NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Givosiran for treating acute hepatic porphyria [ID1549]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY EVALUATION

Givosiran for treating acute hepatic porphyria [ID1549]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ECD)**

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3. **Consultee and commentator comments on the Evaluation Consultation Document** from:
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4. **Evidence Review Group critique of company comments on the ECD**

5. **Evidence Review Group post committee analysis**

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

Givosiran for treating acute hepatic porphyria

Highly Specialised Technology Evaluation

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Alnylam	See committee papers for company ECD response	Comments noted. See FED for details on how the company's ECD response was incorporated into the appraisal.
2	Consultee	The British Porphyria Association	**Long-term data:** ECD (p3) 'It is uncertain how effective givosiran is in the long term'. In the UK and internationally, numerous patients have received givosiran on the open label extension for 3+ and 4+ years and for some of these patients, their conditions are continuing to improve. Phase 1 / 2 Part C open label extension may provide useful data here. If this is not sufficient, what does NICE mean by long term? What time frame would NICE be looking at to answer any uncertainties here?	Comment noted. Latest data from the ENVISION open-label extension study were considered at the second evaluation committee meeting.
3	Consultee	The British Porphyria Association	**Age at model entry** ECD (p15): The ECD reveals some level of confusion between the age of diagnosis of acute porphyria (often in a patient's 20s) and the age at which recurrent attacks are more likely to start (more often in a patient's 30s and 40s). Therefore, although anyone newly diagnosed might become eligible to receive givosiran if they started recurrent attacks, this is unlikely to be until their 30s or 40s. Dr Eliane Sardh from Sweden presented data on 15 Swedish patients at the British and Irish Porphyria Network (BIPNET) symposium on 14 June 2021, which detailed the Swedish experience as being similar to the UK experience, and commented on 2 patients who had recently started having recurrent attacks.	Comment noted. The committee discussed age of treatment onset during the second evaluation committee meeting and concluded that the company's scenario of starting age of 37 was suitable for use in decision making (see FED section 4.29)
4	Consultee	The British Porphyria Association	**Stopping treatment / Time on treatment** ECD (p13): An important factor that we would like to expand upon, to ensure the NICE committee have a full understanding, is that if a patient starts givosiran soon after a pattern of recurrent attacks commences, effect of the givosiran on biochemistry and symptoms is rapid. International research is suggesting that treatment may be able to be stopped, or a treatment break offered, after a short period of treatment with givosiran.	Comment noted. These points were considered by the Evaluation Committee when formulating its recommendations.

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			This is in contrast to those who have had established recurrent attacks for many years and may require a longer spell of treatment before the biochemistry reduces to nearer normal levels – even if attack symptoms stop rapidly. These patients might need longer periods of treatment. The French and Swedish experiences may offer a wider perspective of this aspect.	
5	Consultee	The British Porphyria Association	**Quality of life** The ECD highlights that quality of life data from the ENVISION trial does not fully capture the profound impact that acute porphyria has on quality of life, nor does it demonstrate the immense changes that givosiran can make to patients. Standard instruments fail to reveal the enormity of the benefit arising from treatment with givosiran. In the absence of strong data, and with the utilities from relapsing-remitting multiple sclerosis having some similarities, but also a number of differences with acute porphyria, the BPA would like to re-draw the committee's attention to the following sources of information on quality of life: • An article relating to quality of life, which was initially submitted as academic in confidence, but is now peer reviewed and published: Gill, L., Burrell, S., Chamberlayne, J. *et al.* Patient and caregiver experiences of living with acute hepatic porphyria in the UK: a mixed-methods study. *Orphanet J Rare Dis* **16,** 187 (2021). https://doi.org/10.1186/s13023-021-01816-2 • Qualitative testimonials from patients experiencing recurrent attacks (as submitted with the BPA submission). Three of the seven patients were able to directly compare life on haem arginate and life on treatment with givosiran. Haem arginate has been noted by patients to be an effective treatment that stops them from dying, but it does not provide the immense improvements to every aspect of a patient's life that givosiran does.	Comment noted. These points were considered by the Evaluation Committee when formulating its recommendations.
6	Consultee	The British Porphyria Association	**Additional expertise** It would be valuable to invite either Dr Eliane Sardh from Sweden, or Dr Laurent Gouya from France to the subsequent evaluation committee meetings. Both are expert porphyria consultants, who are each managing 20 or more patients on Givosiran through the Envision open label extension, or the Early Access Program. Their experience of givosiran on patients would be valuable to the discussion. See, for example comments in 3 and 4 above.	Following discussions with the chair of the evaluation committee, it was decided that 2 clinical experts who work in the NHS should be able to address the key outstanding uncertainties for the committee. These were around starting age of treatments in NHS and associated time on treatment and need for treatment for women around the menopause. The chair considered that these issues are best considered by clinicians familiar with treating people in the NHS rather than experts less familiar with NHS practice.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
7	Consultee	Global Porphyria Advocacy Coalition (GPAC)	GPAC were disappointed to hear the recommendation of 'minded not to recommend' givosiran as an option for the treatment of acute hepatic porphyria patients. GPAC really feel there is an unmet need for those seriously affected by AHP and hope the questions identified can be addressed in a constructive and timely manner in order to make this treatment available to the small number of patients that are in great and urgent need.	Comment noted. Following consultation, the company submitted an analysis against the committee's preferred comparator, prophylactic haem arginate. Based on the updated clinical and cost-effectiveness data submitted, the committee concluded, overall, that givosiran can be considered an appropriate use of NHS resources for highly specialised technologies. It therefore recommended givosiran as an option for treating AHP with severe recurrent attacks.
8	Consultee	Global Porphyria Advocacy Coalition (GPAC)	GPAC has worked with the British Porphyria Association and fully supports the information provided in their ECD response form for all points they have made, including: - Best supportive care - Long-term data - Age at model entry - Stopping treatment/time on treatment - Quality of life	Comment noted.
9	Consultee	Global Porphyria Advocacy Coalition (GPAC)	**Additional international clinical expertise:** GPAC would encourage further input from other international clinicians who have seen larger numbers of patients and for a longer-term. Their insight will further corroborate the experiences presented by the UK clinician expertise. Specifically, Professor Eliane Sardh from the Porphyria Centre, Karolinska University Hospital, Stockholm, Sweden and Professor Laurent Gouya from the Centre Français des Porphyries CRMR – Porphyries in Paris, France. Professor Sardh has treated a large number of patients for over 4 years from the Phase 1/2 Part C givosiran trials, the open label extension and through the early access program. Professor Gouya was heavily involved in the trials and is also currently treating more than 20 patients in France in a flexible manner. Their input should be sought as it would be invaluable in providing more data and insight into 'long-term data', 'age at model entry', 'stopping treatment/time on treatment' and 'quality of life'.	Following discussions with the chair of the evaluation committee, it was decided that 2 clinical experts who work in the NHS should be able to address the key outstanding uncertainties for the committee. These were around starting age of treatments in NHS and associated time on treatment and need for treatment for women around the menopause. The chair considered that these issues are best considered by clinicians familiar with treating people in the NHS rather than experts less familiar with NHS practice.
10	Consultee	[International Porphyria Patient Network (IPPN)]	On ECD page 4¶ 2.2, the prevalence of AHP is given as 1 in 100,000 people in Europe. Current publications estimate the prevalence of acute intermittent porphyria which is the most frequent form of AHP in Europe to be 1 in 1,700: "The prevalence of mutations among patients with acute intermittent porphyria (the most common subtype of acute hepatic porphyria) is approximately 1 in 1700 in	Comment noted. The FED has been updated to specify that the prevalence of 1 in 100,000 refers to symptomatic AHP (see section 2.2).

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			Western countries, [9,10] although disease penetrance is low, with less than 10% of patients ever having disease symptoms develop.[1]" (Sardh et al. 2019, NEJM DOI: 10.1056/NEJMoa1807838) The ECD should either correct the number or specify that the reported prevalence refers to symptomatic AHP.	
11	Consultee	[International Porphyria Patient Network (IPPN)]	Inconsistent information: On page 4 ¶ 2.2, the ECD states that there are currently 35 patients with acute porphyria having treatment for recurrent acute attacks in the UK. The presentation that was shown at the committee meeting 1 (13 May 2021, document: ID1540 givosiran part 1 slides to PM for public [redacted], p. 3) states that "currently 26 people are treated for recurrent attacks in the UK".	Comment noted. Based on consultation comments from the National Acute Porphyria Services, the FED has been updated to state that there are currently 27 people with acute porphyria having treatment for recurrent acute attacks in the UK (see section 2.2.).
12	Consultee	[International Porphyria Patient Network (IPPN)]	Pricing remains opaque: On page 5 ¶ 3 of the ECD, the price of givosiran is given as 41,884.43 GBP per 189-mg vial, with a recommended dose of 2.5 mg per kg body weight once a month. However, the paragraph also states that the company has a commercial arrangement, i.e., a simple discount patient access scheme. This means that the actual price is not accessible to the stakeholders or the public, which prevents these stakeholder groups form providing meaningful feedback regarding the cost effectiveness.	Comment noted. Based on NICE's processes of technology appraisals, details of simple discount patient access schemes which have been agreed as confidential with NHS England cannot be shared with consultees, commentators or released into the public domain.
13	Consultee	[International Porphyria Patient Network (IPPN)]	The implications of the current treatment options are not comprehensively discussed: On page 7 ¶ 4.2, the clinical experts explained that liver transplant is performed when haem arginate is no longer an option. While a liver transplantation cures AHP, it is connected to accompanying lifelong adverse consequences, symptoms of different nature and health risks. We miss the discussion on the fact that givosiran could prevent these adverse effects in people with AHP while at the same time saving valuable donor organs for other groups of patients.	Comment noted. The views of clinical experts and patient/carer representatives were considered by the Evaluation Committee when formulating its recommendations. The potential impact of givosiran beyond direct health benefits (including on reduction in need of liver transplantation) is discussed with section 4.34 of the FED.
14	Consultee	[International Porphyria Patient Network (IPPN)]	Experience with givosiran in the clinical practice: On page 7-8 ¶4.4, the ECD describes the experience with givosiran in the clinical practice. The description in our opinion does not capture the full benefit as detailed by the clinical and patient experts, i.e., the degree of freedom from acute attacks and other insights provided at the committee meeting on 13 May 2021 and in the submissions of the patient organisations. Side note: The presentation that was shown at the committee meeting 1 (13 May 2021, document: ID1540 givosiran part 1 slides to PM for public [redacted], p. 10) on the patient and carer organisation submissions states that submission were received from 2 organisations – the British Porphyria Association (BPA), Global Advocacy Coalition (GPAC).	Comment noted. The views of clinical experts and patient/carer representatives were considered by the Evaluation Committee when formulating its recommendations.

