comment. The population has been amended to only include adults and young people aged 12 years or older with recurrent severe acute hepatic porphyria.
	The British Porphyria Association	The population is defined appropriately. We have not identified any groups within the population that should be considered separately.	Thank you for your comment. Based on discussions at the scoping workshop, the population has been amended to only include adults and young people aged 12 years or older with recurrent severe acute hepatic porphyria.
	British Society of Gastroenterology	Yes	Thank you for your comment. Based on discussions at the scoping workshop, the population has been amended

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			to only include adults and young people aged 12 years or older with recurrent severe acute hepatic porphyria.
	Global Porphyria Advocacy Coalition	Yes, the population defined appears appropriate. No, we have not identified any groups that need considering separately.	Thank you for your comment. Based on discussions at the scoping workshop, the population has been amended to only include adults and young people aged 12 years or older with recurrent severe acute hepatic porphyria.
	NHS England and Improvement	The population is appropriately defined	Thank you for your comment. Based on discussions at the scoping workshop, the population has been amended to only include adults and young people aged 12 years or older with recurrent severe acute hepatic porphyria.
	British Association for the Study of the Liver	Yes	Thank you for your comment. Based on discussions at the scoping workshop, the population has been amended to only include adults and young people aged 12 years or older with recurrent severe acute hepatic porphyria.

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	National Acute Porphyria Service and British and Irish Porphyria Network	We expect that only the most severely affected patients with recurrent attacks of acute porphyria would be treated with givosiran. In practice, it is very rare for children with acute porphyria to present with an acute attack and exceedingly rare for them to have recurrent attacks.	Thank you for your comment. The population has been amended to only include adults and young people aged 12 years or older with recurrent severe acute hepatic porphyria.
	International Porphyria Patient Network	Yes	Thank you for your comment. Based on discussions at the scoping workshop, the population has been amended to only include adults and young people aged 12 years or older with recurrent severe acute hepatic porphyria.
Comparators ***Is this (are these) the standard treatment(s) currently used with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?***	Alnylam	We agree that established clinical management without givosiran is the appropriate comparator regimen. We also agree that this regimen may include the avoidance of known triggers, and the use of gonadotrophin analogues to decrease the frequency of attacks. The use of gonadotrophin analogues is relatively infrequent according to a large, international study (that included UK participation) of the natural history of AHP, where only 6% patients received these agents. [Gouya 2020] Intravenous glucose is rarely used to treat attacks in the UK due to the risk of exacerbating hyponatraemia [Stein 2012; Stein 2017]. Haem arginate is used to ameliorate established acute attacks. None of these separate components used in the established clinical management of AHP should be considered individually as comparators because they may or may not be used, according to the needs of individual patients. Therefore, established clinical management without givosiran, that may	Thank you for your comment. Based on comments during the draft scope consultation and the scoping workshop, the comparators listed as part of established clinical management without givosiran have been identified as haem arginate, gonadotrophin analogues and liver transplantation. It is acknowledged that not all the listed comparators will be

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		include varying combinations of these treatments, is the appropriate comparator regimen. In the pivotal ENVISION trial of givosiran, acute porphyria attacks could be managed according to the local standard of care, so many of these components of the established clinical management defined in the scope were used for the treatment of acute attacks as required. However, prophylactic use of some of these treatments in ENVISION was subject to restrictions in order to prevent confounding of efficacy and safety signals related to givosiran. **Haem arginate** Haem arginate is licensed for the treatment of acute attacks in patients with AHP. It is also sometimes used outside its marketing authorisation to prevent acute attacks. Use of haem arginate to ameliorate established acute attacks should be considered as a key component of established clinical management in the UK. As with the other individual treatments used in the currently established clinical management, it should not be considered separately as a comparator, but only as a component of this regimen. **Liver transplantation** We do not believe that liver transplantation (LT) is an appropriate comparator for givosiran for the following reasons: • In the UK, LT is reserved only for patients who meet the stringent criteria of "recurrent refractory attacks or a severe attack with neurological deficit despite medical therapy". [NHS Blood and Transplant guidelines for referral of liver transplant assessment] • This extremely narrow group of patients represents a different population to that which would be considered for treatment with givosiran • LT is considered as a treatment of last resort when all other options have been exhausted, especially due to the high risk of hepatic artery thrombosis and other complications, so is not	appropriate for all people with acute hepatic porphyria. Avoidance of known triggers and glucose have been removed as comparators.

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		routinely performed in the UK. Fewer than one transplant procedure per year has been performed in AHP patients since 2012. [Dowman 2012] • Further evidence of the experimental and high-risk nature of this approach is provided by the recent observation that only 38 transplants were performed in AHP patients over the last 17 years across 12 European countries [Lissing 2020] Gouya et al. EXPLORE: A Prospective, Multinational, Natural History Study of Patients with Acute Hepatic Porphyria with Recurrent Attacks. *Hepatology.* 2020;71(5):1546-1558. Stein et al. Acute intermittent porphyria: fatal complications of treatment. *Clinical Medicine.* 2012;12(3): 293-294. Stein et al. Update review of the acute porphyrias. *British Journal of Haematology.* 2017;176:527-538. Schmitt et al. Recurrent attacks of acute hepatic porphyria: major role of the chronic inflammatory response in the liver. *J Intern Med*. 2018;284(1):78-91. Dowman JK et al. Liver Transplantation for Acute Intermittent Porphyria is Complicated by a High Rate of Hepatic Artery Thrombosis. *Liver Transpl.* 2012;18(2):195–200. **Lissing M et al. Liver Transplantation for Acute Intermittent Porphyria in Europe. In press.**	
	The British Porphyria Association	Despite **avoiding known triggers**, some patients continue to have regular and severely debilitating attacks. **Glucose** is largely used alongside pain management and anti-emetics to provide supportive care in attacks, mostly to prevent starvation – a known trigger. Some patients with very mild symptoms may find that they are able to stave off mild attacks with extra glucose, but it is simply ineffective for those with recurrent or severe attacks. **Gonadotrophin analogues (GnRH)** have limited the potential to ameliorate attacks related to the menstrual cycle and Marsden et	Thank you for your comment. Based on comments during the draft scope consultation and the scoping workshop, the comparators listed as part of established clinical management without givosiran have been identified as haem arginate, gonadotrophin analogues and liver transplantation. It is acknowledged that not all the listed comparators will be

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		al. (2015) note that in 13 of 15 patients treated with GnRH, acute attacks continued or the treatment precipitated an acute attack; this is typical of the reports that we hear from patients. It is also not applicable for the few men who suffer recurrent attacks. Finally, this therapy can only be used for a limited length of time. **Haem arginate** is not licensed to be used in a preventative manner for recurrent attacks but has been used in this way for many years (Marsden et al., 2015). Haem arginate is an effective treatment for halting an acute attack. When used prophylactically, haem therapy doesn't prevent attacks from occurring (although it can reduce the frequency and/or severity, it is far from preventative). The side effects of regular haem arginate include venous thrombosis, severe venous access problems and iron overload. Semi-permanent venous access devices are necessary to provide this treatment and maintaining venous access is challenging with the average lifespan of a single device of 1-2 years. Further, haem arginate does nothing to stop chronic pain that requires opiate-based analgesia. There also appears to be a risk of the body becoming 'dependent' upon the intervention and there is difficulty in withdrawing or reducing the frequency of treatment (Neeleman, 2018) **Liver transplantation** would be a last resort option only. Not only are there considerable risks involved, in some patients who have been severely affected by porphyria attacks, lack of venous access or other complications can make the procedure even more risky or impossible.	appropriate for all people with acute hepatic porphyria. Avoidance of known triggers and glucose have been removed as comparators.

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		There is limited availability of donors, a patient could deteriorate in health before getting a donor making the procedure higher risk or unmanageable. There are high financial costs and immense burdens to the patient and their family/carers (and the NHS) in terms of follow-up care, complications, rejection and life on immunosuppressant medications. The comparators mentioned are simply the best therapies available at the moment. These treatments will still have a place in porphyria care, but alone they leave significant unmet need in the current standard of care of those with recurrent attacks of porphyria. Recurrent attacks of porphyria cause significant morbidity and immensely impaired quality of life for both patients and their wider circle of family and carers. We are aware that no one treatment is 100% safe or effective, but we strongly believe the potential magnitude of the benefits of Givosiran are worth investing in for patients, and consequently for their carers and wider family. There are no other relevant comparators that have not been included in the scope.	
	British Society of Gastroenterology	Yes	Thank you for your comment.
	Global Porphyria Advocacy Coalition	None of the current treatments stop recurrent attacks, and many have little effect on the most severely affected patients.	Thank you for your comment. Based on comments during the draft scope consultation and the scoping workshop, the

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		Haem arginate is effective in ameliorating a present attack, but it does not stop further attacks from developing. Givosiran is currently the only licensed drug for the treatment of recurrent attacks of acute porphyria. It has been shown to reduce the frequency of attacks (potentially preventing attacks in over 60% of patients) while also reducing pain levels and increasing overall physical health (Sardh, 30-June-2020). In terms of the identified comparators: *Avoidance of known triggers* is important alongside other treatments. But even with avoidance some patients still proceed to have recurrent and severe attacks. *Gonadotrophin analogues* can only be used for short periods of time (and only for women) and are only successful in a very small number of cases (Marsden et al. 2015). *Glucose* is not sufficient to stop attacks for patients with severe or recurrent attacks. *Haem arginate* is the current 'best available' treatment, but it is not licensed for preventative use. Importantly, haem arginate does not prevent attacks from occurring and it does not treat pain. It is still very effective in treating an individual attack. It should be noted that its administration is complex for regular and repeated use as many side effects can be generated. These include: venous access problems and thrombosis, as well as iron overload, which can all be serious and can cause life threatening problems (Marsden et al. 2015).	comparators listed as part of established clinical management without givosiran have been identified as haem arginate, gonadotrophin analogues and liver transplantation. It is acknowledged that not all the listed comparators will be appropriate for all people with acute hepatic porphyria. Avoidance of known triggers and glucose have been removed as comparators.