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			As a clarification, the International Porphyria Patient Network (IPPN) and the BPA made a joint submission, with the IPPN forgoing an own submission but supporting the BPA's.	
15	Consultee	[International Porphyria Patient Network (IPPN)]	Comment on comparators (ECD p. 8 ¶ 4.5): The ECD states that: "The company submission only included evidence comparing givosiran with best supportive care. This was different to the NICE scope, which specified haem arginate, GnRH analogues and liver transplant as comparators. […] The committee agreed that all treatment options currently used in NHS clinical practice should have been considered. It concluded that prophylactic haem arginate is the most appropriate comparator for this appraisal." The clinical experts at the committee meeting (13 May 2021) explained that there is no clear distinction between prophylactic haem arginate and haem arginate to treat an acute attack in people with recurrent severe attacks. Further, as outlined above (point 1), haem arginate was used in the clinical trial (ENVISION) to treat acute attacks if deemed necessary by the treating physician. The opinion of the clinical experts should be given more weight for this decision.	Comment noted. Following consultation, the company submitted an analysis against the committee's preferred comparator, prophylactic haem arginate. Based on the updated clinical and cost-effectiveness data submitted, the committee concluded, overall, that givosiran can be considered an appropriate use of NHS resources for highly specialised technologies. It therefore recommended givosiran as an option for treating AHP with severe recurrent attacks.
16	Consultee	[International Porphyria Patient Network (IPPN)]	The ECD on p. 11 ¶ 4.10 describes the quality-of-life results obtained by the EQ-5D-5L instrument in the ENVISION trial and states: "The committee noted that fewer attacks did not lead to improved health-related quality of life and considered this to be unexpected. It was aware that health-related quality of life is affected by many factors including chronic symptoms and psychological factors. It recalled that chronic symptoms may not reduce as quickly as the frequency of attacks and that 6 months might be too short to capture givosiran's full benefits." The EQ-5D-5L is not validated for acute porphyrias and its sensitivity for capturing disease characteristics and treatment effects in acute porphyria is not known. During the HST committee meeting for givorsiran held on 13 May 2021, the clinical and patient experts explained that the EQ-5D-5L instrument asks about the quality-of-life of the present day. The acute porphyrias however are characterised by intermittent symptoms. The HST committee in previous appraisal procedures accepted that the EQ-5D instrument is not suitable for capturing intermittent symptoms (e.g., HST13: volanesorsen for treating familial chylomicronaemia syndrome). In order to be consistent with previous appraisal procedures and to reflect the full discussion of the committee meeting, the inputs provided by the clinical and patient experts should be included in the paragraph describing quality-of-life in the ECD.	Comment noted. These points were considered by the Evaluation Committee when formulating its recommendations.

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17	Consultee	[International Porphyria Patient Network (IPPN)]	Comment: The ECD describes the company's model which contains 4 health states defined by the number of attacks in the last 12 months (p.11 ¶ 4.11): "The company's economic model compared givosiran with best supportive care. The Markov model contained 4 health states and 1 absorbing state (death). The health states were defined by the number of severe attacks (attacks needing hospitalisation, an urgent healthcare visit or intravenous haem arginate) in 12 months: - asymptomatic (0 attacks) - symptomatic (4 or less attacks) - recurrent (4 to 14 attacks) - severe (more than 24 attacks)." Therefore, people having 4 attacks per year can be either in the "symptomatic" or "recurrent" state which is ambiguous.	Comment noted. This was a typographical error which has been corrected in the FED (section 4.11). Health states used in the company's model were defined on the basis of frequency of attacks per year as follows: • asymptomatic (0 attacks) • symptomatic (4 or less attacks) • recurrent (5 to 24 attacks) • severe (more than 24 attacks).
18	Consultee	[International Porphyria Patient Network (IPPN)]	Comment: On p. 12 ¶ 4.12-4.13, the assumptions of the economic model are given. A 60-years time horizon is adopted, with a starting age of 42 years. Taken the starting age and the time horizon together, this would imply a very long life-time of 102 years.	Comment noted. The length of the model time horizon is intended to capture the full potential benefits and costs of treatment, and the model accounts for general population mortality during that timeframe.
19	Consultee	[International Porphyria Patient Network (IPPN)]	Comment on stopping the treatment and time on treatment (ECD p. 13-14 ¶ 4.16 and 4.17): In the Swiss experience (n=3 patients receiving givosiran), patients who do not experience a benefit decide to stop the treatment (Anna Minder MD, presentation Netzwerk Metabolik 20 October 2020). Therefore, no costs should be expected from people not sufficiently benefitting from the treatment.	Comment noted. During the first evaluation committee meeting, the committee heard from clinical experts that additional stopping criteria may be used. However, as the potential use of these criteria is currently unknown (e.g. the number of people who would stop treatment, when they would stop, the potential impact of stopping, and when they would restart), the committee did not feel it was able to consider the use of stopping rules in the economic model.
20	Consultee	[International Porphyria Patient Network (IPPN)]	Stakeholders of the appraisal proceeding had the opportunity to request access to the economic model produced by Alnylam Pharmaceuticals. However, the HST committee based their discussion on cost effectiveness of givosiran on "the ERG's approach of using utilities from relapsing–remitting multiple sclerosis as the best available proxy for the chronic symptoms." (ECD p. 14-15 ¶ 4.19). The stakeholder did not have access to the ERG's model.	NICE's processes of technology appraisals specifies that executable economic models used by companies in their submission will be made available (on request) to consultees and commentators who have signed a confidentiality agreement. The ERG's preferred model assumptions and changes to the company approach are explained within the ERG report.
21	Consultee	National Acute Porphyria Services at Cardiff and Vale	As clinical experts we are very disappointed that givosiran will not be available to treat patients with severe acute porphyria straight away. We have a small number of patients whose illness has progressed to a critical stage where haem arginate has limited benefit and the necessary central venous access can no longer be	Comment noted. Following consultation, the company submitted an analysis against the committee's preferred comparator, prophylactic haem arginate. Based on the updated clinical and cost-effectiveness

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		University Hospital and at King's College Hospital	maintained. It is highly likely that givosiran would be effective in these patients, but their disease is progressively worsening, and as a consequence we have had to restart referrals for liver transplantation. Our clinical experience, and that of porphyria specialists in Europe, is that givosiran is extremely effective in carefully selected and managed patients with severe acute porphyria and can transform the lives of these typically young patients. Givosiran is recognised by porphyria experts all over the world as a huge step change in the management of this small but very severely affected group of patients. All 5 UK patients currently being treated with givosiran stopped having attacks and stopped needing haem arginate within 6 months of starting the drug. They have now been on givosiran for between 3 and 4+ years with no loss of treatment efficacy. Chronic pain and fatigue had either disappeared or greatly improved within 12 months, with none of the patients currently requiring regular analgesia. 4 of the 5 patients are now in full time or part time employment having previously been unable to work. Givosiran is a far more effective treatment than haem arginate, with far fewer side effects. We understand that published evidence is limited given that givosiran is so new, and we encourage the committee to seek additional clinical opinion from experts in other countries where the drug is being used and experience is being rapidly gained (such as Sweden and France).	data submitted, the committee concluded, overall, that givosiran can be considered an appropriate use of NHS resources for highly specialised technologies. It therefore recommended givosiran as an option for treating AHP with severe recurrent attacks.
22	Consultee	National Acute Porphyria Services at Cardiff and Vale University Hospital and at King's College Hospital	The evaluation consultation document notes that there are 35 patents in the UK receiving treatment for recurrent acute attacks. We currently have only 27 patients (21 being managed with haem arginate infusions in various regimes, 6 on givosiran provided by the company through their post-trial Expanded Access Program, and none on gonadotrophin analogues). However it is wrong to assume that all 21 patients currently being managed with haem arginate would switch to givosiran. It is likely that those who have been stable on haem arginate, without an acute attack in the past 2-years, would stop this treatment to determine whether attacks recurred and if further therapy was needed. In addition, some patients may not want to change to givosiran for a variety of reasons.	Comment noted. The number of people currently receiving treatment for recurrent acute attacks has been updated within the FED to 27 (see section 2.2).
23	Consultee	National Acute Porphyria Services at Cardiff and Vale University Hospital and at King's College	Best supportive care for recurrent porphyria attacks is not "without haem arginate". It involves using haem arginate "on demand" as a reactive treatment for attacks, rather than giving it regularly to try to prevent attacks. However in practice the difference between these two approaches is blurred. Patients with severe recurrent attacks of porphyria have daily pain and other symptoms, and they typically need a haem arginate infusion every 6-10 days as treatment, which is very similar to the standard prophylactic regime of a regular haem arginate	Comment noted. These points were considered by the Evaluation Committee when formulating its recommendations.