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		Difficulties have also been observed in withdrawing or reducing the frequency of haem arginate (Stein et al. 2013). As mentioned in the Background information section, *liver transplantation* would only be considered as a last resort.	
	NHS England and Improvement	The comparators are appropriate	Thank you for your comment.
	British Association for the Study of the Liver	Yes	Thank you for your comment.
	National Acute Porphyria Service and British and Irish Porphyria Network	Avoidance of known triggers is not regarded as a standard treatment for recurrent attacks. It is the default position for all patients with acute porphyria regardless of whether they have attacks or not. As a sole measure, it is not effective in preventing recurrent attacks. Glucose is not a standard treatment for recurrent attacks in the UK. Gonadotrophin analogues may be useful as a first line treatment in women with hormonally driven attacks, but have limited efficacy, can only be used for a limited time (up to 2 years), and oestrogen deficiency side effects are often a problem. Prophylactic (off label) use of haem arginate typically administered via a port-a-cath every one to four weeks is regarded as “best alternative care” for treatment of recurrent attacks. Although this usually provides some benefit, many patients continue to have	Thank you for your comment. Based on comments during the draft scope consultation and the scoping workshop, the comparators listed as part of established clinical management without givosiran have been identified as haem arginate, gonadotrophin analogues and liver transplantation. It is acknowledged that not all the listed comparators will be appropriate for all people with acute hepatic porphyria.

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		attacks and hospital admissions, as well as debilitating symptoms such as pain, nausea, and fatigue, which have a profound negative impact on all aspects of their lives. Side effects, particularly difficulty maintaining central venous access, and liver iron overload mean that haem infusions cannot continue indefinitely. Haem arginate is a potentially toxic molecule, which is taken up by the liver following infusion. Recent published evidence shows that regular haem arginate infusions can cause chronic hepatic inflammation, which may be contributing to prolonged recurrence of attacks. (Schmitt *et al.* Recurrent attacks of acute hepatic porphyria: major role of the chronic inflammatory response in the liver. J Intern Med. 2018 284:78-91). Liver transplantation is not regarded as a “standard treatment” for recurrent attacks in the UK. It is a last resort option which is considered when no other treatments are possible or effective. Concerns include the requirement for long term immunosuppression, anticoagulation and their effect on renal function. Only one UK patient has had a liver transplant since the start of NAPS in 2012.	Avoidance of known triggers and glucose have been removed as comparators.
	International Porphyria Patient Network	Yes	Thank you for your comment.
Outcomes	Alnylam	We agree that number of acute attacks, porphyrin precursor concentrations, mortality, adverse effects and health related quality of life are appropriate outcome measures which capture the most important	Thank you for your comment. It was noted at the scoping

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Will these outcome measures capture the most important health related benefits (and harms) of the technology?		health related effects of givosiran. These were included as endpoints in the pivotal ENVISION trial. However, neurological impairment and autonomic function are not generally considered to be relevant outcomes in AHP. There is no established disability or impairment scale specific to the measurement of porphyric neuropathy that is used in routine clinical practice and, as such, these outcomes are not available in the literature and were not collected in the ENVISION trial.	workshop that neurological impairment and autonomic function are important outcomes. No changes to the scope are needed.
	The British Porphyria Association	The outcome measures to be considered are all appropriate. Outcome measures should also include long-term complications. Reduction in pain would be a good outcome measure. Health-related quality of life needs to include the wider burden of illness on patients including the psychological and socio-economic effects such as inability to work (which occurs in 63.6% of recurrent cases according to Neeleman et al. 2018). Carer disutility: We would expect caregiver and family quality of life to be an important outcome measure as their lives and abilities to work/study are highly impacted by the patient's debilitating attacks, regular hospital stays, intensive treatments and impaired ability to work and look after children. There are at least as many relatives and carers whose lives are severely affected by those with recurrent attacks as there are patients.	Thank you for your comment. The outcomes listed are the key outcomes which should be considered and is not exhaustive. Detail has been added to the outcome of health-related quality of life to specify this is for both patients and carers.