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		Hospital	infusion every 7 days.	
24	Consultee	National Acute Porphyria Services at Cardiff and Vale University Hospital and at King's College Hospital	We would like to reiterate the limited effectiveness and acceptability of the current treatment options for this patient group: Gonadorelin analogues are not suitable for males and have limited efficacy in a minority of female patients in whom recurrent attacks are clearly premenstrual. This treatment effectively induces a chemical menopause in young women, with all of the attendant symptoms and complications. For these reasons it is rarely used in the UK, and not considered as an option in most other European countries. Liver transplantation has been used in a few patients when medical therapies are no longer effective or when acute attacks are associated with recurrent life threating complications. However this remains a treatment of last resort and is associated with a new set of health problems. Many patients also develop impaired renal function, which then requires a combined liver and kidney transplant with additional risks and complications. The committee is correct that the main management strategy for patients with severe recurrent attacks of porphyria is to administer haem arginate infusions regularly at a frequency of 1-4 infusions per month. However there is no evidence base for this treatment and it provides limited clinical benefit. Although prophylactic haem arginate has some effect on reducing attack frequency, patients remain very unwell. They continue to have disabling pain and other chronic symptoms, together with breakthrough attacks requiring extra haem arginate infusions and hospital admissions. These patients are highly dependent on haem arginate and also on maintaining central venous access. Delays in their regular treatment can result in life threatening attacks. In the past year, a young patient with acute intermittent porphyria whose infusion was delayed for two days had a very severe attack complicated by paralysis and respiratory arrest. This delay occurred because of difficulties with venous access, which is a particular problem associated with frequent haem arginate infusions.	Comment noted. These points were considered by the Evaluation Committee when formulating its recommendations. The potential impact of givosiran beyond direct health benefits and limitations of current treatment options is discussed with section 4.34 of the FED.
25	Consultee	National Acute Porphyria Services at Cardiff and Vale University Hospital and at King's College Hospital	Age at model entry: It seems unlikely that the majority of patients will need to continue givosiran until the menopause. Younger patients who start givosiran as soon as they are diagnosed with recurrent attacks have fewer chronic symptoms and co-morbidities and are expected to respond better than patients who switch to givosiran after being managed with haem arginate for many years. Experience from other European centres already using givosiran suggests that patients with a shorter duration of recurrency respond more quickly and completely to givosiran and do not relapse when the drug is stopped. In addition some patients can tolerate less than monthly dosing. Tachyphylaxis has not been seen in patients on givosiran, and if anything response improves over time, with gradually improving urine biochemistry (falling urine porphobilinogen concentrations) and fewer chronic	Comment noted. The points were considered by the Evaluation Committee when formulating its recommendations.

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			symptoms. All this suggests that patients who are started on givosiran early in the natural history of their disease are likely to need only short periods of treatment, perhaps for a few years.	

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology

Givosiran for treating acute hepatic porphyria [ID1549]

Company resubmission post-ECD

July 2021

File name	Version	Contains confidential information	Date
ID1549 Alnylam Givosiran HST Resubmission post-ECD v1.0.docx	**1.0**	**Yes**	**30 July 2021**

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1 Introduction

Alnylam wishes to express our gratitude to the HST Evaluation Committee and the ERG for their careful consideration of our company submission (CS) for givosiran for treating acute hepatic porphyria (AHP). Following our review of the ECD,[1] we have made substantive changes to our cost-effectiveness analysis (CEA) to address the Committee's requests. To facilitate comparisons for the Committee and the ERG, we have implemented these changes in the ERG's version of the cost-effectiveness model (*ID1549 givosiran ERG model 03022021CM from ERG.xlsm*).

In this resubmission document we describe only the revised methods and results arising from the changes we have implemented. Please refer to our original CS for an overview of the pathophysiology and disease burden of AHP, description of current clinical practice, details of relevant evidence sources, and documentation of aspects of the CEA that did not need to be modified for this resubmission.

The most prominent change in the revised CEA is that the model now compares givosiran with prophylactic haem arginate. In the original CS, the comparator was best supportive care (BSC), including haem arginate as rescue therapy to treat acute porphyria attacks. However, in the ECD the Committee concluded that hemin prophylaxis should be modelled as the comparator for this appraisal on the basis of the use of prophylactic haem arginate in NHS clinical practice for AHP patients with repeated porphyria attacks.[1] Details of how we have implemented this revision are reported in Section 2.1.

In addition, the revised base-case CEA generally adopts the Committee's preferred assumptions, as listed in Section 4.23 of the ECD,[1] on other aspects of the model unrelated to hemin prophylaxis. These assumptions include:

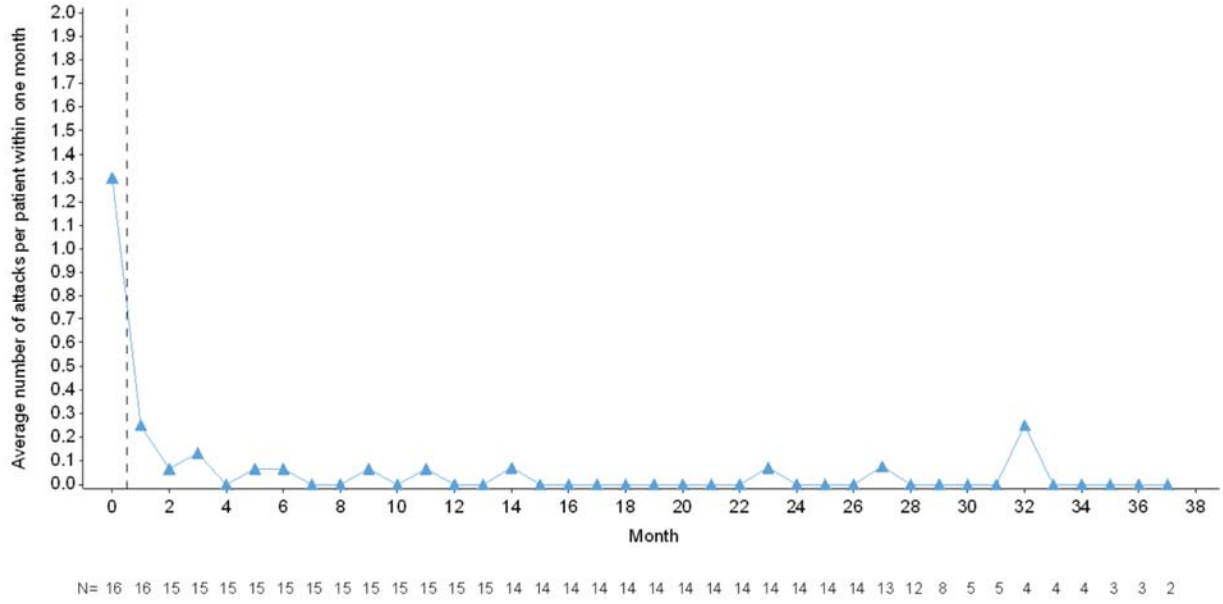
- Basing transitions in the BSC arm on data from the 6-month, double-blind period of the ENVISION phase 3 trial[2] for cycle 1 of the model, followed by freezing of BSC transitions thereafter
- Using a log-logistic model to extrapolate time on treatment (ToT) for givosiran
- Continuing treatment until menopause for most women and throughout the time horizon of the model for men and some women (see further details in Section 2.2)
- Including opioid dependency costs

Two of the Committee's preferred assumptions listed in the ECD have been approached differently in our revised base-case CEA. Based on the latest, currently available evidence from the ENVISION trial, we have extrapolated givosiran transitions out to 3 years (i.e., 36 months), instead of applying assumed efficacy for the first 18 months of data then freezing transition probabilities. The latest available data from the ENVISION study support continuing clinical improvement beyond the 18-month duration of observed transition data described in our original submission, confirming the continued efficacy of givosiran for at least 36 months of treatment (Figure 1A). Furthermore, the latest analysis of data from the phase 1/2 OLE supports this benefit over more than 3 years (Figure 1B).

Figure 1. Attack rate in (A) the ENVISION trial and OLE and (B) the phase 1 study and phase 1/2 OLE

A) ENVISION DB period and OLE

B) Phase 1 study and phase 1/2 OLE



Sources: Alnylam, ENVISION data on file; Phase 1/2 Study Clinical Study Report[3]
Note: Dashed line in (B) indicates the gap in time between phase 1 Part C baseline and the first visit in phase 1/2 OLE
DB: double-blind; Givo: givosiran; Pbo: placebo; OLE: open-label extension

Second, the base-case utilities for model health states in the revised CEA correspond to AHP symptoms reported in the long-term natural history study by Neeleman et al. (2018)[4] as previously described in the CS, rather than using proxy values for relapsing-remitting multiple sclerosis (RRMS) based on Hawton et al. (2016)[5] as proposed by the ERG and Committee. This decision was taken because the disease

processes and resulting symptoms differ greatly between AHP and RRMS, and thus using RRMS utilities cannot be expected to capture the health-related quality of life (HRQoL) burden of AHP, as explained in detail in Section 2.2. Therefore, we maintain it is most appropriate to use a utility estimation approach that is anchored in the established disease burden of AHP specifically, rather than relying wholly on RRMS utilities which may have questionable generalisability to AHP. Nevertheless, we have performed a scenario analysis using these RRMS proxy values (see Section 2.5).

In addition to the above revisions to the model, to address requests from the Committee and the ERG we have performed scenario analyses to explore how the starting age for treatment and the number of people stopping treatment at menopause affect cost-effectiveness (see Sections 2.3 and 2.4, respectively).

Finally, to address the question of the Committee regarding the source of some costs of chronic conditions included in the analysis, we performed an updated targeted literature search and updated the respective chronic conditions' costs in the model.