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		The issues listed under “Nature of the condition”, and “Clinical effectiveness” are all relevant and need to be considered when evaluating the benefits of Givosiran.	
	British Society of Gastroenterology	Yes	Thank you for your comment. No changes to the scope are needed.
	Global Porphyria Advocacy Coalition	All of the outcome measures identified are appropriate. However, it is vital that the *health-related quality of life* outcome measure must be considered fully and should include the magnitude of the full impact/burden of the condition on the patient’s (and their family’s) whole life, including psychological, sociological and economic aspects. For patients with recurrent AHP attacks, their QoL is significantly negatively impacted upon (Neeleman et al. 2018; Naik et al. 2016).	Thank you for your comment. Detail has been added to the outcome of health-related quality of life to specify this is for both patients and carers.
	NHS England and Improvement	In relation to the outcomes, these are reasonable, it would be helpful to include quality of life as well as the health-related quality of life, severity of attacks and impact on pain.	Thank you for your comment. The outcomes listed are the key outcomes which should be considered and it not exhaustive.
	British Association for the Study of the Liver	Yes	Thank you for your comment. No changes to the scope are needed.

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	National Acute Porphyria Service and British and Irish Porphyria Network	Suggest removing the outcome measures of neurological impairment and autonomic function which are difficult to measure objectively.	Thank you for your comment. It was noted at the scoping workshop that neurological impairment and autonomic function are important outcomes. No changes to the scope are needed.
	International Porphyria Patient Network	Yes	Thank you for your comment. No changes to the scope are needed.
Equality ***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***	Alnylam	A timely HST evaluation of givosiran would support the ongoing commitment of NICE to promote equality. The disease predominately afflicts young women and is associated with often excruciating pain, opioid use and the potential for dependence, mental health issues and a social care burden such that the performance of daily activities, including childcare and maintaining employment may become impossible.	Thank you for your comment. Equality issues will be considered during the evaluation of this topic. Please see the Equality Impact Assessment (scoping) for further information.
	The British Porphyria Association	Haem arginate may not be an acceptable treatment for Jehovah's Witnesses. Similarly, organ transplantation is unlikely to be an option for Jehovah's witnesses due to the need for blood products. We are concerned that there could be patients who are disadvantaged by the need to travel to porphyria centres for care. These patients could potentially be those in the greatest need who are very unwell or disabled and/or have limited financial resources. We have not identified any other equality issues.	Thank you for your comment. Equality issues will be considered during the evaluation of this topic. Please see the Equality Impact Assessment (scoping) for further information.

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proposed remit and scope: • ***could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/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***			
	British Society of Gastroenterology	Is fine	Thank you for your comment.
	Global Porphyria Advocacy Coalition	It should be noted that for many Jehovah's Witnesses, liver transplantation and the use of haem arginate are not likely to be acceptable treatments – thus another treatment option is needed. It should also be noted that haem arginate needs to remain available to patients. We do not expect Givosiran to replace haem arginate which will still have an important role in porphyria care. Both treatments need to be available for use under the guidance of expert porphyria clinicians.	Thank you for your comment. Equality issues will be considered during the evaluation of this topic. Please see the Equality Impact Assessment (scoping) for further information.
	NHS England and Improvement	Acute hepatic porphyria's are very rare conditions and patients in England benefit from a single national expert service delivered from two centres who also provide outreach clinics , face to face and virtual. We are not aware of any specific access issues relating to people with protected characteristics or that commissioning this drug would disadvantage any groups.	Thank you for your comment.
	British Association for the Study of the Liver	Is fine	Thank you for your comment.

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disability or disabilities. ***Please tell us what evidence should be obtained to enable the Highly Specialised Technologies Evaluation Committee to identify and consider such impacts.***	National Acute Porphyria Service and British and Irish Porphyria Network	There is a need to ensure equal access for all patients in the UK who would benefit regardless of geographical location. Some patients who would be eligible for this treatment have suffered severe and frequent acute attacks causing complications which have resulted in permanent disability.	Thank you for your comment. Equality issues will be considered during the evaluation of this topic. Please see the Equality Impact Assessment (scoping) for further information.
	International Porphyria Patient Network	Patients without diagnosis will not be able to profit from any of the specific treatments available for AHPs, and therefore consideration should be given to how to increase awareness and testing for the porphyrias.	Thank you for your comment. Awareness and testing is outside the remit of this appraisal.
Other considerations	Alnylam	We have no additional comments.	Thank you for your comment.
	The British Porphyria Association	The issues listed under “Nature of the condition”, and “Clinical effectiveness” are all relevant and need to be considered when evaluating the benefits of Givosiran.	Thank you for your comment.
	Global Porphyria Advocacy Coalition	The elements identified in *Nature of the condition, Clinical effectiveness* and *Value for money* all need considering fully by NICE.	Thank you for your comment.
	International Porphyria Patient Network	The IPPN considers givosiran as a step change for AHP patients with recurrent attacks. However, consideration should be given to the possibility that by treating patients with givosiran instead of haem-arginate, the latter might become less accessible. Haem-arginate is currently the only available treatment for acute attacks.	Thank you for your comment. Issues regarding treatment accessibility will be considered by the committee during the evaluation of this topic.

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Innovation ***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)?***	Alnylam	In the pivotal ENVISION trial, givosiran met its primary endpoint with a mean annualised attack rate of 3.2 in the givosiran group compared with 12.5 in the placebo group, representing a 74% lower rate in givosiran patients (P<0.001). [Balwani 2020] These results suggest givosiran has the potential to have a significant benefit on the health of patients with AHP and can be regarded as a step change in the management of the condition. In the context of these results, givosiran was granted accelerated assessment, following the earlier Orphan Drug and Priority Medicines (PRIME) designations, in line with the EMA aim to bring new treatments of major public health interest and therapeutic innovation to patients more quickly. Givosiran is a subcutaneously administered RNA interference therapeutic targeting hepatic ALAS1 messenger RNA (mRNA). The technology is effective in reducing elevated levels of ALAS1 mRNA, leading to a reduction of neurotoxins ALA and PBG which are believed to cause the acute attacks and other manifestations of AHP. Givosiran is the second medicine to work through RNA interference (RNAi). **Balwani M et al. Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria. *N Engl J Med* 2020;382:2289-2301**	Thank you for your comment. The innovative nature of this technology will be considered by the committee during the appraisal. No changes to the scope are needed.
	The British Porphyria Association	Givosiran marks a huge step-change in treatment for acute porphyria. The treatment is innovative in its potential to make an impact in an area of considerable unmet need for patients who experience recurrent attacks of acute porphyria. There is currently no licensed treatment that prevents attacks, so these patients live in a world of pain and multiple symptoms, complications and disabilities that have a devastating impact on their (and their families' and carers') quality of life.	Thank you for your comment. The innovative nature of this technology will be considered by the committee during the appraisal. No changes to the scope are needed.

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		Givosiran has been shown to reduce or completely eliminate pain, acute attacks, hospital admissions and enable visible improvement from paralysis. As well as a dramatic improvement in patient health and quality of life, this treatment leads to a reduction in hospital admissions, dependence on clinical care and supportive care resources, such as the burden on carers and the ability to return to work.	
	British Society of Gastroenterology	Yes	Thank you for your comment. The innovative nature of this technology will be considered by the committee during the appraisal. No changes to the scope are needed.
	Global Porphyria Advocacy Coalition	Yes. The use of Givosiran as a treatment for the AHPs offers a huge step-change in terms of its innovation, the manner in which it is administered and in its effectiveness in not only reducing the number of attacks and hospital admissions, but also reducing the additional healthcare resources needed. Givosiran has also been shown to reduce and, in some cases, eliminate pain in patients that had previously been dependent on regular and strong opioid analgesia (Sardh, 30-June-2020). Moreover, Givosiran has been shown to significantly improve patient quality of life and overall health in those suffering from regular and recurrent AHP attacks (Balwani et al. 2020).	Thank you for your comment. The innovative nature of this technology will be considered by the committee during the appraisal. No changes to the scope are needed.

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		Thus, Givosiran offers significant improvement in an area of unmet need in patients affected by recurrent AHP attacks.	
	NHS England and Improvement	This is an innovative technology and will make a significant and substantial impact on health-related benefits for these cohorts of patients. This technology is a significant step change in the management of this disease	Thank you for your comment. The innovative nature of this technology will be considered by the committee during the appraisal. No changes to the scope are needed.
	British Association for the Study of the Liver	Yes	Thank you for your comment. The innovative nature of this technology will be considered by the committee during the appraisal. No changes to the scope are needed.
	National Acute Porphyria Service and British and Irish Porphyria Network	Givosiran is the only new treatment for acute porphyria in the past 30 years and the only licensed treatment to prevent attacks. It has the potential to transform treatment and dramatically improve the health and quality of life of the most severely affected patients with recurrent attacks of porphyria who are typically young adults with families, jobs and other responsibilities, and who currently depend on treatments which are poorly effective and have significant side effects.	Thank you for your comment. The innovative nature of this technology will be considered by the committee during the appraisal. No changes to the scope are needed.
	International Porphyria Patient Network	A comparable technology, patisiran for treating hereditary transthyretin amyloidosis, has a marketing authorisation for the UK	Thank you for your comment. The innovative nature of this technology will be considered by the committee during the