We hope that this resubmission with the revised model will adequately address the Committee's requests. We wish to note that this resubmission document contains confidential information that has been marked accordingly.

2 Revised CEA Methods

2.1 New base-case comparator: prophylactic haem arginate

2.1.1 Overview of hemin prophylaxis

The ECD notes that in NHS clinical practice haem arginate is used outside its marketing authorisation as prophylaxis against acute attacks.[1] This use underlies the Committee's request to model hemin prophylaxis as the comparator to givosiran.

Although Alnylam has made a good-faith effort to incorporate hemin prophylaxis in the revised CEA as requested, we must caution that a paucity of evidence precludes drawing reliable causal inferences about the clinical effects of hemin prophylaxis. In contrast to the high-quality randomised controlled trials (RCTs) supporting the efficacy and safety profile of givosiran,[2,6] all studies to date reporting data for hemin prophylaxis have been either uncontrolled[7] or observational.[4,8,9] Notably, none of these studies had as their first objective to assess the effectiveness of hemin prophylaxis; they were generally concerned with reporting the natural history of AHP and evaluating healthcare resource use. Also, the reported results are confounded by insurmountable issues such as incomplete chart records, recall bias, and selection bias. Reflecting these limitations, the ERG Report on our CS states that "following a review of the evidence for prophylactic IV heme, the ERG considered that the evidence base is of a very poor standard, and would be unlikely to demonstrate the true clinical effectiveness of treatment. As a consequence, the ERG did not consider that the inclusion of evidence for prophylactic IV heme would have been useful for decision-making."

An independent evidence review by Analysis Group confirmed that there are important differences between published studies in several aspects of hemin use, including variation in the regimens employed within patients over time and between patients, as well as multiple dosing frequency changes in many patients due to loss of efficacy (increased dosing), complications (decreased dosing), or discontinuation of hemin prophylaxis.[10] In addition, the evidence review noted that studies differ on whether hemin prophylaxis used Normosang® (haem arginate) or Panhematin® (lyophilised hematin), two different products for which bioequivalence has not been demonstrated in the context of either episodic or prophylactic use; their comparative efficacy has also not been studied.

Hemin was first used to treat patients with AHP more than four decades ago,[11] and it is noteworthy that no adequate evidence supporting hemin prophylaxis has emerged since then. Indeed, there has never been a formal prospective study of hemin prophylaxis. Panhematin is currently being investigated for the prevention of acute attacks of porphyria in a phase 2 RCT, but this trial is still in recruitment and final collection of data for the primary endpoint is not expected until September 2022.[12] Notably, this is a short-term (4-week), single-centre study with a planned enrolment of only 20. Recruitment has been proceeding for more than 5½ years but remains incomplete. Even if this small Panhematin prophylaxis study eventually yields results, it is unclear how relevant its results will be to Normosang, the brand of hemin available in the UK, because haem arginate in Normosang is a different compound from the hematin in Panhematin, as noted above. Therefore, the evidence for haem arginate prophylaxis is at best anecdotal and will remain so for the foreseeable future.

These evidence limitations were acknowledged by clinical experts at the National Acute Porphyria Service (NAPS) in the first Committee meeting, and provide part of the basis for the warning in the Normosang SmPC that haem arginate "should not be used as a preventive treatment since available data is too limited [our emphasis] and long term administration of regular infusions carries the risk of iron overload."[13]

While the clinical benefits of hemin prophylaxis are uncertain, its clinical limitations are well characterised. Beyond the risk noted in the SmPC of iron overload, which can cause chronic hepatic inflammation, these limitations include tachyphylaxis, dependency, and problems maintaining venous access because hemin is damaging to the vasculature.[8,14-18] In the first Committee meeting, NAPS expert Dr. Penny Stein explained the mechanism underlying the waning effectiveness of hemin prophylaxis over time, a characteristic that we have incorporated in the revised CEA. Studies in a mouse model of AHP and human liver samples demonstrated that regular hemin administration induces haem oxygenase 1 in the liver, leading to exacerbation of haem breakdown and increased expression of delta aminolaevulinic acid synthase 1 (ALAS1), which in turn promotes overproduction of the toxic intermediates aminolaevulinic acid (ALA) and porphobilinogen (PBG).[9] Because uncontrolled ALA and PBG levels drive both the acute and chronic aspects of AHP,[15,17,19] this research indicates that repeated administration of hemin actually promotes attack recurrence. Given its uncertain clinical benefits and established harms, prophylactic haem arginate should be considered to be a treatment of last resort in patients with no other options.

None of these limitations apply to givosiran, which shows sustained and increasing efficacy over time (Figure 1). Givosiran treats AHP by silencing expression of the messenger ribonucleic acid (RNA) for ALAS1, thereby reducing levels of ALA and PBG.[20,21] In contrast to the waning effectiveness of hemin prophylaxis, there is no basis to expect that direct silencing of the disease-causal mechanism by givosiran could wear off over time periods longer than the multi-year data currently available. In fact, durable action could be considered an established feature of RNA interference (RNAi) therapies like givosiran.[22-27]

2.1.2 Clinical evidence search

Alnylam has conducted exhaustive evidence searches to identify all relevant data on use of hemin in AHP patients, and is thus confident that no potentially relevant evidence has been overlooked. Efforts undertaken to capture data on hemin include the systematic literature review (SLR) and update conducted in accordance with NICE requirements for the CS, an in-depth analysis of the results of the SLR conducted by Analysis Group, and a targeted literature search performed for this resubmission to capture any new evidence that might have appeared since the SLR update in August 2020.

2.1.2.1 Systematic literature review

As described in detail in Sections 9.1–9.4 and Appendix 1 of the CS, the original SLR was run on 9 June 2019 and the update was conducted on 11–13 September 2020.[28,29] These searches employed keywords relating to AHP, including its subtypes. No articles were excluded on the basis of treatment, and therefore studies on hemin use in patients with AHP were captured. The 16 studies including hemin that were retrieved in these searches are shown in Table 1. Hemin was evaluated in 1 RCT,[30] 5 single-arm interventional studies,[7,31-34] and 10 observational studies.[4,8,9,11,35-40] Among the 16 studies identified, 11 considered hemin in the treatment of acute attacks only,[11,30-39] 2 assessed patients treated with hemin prophylaxis,[4,9] and 3 studies evaluated hemin in both acute attacks and as prophylaxis.[7,8,40] The only RCT for hemin that was identified was a small study (N=12) of treatment of acute attacks[30]; no RCTs of hemin prophylaxis were found. Hemin dosing frequencies were only reported in 4 of the 16 hemin studies.[2,7,8,40] These findings attest to the weak evidence base for hemin, especially when used for prophylaxis.

Table 1. List of included published studies on hemin from the CS SLRs

Primary study reference	Population	Intervention	Comparator
Hemin – acute treatment RCT			
Herrick et al. (1989)[30]	• Patients with AIP experiencing recurrent attacks (N=12) • Mean age: 31.4 years • Patients were randomised to either hemin or placebo during admission for an acute attack • 9 of the 12 patients received the alternate treatment upon readmission for subsequent acute attack	Hemin	Placebo

Primary study reference	Population	Intervention	Comparator
Hemin – acute treatment non-randomised studies			
Mustajoki and Nordmann (1993)[37]	• 24 emergency-admitted cases of AIP (n=22) and VP (n=2) • Mean age: 37.35 years (range: 21–67 years) • Previously diagnosed based on PBG≥5xULN, severe abdominal or non-abdominal pain with at least one other symptom	Hemin	None
Bissell (1988)[31]	• AIP established by quantitative assays of urine, faeces, and erythrocytes (N=8) • Mean age: 38.6 years (range: 22–66 years)	Hemin	None
Devars du Mayne et al. (1986)[32]	• Acute attack, clinical symptoms compatible with AIP (N=5) • Age not reported • Elevated ALA and PBG • Administered French hemin of equine origin or haem arginate	Hemin (2 types)	None
Lamon et al. (1977)[33]	• Clinical evidence of active disease (acute porphyria attack) with elevated ALA and PBG (N=7) • Age not reported	Hemin	None
Herrero et al. (2015)[35]	• Patients with acute attacks of AIP attending a hospital (N=35) • Mean age: 28 years (range:13–58 years) • Diagnosis made according to the criteria of the European Porphyria Initiative	Hemin	None
Hift et al. (2005)[36]	• Patients with AIP or VP admitted to hospital with a diagnosis of acute attack (N=25) • Median age at first attack: 27 years (range: 20–36)	Hemin	None
Nordmann et al. (1995)[34]	• Patients with acute attacks of AIP treated in hospital (N=70) • Age not reported	Hemin	None
Kostrewska et al. (1991)[38]	• Patients with acute attack of AHP treated in hospital (N=47) • Age: Women (range: 14–58 years) and Men (range 23–48 years)	Hemin	None
Mustajoki et al. (1986)[39]	• Patients with AIP or VP; acute attacks or in remission (N=14) • Age not reported	Hemin	None
Pierach et al. (1980)[11]	• Patients with acute attack of AHP (N=57). • Age not reported=57	Hemin	None
Hemin – prophylaxis non-randomised studies			
Gouya et al. (2020)[40] EXPLORE NCT02240784	• Observational, prospective study with up to 12 months of follow-up • N=112: prior hemin prophylaxis (n=52); No prior hemin prophylaxis (n=60)	Hemin	None
Schmitt et al. (2018)[9]	• Patients with symptomatic AIP (n=602) of whom 46 had recurrent disease and of which 27 received hemin prophylaxis • Mean age: 44 years (range: 27–66)	Hemin	None
Neeleman et al. (2018)[4]	• Patients with AIP (recurrent, n=11; symptomatic, n=24; asymptomatic AIP carriers, n=53). Hemin prophylaxis was assessed in the 11 patients with recurrent attacks. • Median age at onset in the 11 recurrent cases: 36 years (range: 16–56)	Hemin	None