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			appraisal. No changes to the scope are needed.
Questions for consultation	Alnylam	1) *Would givosiran only be used in people with recurrent acute attacks of AHP?* A. Yes. Givosiran use would be limited to patients with recurrent acute attacks of AHP. 2) *Would givosiran be used as a treatment for acute attacks of AHP or as a treatment for prevention of attacks in people who have had recurrent attacks?* A. Givosiran would not be used as a treatment for acute attacks of AHP. It would be used for prevention of attacks in people who have had recurrent attacks. 3) *In NHS clinical practice, would recurrent acute attacks be defined by 'at least 2 previous acute porphyria attacks in the past 6 months'?* A. The definition of recurrent acute attacks used in NHS clinical practice is ≥4 attacks per year. This is very closely aligned with the definition used in the pivotal ENVSION trial of givosiran of 'at least 2 previous acute porphyria attacks in the past 6 months'. 4) *Have all relevant comparators for givosiran been included in the scope?* A. Yes. All relevant comparators for givosiran have been included in the scope. We believe some of these currently included in the draft scope would be inappropriate, as outlined in the comparator section of "Comment 2: the draft scope". We do not believe that liver transplantation is an appropriate comparator for givosiran. 5) *Can haem arginate, glucose, gonadotrophin analogues and liver transplantation be considered as established clinical management of AHP*	Thank you for your comment. The population has been amended to only include adults and young people aged 12 years or older with recurrent severe acute hepatic porphyria. Based on comments during the draft scope consultation and the scoping workshop, the comparators listed as part of established clinical management without givosiran have been identified as haem arginate, gonadotrophin analogues and liver transplantation. It is acknowledged that not all the listed comparators will be appropriate for all people with acute hepatic porphyria. It was noted at the scoping workshop that neurological impairment and autonomic function are important outcomes.

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		in the NHS? If yes, can you define the populations likely to receive haem arginate, glucose, gonadotrophin analogues and/or liver transplant? A1. Yes. These may be considered as components of the established clinical management of AHP in the NHS, subject to the limitations described in the comparator section of "Comment 2: the draft scope". We do not believe that liver transplantation should be considered as part of the established clinical management of AHP as it is not routinely performed in the NHS. *6) Does haem arginate cause any issues for any religious or cultural groups?* A. We have no comments on this question. *7) Are the outcomes listed appropriate?* A. Yes. We believe that the outcomes are appropriate, except neurologic impairment and autonomic function, as summarised in the outcomes section of "Comment 2: the draft scope". *8) Are there any subgroups of people in whom givosiran is expected to be more clinically effective and cost effective or other groups that should be examined separately?* A. No. The treatment benefit was maintained across all pre-specified subgroups in the pivotal ENVISION trial. 9) Please refer to the equality section of *"Comment 2: the draft scope"* for answers to the questions regarding equality. *10) Do you consider givosiran 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)?* A. Yes. Please refer to the innovation section of *"Comment 2: the draft scope"* for answers to the questions regarding givosiran being innovative.	All other points will be considered during the evaluation of this topic and do not need changes to the scope.

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		11) Do you consider that the use of givosiran can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? A. Yes. Additional health-related benefits associated with givosiran use that are unlikely to be included in the QALY calculation include the impact on patients' families, impacts on childcare and employment, opioid dependence and mental health issues. *12) To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.* A. We believe there would be minimal impact on the AHP service in the NHS due to implementation through NAPS HSS. The NAPS centre in London is a givosiran clinical trial site experienced in the use of this treatment as part of phase I/II open label extension studies and the pivotal ENVISION trial. The NAPS already manage distribution of haem arginate nationally. Administration of givosiran requires minimal health care resource use as a monthly subcutaneous injection. Clinical assessment and monitoring will not be significantly different from the currently existing schedule for severely affected patients at the NAPS.	
	The British Porphyria Association	Questions not already answered above: 1. Would Givosiran only be used in people with acute recurrent attacks? *That would be our general expectation.* 2. Would Givosiran be used as a treatment for acute attacks of AHP or as a treatment for prevention of attacks in people who have had recurrent attacks? *Expected to be treatment for prevention of recurrent attacks*	Thank you for your comment. The population has been amended to only include adults and young people aged 12 years or older with recurrent severe acute hepatic porphyria. Based on comments during the draft scope consultation and the scoping workshop, the comparators listed as part of

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		3. In NHS clinical practice, would recurrent acute attacks be defined by 'at least 2 previous acute porphyria attacks in the past 6 months'? *This sounds likely.* 4. Do you consider that the use of Givosiran can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? *We believe the EQ-5D used in studies is unlikely to fully identify the extent to which patients benefit from the treatment. In these severely affected patients even small incremental changes that the questionnaire might not enable them to define are likely to have huge impacts on day-to-day health. Patient testimony must therefore be given high importance.* 5. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? *Some patients may find travel to a porphyria centre unfeasible due to disability or financial resources; therefore, we would hope there to be a homecare element at a relatively early stage of treatment.* 6. Is it appropriate that Givosiran is appraised through the HST process? *Yes, we believe that to be the most appropriate process.*	established clinical management without givosiran have been identified as haem arginate, gonadotrophin analogues and liver transplantation. It is acknowledged that not all the listed comparators will be appropriate for all people with acute hepatic porphyria. All other points will be considered during the evaluation of this topic and do not need changes to the scope.