Primary study reference	Population	Intervention	Comparator
Marsden et al. (2015)[8]	• Patients with acute porphyria who had started prophylactic haem arginate infusions between 1999 and 2012 (N=22) • Median age at start of prophylaxis: 28 years (range: 13–58)	Hemin	None
Hemin – acute treatment and prophylaxis non-randomised studies			
Anderson et al. (2006)[7]	• Patients with acute porphyria (AIP, VP, HCP, ADP) • Mean age: 40.3 years (SD:12.3) • Hemin prescribed for acute attacks (n=90) and for prophylaxis (n=40)	Hemin	None

ADP: aminolaevulinic acid dehydratase porphyria; AHP: acute hepatic porphyria; AIP: acute intermittent porphyria; ALA: aminolaevulinic acid; CS: company submission; HCP: hereditary coproporphyria; PBG: porphobilinogen; RCT: randomised controlled trial; SD: standard deviation; SLR: systematic literature review; VP: variegate porphyria

2.1.2.2 Analysis Group evidence review

In response to ERG's request to explain why haem arginate was not modelled as part of the comparator within the CEA in the original CS, Alnylam commissioned an assessment from Analysis Group to evaluate the feasibility of conducting a formal indirect treatment comparison (ITC) between givosiran and hemin prophylaxis.[10] Analysis Group reviewed in depth the 5 studies of AHP patients identified in the SLR in which some or all patients were treated with hemin prophylaxis. Aspects of these studies relevant to the question of comparing givosiran versus hemin prophylaxis are summarised in Section 2.1.3.

The conclusion of the Analysis Group feasibility assessment was that several important limitations prevented the conduct of valid and interpretable ITCs of givosiran versus hemin prophylaxis using any of these studies.[10] As quoted above, the ERG also arrived at the same conclusion. Nevertheless, in the absence of better evidence sources, we have used the totality of the studies considered by Analysis Group to attempt to construct a clinically plausible range of effectiveness for hemin prophylaxis so that we can address the Committee's request. Parameters for hemin prophylaxis effectiveness were drawn from the studies by Marsden et al. (2015),[8] Neeleman et al. (2018),[4] Anderson et al. (2006),[7] and Schmitt et al. (2018).[9] Hemin prophylaxis parameters were not derived from the EXPLORE natural history study[40] due to issues with under-reporting of attack frequency on study, as explained in the Analysis Group report.[10] However, the revised model uses the identical EXPLORE parameters as the original CEA for per-attack disutility and attack duration, which should not be impacted by under-reporting.

2.1.2.3 Hemin prophylaxis evidence update

To ensure that no new and potentially relevant data on hemin prophylaxis have been published since the SLR update, a targeted literature search was conducted on 2 July 2021. Search strategies and results of this targeted literature search are presented in the Excel file embedded in Appendix 1. Briefly, searches were performed in PubMed, Cochrane Central, the International HTA database (INAHTA), ClinicalTrials.gov, and the WHO International Clinical Trials Registry (ICTRP) using combinations of terms related to AHP and hemin. Databases were searched back to 1 August 2020 to ensure capture of any sources that may not yet have been indexed when the SLR update was performed in September 2020. As

documented in the Excel file, the targeted literature search identified no new relevant evidence on hemin prophylaxis.

2.1.3 Hemin prophylaxis evidence sources

2.1.3.1 Marsden et al. (2015)

Marsden et al. conducted a retrospective audit of records for 22 patients who started regular prophylactic haem arginate from 1999 to 2012.[8] Patients were identified from records of the NAPS centres in Cambridge, Cardiff, and London, outreach clinics in Leeds and Salford, and the suppliers of haem arginate in the UK.

The authors suggested that "initiating regular haem arginate coincided with clinical improvement in 50–70% patients," over median of 50 months' duration (range 1–150 months).[8] However, estimates of the reduction in number of attacks for these patients are hampered by several limitations. First, the collection of data on attacks was retrospective, and obtained through examination of patient records, supplemented by patient recall. There was very limited information available on important aspects of the extraction of data on attacks both from inpatient records and the collection based on patient recall. Attempts to corroborate data recalled by patients against other sources (e.g., patient records, caregiver recall), if any, were not reported.

Second, the definition of attack used in this study was not reported, though the NAPS clinical team (who were authors on the study) have informed Alnylam that the attacks reported by Marsden et al. appear very likely to be only those attacks requiring hospitalisation. This limitation is also indicated by the extremely close match between number of attacks and number of hospitalisations reported in this study,[8] suggesting that attacks may have been defined mainly via hospitalisations. As such, Marsden et al. (2015) may be missing attacks that would have been captured in the ENVISION trial, which included rigorously defined attacks that required hospitalisation, urgent healthcare visits, or intravenous (IV) hemin treatment at home in its composite annualised attack rate (AAR) primary endpoint.[2] This discrepancy in capturing attacks between Marsden et al. (2015) and ENVISION argues against using Marsden et al. as a primary estimate of AAR reduction with hemin prophylaxis for comparison with givosiran. Furthermore, data collection on attacks was gathered through medical records, which were also informed by patients' recall on the occurrence of attacks. Therefore, it cannot be determined with any certainty whether the reduction of attack frequency in some patients receiving hemin prophylaxis, as reported by Marsden et al., truly reflects effectiveness of the intervention or is due to inherent limitations in the method of data collection.

Additional limitations of Marsden et al. (2015) that confound calculation of AAR reduction include the wide variation between patients in the time duration considered before and during hemin prophylaxis, and the fact that several patients had missing data on number of attacks, hospital admissions, duration of the pre-prophylaxis period, and/or hemin doses to treat acute attacks.[8] There was also no standardisation of prophylactic regimens, with an extremely wide range of frequencies of dosing—from once to eight times per month.

Finally, it should be noted that the study period of 1999 to 2012 in Marsden et al. ended nearly a decade ago, so the results may not reflect current NHS clinical practice for this patient population.

All of the above limitations suggest that Marsden et al. (2015) cannot be used to derive reliable estimates of the magnitude of the AAR reduction expected with hemin prophylaxis. Nevertheless, this study remains the only UK-specific evidence source relevant to the effectiveness of prophylactic haem arginate. Therefore, we have incorporated in the revised CEA the authors' conclusion that 50%–70% of patients on hemin prophylaxis experienced clinical improvement, as explained in Section 2.1.4.2 below. However, we believe even this conclusion should be interpreted with caution in light of the significant study limitations described above.

2.1.3.2 Neeleman et al. (2018)

Neeleman et al. conducted a retrospective, longitudinal, observational cohort study that included all patients with acute intermittent porphyria (AIP; the most common form of AHP) who attended the Porphyria Centre in the Erasmus Centre in the Netherlands between 1960 and 2016.[4] A total of 88 patients were included in the study cohort, of whom 11 had recurrent disease, classified by Neeleman et al. as patients who had more than 4 attacks in any year or who were on prophylactic haem arginate therapy.

The collection of data in this study was based on retrospective extraction from patients' electronic and paper charts by two reviewers, and from self-reported questionnaires.[4] The definition of a confirmed acute porphyria attack used in this study was "an episode of abdominal pain in parallel with a significant rise in urinary ALA and PBG levels (≥4 times the upper limit of normal) which necessitated a verified visit or admission to a hospital for diagnosis and treatment." Based on these criteria, Neeleman et al. included both attacks treated in hospitals and attacks treated in medical visits, which is closer to the acute attack definition in ENVISION in comparison with the hospital-treated attacks that appear to comprise all attacks considered by Marsden et al. (2015).

All 11 of these recurrent patients were on hemin prophylaxis.[4] The authors reported that all 11 made attempts to be weaned off hemin prophylaxis, which triggered acute attacks in 9 patients. One patient was weaned off hemin by slowly reducing the amount over a period of 1 year, followed by a liver transplantation.

For these 11 patients, Neeleman et al. reported a 51.3% reduction in number of attacks with hemin prophylaxis, calculated based on an AAR of 2.28 before hemin prophylaxis and 1.11 during hemin prophylaxis.[4] However, given the responses described above to attempts to wean these patients off prophylactic treatment, this should be considered as the AAR reduction among only those patients benefitting from hemin prophylaxis, rather than the AAR reduction that would be seen in a larger population of responders and non-responders.

2.1.3.3 Anderson et al. (2006)

Anderson et al. performed an open-label study of Panhematin in the US.[7] Hemin was administered to 111 patients for treatment of 305 acute attacks and to 40 patients for prophylaxis. Results for hemin prophylaxis did not allow estimation of the average reduction in AAR. The authors reported, "Of the 31 patients who received prophylaxis for at least 1 month, 15 (48%) received hemin only for prophylaxis and thus presumably had no acute attacks during the study. An additional 6 patients had up to 3 treatments for acute

attacks, then began receiving prophylaxis and had no subsequent hemin treatments for acute attacks. Thus, prophylaxis may have successfully prevented attacks in 21 of 31 patients (68%)."

As Anderson et al. conceded, limitations of their study include the fact that diagnostic criteria were not established (biochemical confirmation of acute porphyria was recorded in only 10% of patients who received prophylaxis), clinical indications for acute versus prophylactic treatment were not specified, and information about duration of prophylactic treatment and the frequency of attacks before and during treatment was not recorded.

Although this study provided an estimate of the proportion of patients experiencing clinical improvement on hemin prophylaxis, the US patient population and use of Panhematin instead of Normosang make it less generalisable to the UK population than the audit by Marsden et al.

2.1.3.4 Schmitt et al. (2018)

In a case series, Schmitt et al. reported results of hemin prophylaxis for 46 patients with AIP identified as "recurrent", defined as ≥4 acute attacks for 1 or more years.[9] The authors noted that 18 of 32 patients still experiencing recurrent attacks were on hemin prophylaxis, but no estimate of average AAR reduction is possible from the data presented. Overall, this study is a weaker evidence source than the three considered above.

2.1.3.5 Summary

The preceding study synopses reveal that there is limited evidence on AAR reduction with hemin prophylaxis. To address the request from Committee, evidence from this literature was synthesised and assumptions were made to create a number of scenarios to estimate the impact of hemin prophylaxis on AAR reduction. Data were used from two of these studies: Marsden et al. (2015),[8] and Neeleman et al. (2018).[4] Key findings were discussed with Dr. Stein on 27 July 2021 to verify their clinical plausibility. See Section 2.1.4.2 for details on how these sources were used to derive effectiveness parameters for hemin prophylaxis in the revised CEA.

2.1.4 Implementation of AAR reduction with hemin prophylaxis in revised CEA

2.1.4.1 Modelling approach

To model prophylactic haem arginate as a comparator to givosiran, we adopted a threshold analysis approach constrained to hypothetical boundaries of hemin prophylaxis informed by the available evidence. The methods we used represent an advance over the suggestion raised in the Committee meeting to perform a threshold analysis.[41] A simple threshold analysis would calculate the hypothetical values of hemin prophylaxis effectiveness against which givosiran would be considered cost-effective at given willingness-to-pay thresholds. We gave this approach serious consideration because it avoids having to make *a priori* assumptions about the effectiveness of hemin prophylaxis, thus circumventing the paucity of data.

However, we concluded that a simple threshold analysis without any grounding in clinical reality would not be informative for decision-making. For example, Dr. Stein has suggested that an assumption of equal

effectiveness between hemin prophylaxis and givosiran would be unreasonable. Therefore, we performed a more tailored threshold analysis approach constrained to hypothetical boundaries of hemin prophylaxis (i.e., a higher and lower bound) which are informed by the available literature and clinical opinion. This presumed effectiveness was then applied against data for BSC, as observed in the placebo arm of the ENVISION study. This approach allowed us to take advantage of the high-quality data for the placebo group in ENVISION, the basis for the transition probabilities for the BSC arm in our previous CEA.

2.1.4.2 Clinical effectiveness parameters

Calculation of hemin prophylaxis effectiveness

Marsden et al. suggested that initiating hemin prophylaxis can lead to a clinical improvement in 50%–70% of patients. Dr. Stein informed us that she considered the 70% end of this range to be more probable than 50%, so we used the 70% estimate in the revised CEA. However, as noted in Section 2.1.3.1, Marsden et al. cannot be used to calculate reliably the degree of reduction in AAR associated with hemin prophylaxis.

To address this limitation in Marsden et al. (2015), the degree of AAR reduction in the revised CEA was informed by the study by Neeleman et al. (2018). Neeleman reported that before hemin prophylaxis there were 2.28 attacks per year, whereas during hemin prophylaxis there were 1.11 attacks per year, corresponding to an estimated AAR reduction of 51%. Use of this 51% estimate in the revised CEA should be regarded as highly conservative because Dr. Stein informed us that a 50% attack rate reduction would be an absolute best-case scenario for hemin prophylaxis over the long term.

Combining these data from Marsden et al. and Neeleman et al., we estimated in the base case an average total AAR percentage reduction of 36%, based on 70% who benefited multiplied by 51% AAR reduction, in the overall population after hemin prophylaxis treatment. This 36% assumed effectiveness should be regarded as an overestimate of the true clinical benefit of hemin prophylaxis because it relates solely to reduction in attack frequency without considering any other symptoms of AHP, such as chronic pain, neurological dysfunction, and psychiatric symptoms. Dr. Stein noted that virtually no patients become symptom-free on hemin prophylaxis; instead, patients typically continue to experience a high symptom burden. In other words, the upper estimate of 70% of patients benefitting refers solely to attack reduction, whereas the proportion of patients achieving both attack reduction and symptomatic improvement on hemin prophylaxis would be substantially lower. Notably, the model considers both attacks and chronic symptoms of AHP, so the base-case setting of 36% effectiveness for hemin prophylaxis (which incorporates 70% of patients benefitting) should be regarded as a conservative assumption.

To address the uncertainty surrounding the evidence base, we also performed a scenario analysis using the lower estimate by Marsden et al. of the proportion of patients benefitting, yielding an AAR reduction of 26% (i.e., 50% benefitting $\times$ 51% AAR reduction), as well as a scenario analysis in which it was assumed that 100% of a cohort on hemin prophylaxis would achieve the 51% AAR reduction reported by Neeleman et al. It is important to emphasise that we deem the latter scenario to be clinically implausible because it implies hemin prophylaxis effectiveness approaching that of givosiran, an assumption that conflicts with

clinical expert opinion. An additional scenario analysis with a 10% AAR reduction was assessed to model the minimum average incremental benefit vs BSC expected from hemin prophylaxis treatment, the assumption being that clinicians would be unlikely to prescribe hemin prophylaxis if this benefit were smaller than 10%.

Amortisation period of hemin prophylaxis effectiveness

When considering the AAR reduction that might be achieved with hemin prophylaxis it is necessary to consider the time period over which the effect of hemin prophylaxis is realised, a duration which we term the amortisation period. We defined the amortisation period as the time from initiation of hemin prophylaxis until its maximum effect, plus the duration of the plateau before waning occurs.

The amortisation period over which the effect is expected to be observed was tested under several scenarios, given that there is insufficient evidence to define a point estimate with certainty. The mean observation period in patients who had an improvement with hemin prophylaxis in the study by Marsden et al. was 6.5 years (with a median of 6 years). The duration of hemin prophylaxis in Neeleman et al. was 5.2 years on average (with a median of 4.2 years). Furthermore, Dr. Stein informed us that in her experience the effect of hemin prophylaxis would reach a maximum in the first year of treatment (which corresponds to cycles 1 and 2 in the model) and then plateau out to approximately 5 years before starting to wane. Thus, we considered that 4 to 7 years represents a reasonable range over which to simulate the amortisation period, and we selected 5 years for the base case.

However, to be conservative the revised model also considers the same effect periods over which the effect of givosiran can be applied in the model. Accordingly, we modelled the following six alternative scenarios for amortisation periods of hemin prophylaxis effect:

- 18 months
- 3 years
- 4 years
- 5 years (base-case scenario)
- 6 years
- 7 years

Hemin prophylaxis transition probabilities

As previously mentioned, estimation of transition probabilities for hemin prophylaxis in the revised CEA was anchored to BSC based on ENVISION. In order to simulate the effect of hemin prophylaxis in the current CEA, the model requires estimation of transition probabilities between Asymptomatic (AAR=0), Symptomatic (0<AAR≤4), Recurrent (4<AAR≤24), and Severe (AAR>24) health states. Hemin prophylaxis transition probabilities per cycle were estimated considering a percentage reduction in AAR after a period of time *t* of hemin prophylaxis use (amortisation of effect) vs the attack rate observed prior to hemin

prophylaxis treatment (i.e., on BSC). Simulating the effect of hemin prophylaxis in the model was performed according to the following steps:

1. A percentage reduction in AAR was applied to the AAR values observed in the placebo arm at month 6 of ENVISION double-blind period, at the patient level (n=44);
2. The resulting hemin prophylaxis patient-level AAR was used to define the distribution of the cohort between health states after hemin prophylaxis treatment;
3. The health-state distribution of patients after hemin prophylaxis treatment was compared with the distribution of placebo patients at baseline in ENVISION using shift tables. This approach allowed us to simulate the transition of the cohort between health states from before to after initiation of hemin prophylaxis. Table 2 to Table 5 below present the resulting shift tables from baseline health-state distributions to distributions following the total AAR reduction achieved with hemin prophylaxis, for each of the four AAR percentage-reduction scenarios.

Table 2. Number of patients transitioning between health states from baseline to time of achieving total AAR reduction with hemin prophylaxis: 10% relative reduction applied to BSC AAR

From / To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AAR: annualised attack rate; BSC: best supportive care

Table 3. Number of patients transitioning between health states from baseline to time of achieving total AAR reduction with hemin prophylaxis: 26% relative reduction applied to BSC AAR

From / To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AAR: annualised attack rate; BSC: best supportive care

Table 4. Number of patients transitioning between health states from baseline to time of achieving total AAR reduction with hemin prophylaxis: 36% relative reduction applied to BSC AAR

From / To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AAR: annualised attack rate; BSC: best supportive care

Table 5. Number of patients transitioning between health states from baseline to time of achieving total AAR reduction with hemin prophylaxis: 51% relative reduction applied to BSC AAR

From / To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AAR: annualised attack rate; BSC: best supportive care

4. The transition probabilities derived from the shift tables were adjusted to fit the 6-month cycle length in the model using the standard formula *1-(1-Prob)^(6 months/t in months),* where *t* represents the amortisation period over which the total effect of hemin prophylaxis is expected to be observed;
5. The cycle probabilities were applied in the model until the cycle corresponding to time *t*, at which the total effect of hemin prophylaxis is observed.