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		Evidence sources To identify the full impact of the health-related quality of life factors (such as ability to work, care for children, social impact, psychological impact, impact on family and carers) and the QoL gains obtained from treatment that are unlikely to be included in the QALY calculation or gained from published study data, it will be vital to take into account qualitative patient and carer perspectives of treatment. Other data that is available to enable the evaluation committee to take account of these benefits are the results of a Burden of Illness study conducted in association with BresMed, the BPA and Alnylam. This data should be available before the appraisal. A number of specific research papers are noted below: Elder G, Badminton M, Harper P, Sandberg S, Deybach JC. (2013) The incidence of inherited porphyrias in Europe. *J Inherit Metab Dis*. 36(5):849–857. Gouya L, Ventura P, Balwani M, et al. (2020) EXPLORE: A Prospective, Multinational, Natural History Study of Patients with Acute Hepatic Porphyria with Recurrent Attacks. *Hepatology*. 71(5):1546-1558. Marsden JT, Guppy S, Stein P, et al. (2015) Audit of the use of regular haem arginate infusions in patients with acute porphyria to prevent recurrent symptoms. *JIMD Rep*. 22:57-65.	

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		Neeleman RA, Wagenmakers M, Koole-Lesuis RH, Mijnhout GS, Wilson JHP, Friesema ECH, Langendonk JG (2018) Medical and financial burden of acute intermittent porphyria, *J Inherit Metab Dis.* 41: 809-817. Stein P, Badminton M, Rees D (2017) Update review of the acute porphyrias. *Brit J Haemat*, 176: 527-538.	
	Global Porphyria Advocacy Coalition	*Q. Would Givosiran only be used in people with recurrent acute attacks of AHP?* A. Yes – it is our understanding that it would be used for patients with recurrent attacks of AHP. *Q. Would Givosiran be used as a treatment for acute attacks of AHP or as a treatment for prevention of attacks in people who have had recurrent attacks?* A. As a treatment for the prevention of attacks in people who have had recurrent attacks. *Q. In NHS clinical practice, would recurrent acute attacks be defined by 'at least 2 previous acute porphyria attacks in past 6 months?* A. Yes, it is our understanding that this would be the case. *Q. Do you consider that the use of Givosiran can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* A. Yes. Individual patient testimonials must be included and considered by NICE as, unfortunately, the EQ-5D is unlikely to fully	Thank you for your comment. The population has been amended to only include adults and young people aged 12 years or older with recurrent severe acute hepatic porphyria. Based on comments during the draft scope consultation and the scoping workshop, the comparators listed as part of established clinical management without givosiran have been identified as haem arginate, gonadotrophin analogues and liver transplantation. It is acknowledged that not all the listed comparators will be appropriate for all people with acute hepatic porphyria. All other points will be considered during the evaluation

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		capture the real and significant benefits of the treatment, as it is less responsive/sensitive to potentially small and significant changes that may be reported better by disease specific outcome measures (Wailoo et al. 2010). In addition to the patient, a wider spectrum of QoL needs to be considered, including caregivers, children, partners and the wider family unit, in order to fully understand the true impact of the burden of recurrent attacks of AHP. *Q. Please identify the nature of the data which you understand to be available to enable the Evaluation Committee to take account of these benefits.* A. Various references have been made in GPAC's response, including the following: Sardh, E. (30-June-2020) Alnylam reports new 12-month interim data from the ENVISION phase 3 study of Givosiran in acute hepatic porphyria. *Webinar presented by Alnylam Pharmaceuticals Inc.* Balwani, M., Sardh, E., Ventura, P. et al. (2020) Phase 3 trial of RNAi therapeutic Givosiran for acute intermittent porphyria. *New England Journal of Medicine.* 382(24): 2289-2301. Gouya, L., Ventura, P., Balwani, M., et al. (2020) EXPLORE: A Prospective, Multinational, Natural History Study of Patients with Acute Hepatic Porphyria with Recurrent Attacks. *Hepatology*. 71(5):1546-1558.	of this topic and do not need changes to the scope.

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		Marsden, J.T., Guppy, S., Stein, P., Cox, T., Badminton, M., Gardiner, T., Barth, J., Stewart, M., Rees, D. (2015) Audit of the use of regular haem arginate infusions in patients with acute porphyria to prevent recurrent symptoms. *JIMD Rep*. 22:57-65. Naik, H., Stoecker, M., Sanderson, C., Balwani, M., Desnick, R. (2016) Experiences and concerns of patients with recurrent attacks of acute hepatic porphyria: A qualitative study. *Molecular Genetics Metabolism* 119(3):278-283. Neeleman, R.A., Wagenmakers, M., Koole-Lesuis, R.H., Mijnhout, G.S., Wilson, J.H.P., Friesema, E.C.H., Langendonk, J.G. (2018) Medical and financial burden of acute intermittent porphyria, *J Inherit Metab Dis.* 41: 809-817. Simon, A., Pompilus, F., Querbes, W., Wei, A., Strzok, S., Penz, C., Lyon Howe, D., Hungate, J.R., Kim, J.B., Agarwal, S., Marquis, P. (2018) Patient perspective on acute intermittent porphyria with frequent attacks: A disease with intermittent and chronic manifestations. *Patient.* 11(5): 527-537. Stein, P., Badminton, M., Barth, J., Rees, D., Stewart, F. (2013) Best practice guidelines on clinical management of acute attacks of porphyria and their complications. *Annals of Clinical Biochemistry; International Journal of Laboratory Medicine.* 50(3): 217-223. Wailoo, A., Davis., S. Tosh, J. (2010) The incorporation of health benefits in cost utility analysis using the EQ-5D. Report by the Decision Support Unit. *University of Sheffield.* 1-110.	