Simulation of waning effectiveness of hemin prophylaxis

Consistent with the tachyphylaxis effect that is a known limitation of hemin prophylaxis,[18,42] clinical expert input received by Alnylam indicates that the efficacy of prophylactic haem arginate will decline over time, such that the acute attack rate gradually increases. From the cycle after which the full effect of hemin prophylaxis is achieved (i.e., the end of the effect-amortisation period), the model considers the option to assume patients do not transition between health states unless they die (full maintenance of effect) or to assume that there is a waning of effect, whereby the effect achieved with hemin prophylaxis reverses towards the BSC AAR over time. The second option is aligned with evidence of an increase in AAR with long-term use of hemin prophylaxis.[9] The following scenarios were tested in the model since no robust evidence could be identified to establish reliable bounds on the hemin prophylaxis waning effect:

- No waning effect (the cohort remains in health-state at which full effect was achieved unless it dies);
- Reversal of effect over a 3-year period;
- Reversal of effect over the maximum length of the amortisation period assumed; i.e., 7 years;
- Reversal of effect over 23 years, which corresponds to the observation period over which Schmitt et al. (2018) reported an increase in recurrent AIP patients due to hemin prophylaxis use (i.e., from 1995 to 2008 per Figure 1 in this reference).[9]

In our July 27th discussion, Dr. Stein indicated that the effectiveness of hemin prophylaxis wanes gradually, taking on the order of 20 years to taper off. Accordingly, we selected the 23-year estimate based on Schmitt et al. (2018) in our base-case CEA.

The transition probabilities to simulate waning of effect are derived by comparing the health-state distribution after hemin prophylaxis treatment (derived as described above) with the health-state distribution of the BSC cohort considering the AAR seen in the placebo arm of ENVISION at 6 months (Table 6). The

per-cycle probabilities are estimated adjusting the total waning period probability into a cycle probability; i.e., the longer the waning period the smaller the probability. The probabilities of waning effect are applied in the model over the entire waning period and thereafter the cohort is assumed to remain stable unless it dies.

Table 6. Health-state distribution for BSC based on the placebo arm of ENVISION at 6 months

Health state	Number of BSC patients
Asymptomatic	[redacted]
Symptomatic	[redacted]
Recurrent	[redacted]
Severe	[redacted]
Total	[redacted]

BSC: best supportive care

2.1.4.3 HCRU and cost parameters

The acquisition cost of Normosang in the UK was used in the model to estimate the vial cost of haem arginate. According to the MIMS database, the pack price is £1,737 for 4 vials of 250 mg each (25 mg/ml). Thus, the price per 250-mg vial is £434.25. The recommended dose per administration is 3 mg/kg and the number of administrations per month varies greatly across patients. Accordingly, a weighted average frequency of administration was estimated based on the pattern reported by Marsden et al. (2015) (Table 7). The resulting average number of administrations per month is 3.45, corresponding to 20.7 administrations per 6-month model cycle.

Table 7. Administration frequency of hemin prophylaxis in Marsden et al. (2015)[8]

	Patients (N=22)	
Doses per month	n	%
1	4	18.2
2	3	13.6
3	0	0.0
4	13	59.1
5	0	0.0
6	1	4.5
7	0	0.0
8	1	4.5

If the administration frequency reported by Anderson et al. (2006)[7] were to be used instead, the average number of administration per 6-month model cycle would be 22.3. However, the similar frequency of 20.7 administrations per cycle based on the administration pattern reported by Marsden et al. (2015) was selected, given that this NAPS audit is more likely to be reflective of practice in the UK than the US study by Anderson et al.

An administration cost of £92.65 was added for each administration to represent 1 hospital physician consultation (£109/hour; PSSRU 2020) being applied to 85% of the cohort, assuming that 15% of the cohort would administer hemin prophylaxis at home (in line with the assumption for rescue hemin administration).

As a simplifying assumption, no discontinuation was modelled in the hemin prophylaxis arm due to the uncertainty of the time on treatment as well as of the effect post-discontinuation.

2.1.4.4 Adverse events and associated costs

The incidence of adverse events with hemin prophylaxis was based on the study by Anderson et al. (2006).[7] The incidence of adverse events reported over the 10-month follow-up period of this study was adjusted to fit the model cycle length of 6 months using the formula *1-(1-incidence)^(6 months/10 months)*. The resulting cycle probabilities applied to the cohort on treatment with hemin prophylaxis at each model cycle is reported in Table 8. Each adverse event was multiplied by a one-off cost as listed in Table 9.

Table 8. Per-cycle probabilities of adverse events associated with hemin prophylaxis treatment

Adverse event	Probability
Headache	0.023
Nausea	0.037
Pyrexia	0.028
Phlebitis/injection-site phlebitis	0.028
Vomiting	0.019
Catheter-related complications	0.014
Pain	0.014
Convulsion	0.000
Rash	0.014
Pharyngitis	0.000
Diarrhoea	0.014
Adverse drug reaction	0.014
Cellulitis	0.009
Dizziness	0.005
All others	0.115

Source: Anderson et al. (2006)[7]

Table 9. Unit costs for treatment of hemin prophylaxis-related adverse events

Adverse event	Unit cost (£)*	Source
Headache	109.00	PSSRU 2020, Unit Costs of Health and Social Care 2019†
Nausea	109.00	PSSRU 2020, Unit Costs of Health and Social Care 2019†
Pyrexia	298.34	Vouk et al. (2016)[43]
Phlebitis/injection-site phlebitis	788.89	National Schedule of NHS Costs - Year 2018-19
Vomiting	180.45	Vouk et al. (2016)[43]
Catheter-related complications	788.89	National Schedule of NHS Costs - Year 2018-19
Pain	109.00	PSSRU 2020, Unit Costs of Health and Social Care 2019†
Convulsion	298.34	Vouk et al. (2016)[43]
Rash	361.91	Vouk et al. (2016)[43]

Adverse event	Unit cost (£)*	Source
Pharyngitis	109.00	PSSRU 2020, Unit Costs of Health and Social Care 2019†
Diarrhoea	329.18	Vouk et al. (2016)[43]
Adverse drug reaction	109.00	PSSRU 2020, Unit Costs of Health and Social Care 2019†
Cellulitis	109.00	PSSRU 2020, Unit Costs of Health and Social Care 2019†
Dizziness	109.00	PSSRU 2020, Unit Costs of Health and Social Care 2019†
All others	243.29	Average of all other events

*Inflated to 2021 price level
†Assuming 1 visit by the physician

2.2 Additional revised base-case analysis settings

In the revised base-case CEA, model parameters are as shown in Table 10. Notable changes from the model that was submitted in the original CS are the new parameters for hemin prophylaxis, as well as the reduction of extrapolation of givosiran efficacy from 5 years in the CS to 3 years, addressing the concern about extrapolating beyond the duration of observed data. In addition, the cost for chronic conditions associated with AHP has been updated following a targeted literature search conducted in June 2021, as described below. Finally, the [redacted]% PAS discount off the list price of givosiran, which Alnylam previously proposed, has been applied in all scenarios of the revised CEA.

Table 10. Model parameters in the base-case analysis

Parameter	Setting
Health-state definition	
Asymptomatic	AAR=0
Symptomatic	0<AAR≤4
Recurrent	4<AAR≤24
Severe	AAR>24
Discount rate on costs and outcomes	3.5%
Perspective	NHS and PSS
Age at start, weight, and % female	Based on ENVISION EU population
Time horizon	Lifetime
Cycle length	6 months
Efficacy	
Givosiran	Cycle 1 from ENVISION DB, cycle 2 and 3 from OLE (data up to 18 months), recycle of last observed probabilities up to year 3, then freeze
BSC	Cycle 1 from ENVISION DB, then freeze
Hemin prophylaxis	36% total AAR reduction vs BSC with effect amortisation period of 5 years. Waning of effect period, 23 years.
Mortality of attacks	0%
Location of attack treatment	80% hospitalisation, 5% urgent healthcare visit and 15% hemin at home as per NAPS consultation
Hospitalisation LOS	Assumed equal to attack duration
Estimated average cost per attack	Weighted average per attack treatment location

Parameter	Setting
Cost of chronic conditions	From updated target literature search conducted in June 2021, see description below
Chronic conditions considered	Pain, neurological and psychiatric symptoms based on Neeleman et al. 2018. Severe=recurrent (long-terms complications are not included)
Opioid addiction cost	Included
Patient HRQoL	Disutility of attack from EXPLORE + health-state utilities based on utility decrements by condition combined using the multiplicative approach (adjusted by decreasing utility of the general population)
Caregiver disutility	Included based on mapping of AHP severity vs multiple sclerosis severity
Mortality of chronic conditions	Baravelli et al. 2020[44] (HR of 1.3 applied to all health states)
Price per vial of givosiran	£[redacted] (after [redacted]% PAS discount off the list price of £41,884.43)
Cost of givosiran treatment	No vial sharing, average weight of ENVISION EU population, RDI
Price per vial of hemin (Normosang)	£434.25
Cost of hemin prophylaxis	3 mg/kg per admin, 20.7 admin per cycle based on average of reported doses per month in Marsden et al. (2015)[8] and multiplied by cycle length, no vial sharing, average weight of ENVISION EU population
Givosiran and BSC AEs	As per ENVISION
Hemin prophylaxis AEs	As reported in Anderson et al. (2006)[7]
Hemin prophylaxis administration	Assuming 15% administer prophylaxis treatment at home and 85% in a hospital setting
Givosiran treatment discontinuation	Based on Log-logistic parametric extrapolation from ENVISION KM data
Hemin prophylaxis discontinuation	Not included
Effect post-discontinuation	Set equal to BSC for any subsequent cycle post-discontinuation
Menopause stopping rule	All Asymptomatic women at menopause onset stop treatment and remain Asymptomatic
Menopause onset	Probability of menopause onset based on distribution of age at menopause from Greer et al. (2003)[45]

AAR: annualised attack rate; AE: adverse event; AHP: acute hepatic porphyria; BSC: best supportive care; DB: double-blind period; HR: hazard ratio; KM: Kaplan–Meier; LOS: length of stay; NAPS: National Acute Porphyria Service; OLE: open-label extension; RDI: relative dose intensity

Parameters that remain the same as before include the base-case starting age, which is still set at 41.6 years, corresponding to the age of the EU patients in ENVISION at baseline. Following consultation with Dr. Stein, it was agreed that this previous approach remains valid. Alnylam understands that in future, after the commencement of the current cohort on treatment, additional new patients entering the treated population may be of varying age, potentially including younger, incident (i.e., newly diagnosed) patients in addition to older patients who have had AHP for many years. It is, therefore, not possible to predict exactly how the age distribution of the cohort may change over time. First, there is uncertainty on whether incident

patients will indeed be younger than the current cohort. As Dr. Stein described in Committee, there is substantial variation in symptom onset and timing of diagnosis of patients; for example, one newly identified patient was in their 40s. Therefore, it is not a given that the age of the AHP cohort in the UK will trend towards being younger in the future.