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		Two additional Data on File resources will be available shortly to demonstrate further the burden of AHP and its impact on QoL for patients, caregivers and the wider family unit, including: 1. Patient and caregiver experiences of living with AHP in the UK: a mixed methods study (prepared by BPA, Alnylam Pharmaceuticals and BresMed Health Solutions). 2. Concept elicitations study (prepared by Endpoint Outcomes, Alnylam Pharmaceuticals, the BPA and the American Porphyria Foundation). *Q. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.* A. No barriers with regards to the technology, however, a strategy will need to be implemented for the delivery of the treatment – via recognised centres/homecare provision or at a local level, to ensure that the severely affected patients, who may be too unwell/financially unable to pay for transportation to treatment sites, are able to access Givosiran.	
	National Acute Porphyria Service and British and Irish Porphyria Network	*Does haem arginate cause any issues for any religious or cultural groups?* Haem is isolated and purified from red blood cells and could therefore be a concern for Jehovah's Witnesses.	Thank you for your comment. Equality issues will be considered during the evaluation of this topic. Please see the Equality Impact Assessment (scoping) for further information.

Section	Consultee/ Commentator	Comments [sic]	Action
		To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. Patients are spread over a large geographical area and may struggle to attend a specialist porphyria centre for initiation of treatment because of social, family and health reasons.	
	International Porphyria Patient Network	Would givosiran only be used in people with recurrent AHP acute attacks? > Yes Would givosiran be used as a treatment for acute attacks of AHP or as a treatment for prevention of attacks in people who have had recurrent attacks? > Givosiran has not been tested for the treatment of acute attacks and should not be used in people without recurrent attacks of. AHP. In NHS clinical practice, would recurrent acute attacks be defined by 'at least 2 previous acute porphyria attacks in the past 6 months'? > The indication for treatment with givosiran would be in line with the marketing authorisation, however whether patients should qualify for the treatment with givosiran should be the treating physician's decision. We would like to add that only expert physicians should be treating AHP patients. Further, the definition for an acute attack is relevant for the Guidance.	Thank you for your comment. The population has been amended to only include adults and young people aged 12 years or older with recurrent severe acute hepatic porphyria. Based on comments during the draft scope consultation and the scoping workshop, the comparators listed as part of established clinical management without givosiran have been identified as haem arginate, gonadotrophin analogues and liver transplantation. It is acknowledged that not all the listed comparators will be appropriate for all people with acute hepatic porphyria.

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		Have all relevant comparators for givorisan been included in the scope? > The most important comparators seem to have been included in the scope. Can haem arginate, glucose, gonadotrophin analogues and liver transplantation be considered as established clinical management of AHP in the NHS? > We assume - If yes, can you define the populations likely to receive haem arginate, glucose, gonadotrophin analogues and/or liver transplant? > Please see comments from expert physicians in the NHS Does haem arginate cause any issues for any religious or cultural groups? > Not to our knowledge Are the outcomes listed appropriate? > We assume Are there any subgroups of people in whom givorisan is expected to be more clinically effective and cost effective or other groups that should be examined separately? > Preliminary results shared by expert physicians at porphyria meetings and informally suggest that for some patients a long-term	All other points will be considered during the evaluation of this topic and do not need changes to the scope.

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		benefit was seen after cessation of treatment because of adverse events or stopping criteria. Therefore, the potential for dose reductions should be further explored. 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 givosiran 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. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. > No equality issues have been identified Do you consider givorisan 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)? > People with recurrent attacks are severely disabled and givosiran is a step-change for this subgroup of AHP patients.	

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		Do you consider that the use of givorisan can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? > Patients insights should be heard to answer this question Please identify the nature of the data which you understand to be available to enable the Evaluation Committee to take account of these benefits. > Extensive natural history study and RCT and clinical data showing a significant decrease in acute attacks and increase in QoL. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. > No NICE intends to appraise this technology through its Highly Specialised Technology (HST) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). > Being a subgroup of an ultra-rare condition, we support the appraisal under the HST programme	

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

National Acute Porphyria Service, Cardiff and Vale UHB: “We have developed a joint response with the clinicians working in our satellite clinical centre at Salford Royal NHS Foundation Trust and King’s College Hospital NHS Foundation Trust. This document will be submitted by King’s.”