Second, even if there is a disproportionate accrual of younger patients relative to older patients, any reduction in average age will remain gradual, given the low incidence of AHP overall, and the even more infrequent addition to the target population of patients meeting the NAPS definition of "recurrent severe" AHP. In the most robust epidemiologic study of porphyria to date, Elder et al. (2013) estimated an incidence rate in the UK of 0.16 AIP patients per million.[46] This would imply that approximately 10 AIP patients are diagnosed each year in the UK, of whom only 5%[46]—in other words, at most 1 patient—would be expected to be recurrent. Additionally, Elder et al. reported a median age at diagnosis of 33 years. Therefore, even assuming that every incident patient was of this age (which we know is not true, as explained above), mean age would be expected to decrease by only 0.24 years for every 1 incident patient added to the current estimated population of 35 eligible patients.

Finally, it is difficult to predict the average age of these patients 20 or even just 5 years from now since the age of all prevalent patients increases each year and thus the average age would be expected to increase; however, this trend is complicated by the "removal" of female patients who reach menopause and stop therapy as well as patients who die. Importantly, even if the mean age reaches a "steady state" at some future time point, the age range is likely to remain wide.

Calculation of disutilities associated with chronic conditions of AHP is still calculated as in the original CS rather than using proxy values for RRMS as preferred by the Committee and ERG. From a caregiver perspective, disutility in AHP is driven primarily by the cared-for patient's level of functional impairment[47] and thus bears important similarities to caregiver disutility in multiple sclerosis (MS), which is characterised by increasing patient dependence on the caregiver for support with activities of daily living (ADL), and with a growing need for care at home, as the patient's degree of disability increases.[48,49] Because functional impairment drives caregiver burden in both AHP and MS, it was appropriate for us to use caregiver disutility at different severity stages of MS as a proxy for caregiver disutility in the different AHP health states. In our model, we based caregiver disutility on HRQoL data reported in the MS study by Acaster et al. 2013.[50] Note that the MS severity staging system used in this study, PDSS, is exclusively based on patient mobility and ability to perform ADL,[50] which makes it a suitable system for identifying caregiver disutility.

In contrast, from a patient perspective, qualitative research with AHP patients suggests that the main drivers of HRQoL impairment are chronic conditions such as chronic pain, neurologic symptoms, and psychiatric symptoms.[51] Disutilities of different AHP health states are unlikely to be similar to disutility of patients in given RRMS stages because the chronic symptoms of AHP are substantially different from those in RRMS, as would be predicted given the completely dissimilar pathophysiology underlying the two diseases: overproduction of toxic haem precursors[52] vs demyelination,[53] respectively. For example, chronic

abdominal pain is extremely common in AHP, ranging in prevalence from 28% among Asymptomatic patients up to 90.9% in patients with Recurrent AHP as reported by Neeleman et al.,[4] whereas a study of pain among MS patients found that only 2% suffered from chronic abdominal pain.[54]

The ERG's stated rationale for preferring to use RRMS utilities is as follows: "The ERG considered that utility values from RRMS patients may be considered a reasonable proxy for AHP, on the basis that the condition is chronic and progressive in nature and patients have the potential to relapse/experience recurrence (though further clinical opinion is necessary to support this assumption)." Alnylam considers that this rationale is inadequate to justify selection of RRMS as a proxy for AHP in terms of patient utility values because there are many chronic, progressive diseases with the potential for relapse and recurrence other than RRMS, such as chronic migraine,[55] schizophrenia,[56] and rheumatoid arthritis.[57]

Thus, Alnylam disagrees on first principles with using utilities in RRMS instead of the approach we used in the submitted model, which is tailored to the precise symptoms documented for AHP by Neeleman et al.[4] Alnylam knows of no clinical expert opinion to support the contention that patient HRQoL valuations in AHP and RRMS are substantially similar. Due to the completely different disease processes and resulting symptoms in AHP and RRMS, using RRMS utilities cannot be expected to capture the HRQoL burden of on AHP patients. Nevertheless, we have explored using RRMS utilities in a scenario analysis (see Section 2.5).

To ensure the most relevant costs would be captured for the revised CEA, a targeted literature search was conducted in June 2021 to identify studies (not restricted to AHP patients) reporting cost data for the chronic conditions included in the analysis. The search was performed in PubMed using the following terms: "cost" OR "economic burden" OR "cost study" OR "resource use" AND name of each condition [see Table 11 for list] AND (United Kingdom). The cost search was limited to studies conducted in the UK, published in the last 15 years, and prioritised studies conducted in adults (older than 18 years). For all searches, primary research and the most recent studies were prioritized for retrieval. Results of this search are presented in Table 11.

Table 11. Costs of chronic conditions in the revised CEA

Chronic condition	Annual costs (£)*	Source	Notes
Chronic pain			
Headaches	539.14	McCrone 2011[58]	117 GBP per over 3 months. The cost was multiplied by 4 to obtain the annual cost.
Chest pain	3,752.67	Ghosh 2012[59]	Total annual direct cost of 6,797 Euros. The cost was converted from Euros to GBP at the conversion rate of reference year.
Back pain	1,282.03	Hong 2013[60]	Annual direct costs for low back pain on the UK NHS. Indirect costs not included.
Abdominal pain	1,282.03	Soubieres 2015[61]	Average direct costs for both inpatients and outpatients with constipation, change in bowel habit or abdominal pain

Chronic condition	Annual costs (£)*	Source	Notes
Upper extremities pain	1,282.03	Kigozi 2019[62]	Assumed the same as lower extremities pain
Lower extremities pain	1,282.03	Kigozi 2019[62]	The mean NHS costs per patient in primary care for referred leg pain group
Genitalia pain	1,282.03	Soubieres 2015[61]	Assumed the same as abdominal pain
Neurological			
Paraesthesias	136.28	Gauthier 2009[63]	Combining the costs of outpatient and in-patient care
Motor weakness	3,136.33	Pinedo-Villanueva 2019[64]	Mean yearly total costs for participants with muscle weakness excluding informal care
Paralysis	11,349.75	Landfeldt 2014[65]	Mean per patient annual direct medical cost. Transformed from US dollars to GBP at 2012 rate.
Urinary incontinence	887.47	Speakman 2015[66]	Included medical visits, urologist visits, tests, medication and surgery. Transformed from Euro to GBP at 2003 rate.
Advanced neuropathy	3,556.47	Moore 2019[67]	Stage 4 disease
Psychiatric			
Anxiety	697.81	McCrone 2008[68]	
Depression	1,786.39	McCrone 2008[68]	
Psychosis/Hallucinations	13,178.30	McCrone 2008[68]	
Insomnia	697.81	McCrone 2008[68]	
Suicidality	1,888.42	Knapp 2011[69]	

*2021 price level

2.3 New scenario analysis: alternative treatment starting age

To assess the influence on model results of cohort starting age, a scenario analysis was performed in which starting age was set at 37 years. This is similar to (though still younger than) the lower bound of the 95% confidence interval for age at baseline in the ENVISION EU population, as used in the model's one-way sensitivity analysis: 37.9 years (Alnylam, ENVISION data on file). Notably, this is also younger than the median age at baseline in the EXPLORE natural history study (38 years).[40] Thus, the concordance of evidence from ENVISION and EXPLORE supports 37 years being the lowest plausible starting age for a prevalent cohort of these patients.

2.4 New scenario analysis: alternative menopause assumption

To address the question of whether all Asymptomatic female patients would discontinue treatment upon menopause onset, a scenario analysis was performed in which the percentage of the Asymptomatic female cohort discontinuing post-menopause was reduced by 10% (i.e., 90% of these patients went off treatment).

2.5 ERG-preferred scenario analyses

Four additional scenario analyses were performed to explore ERG-preferred assumptions:

- Menopause onset: as an alternative to the probabilistic setting based on Greer et al. (2003),[45] a scenario analysis was performed using a normal distribution fitting the mean and SD age of menopause observed in the UK Women's Cohort Study (50.5 ± 3.86 y; N=914).[70]
- Givosiran ToT: as an alternative to the log-logistic function to model givosiran ToT, a scenario analysis was performed via a piecewise method proposed by the ERG, using values from the Kaplan–Meier (KM) curve for observed data followed by the log-logistic function to extrapolate beyond the observed data.
- Opioid addiction costs: while the Committee agreed to inclusion of opioid addiction costs, it concluded that these should be explored using alternative cost sources. As no suitable alternative cost sources were identified, we performed a scenario analysis in which opioid addiction costs were excluded.
- Health-state utilities: to explore the ERG and Committee's preferred source of health-state utilities, we used proxy utilities derived from Expanded Disability Status Scale (EDSS) Stages for RRMS as reported by Hawton et al. (2016):[5]
  - Asymptomatic: 0.763 (from EDSS Stage 1)
  - Symptomatic: 0.719 (from EDSS Stage 2)
  - Recurrent: 0.596 (from EDSS Stage 3)
  - Severe: 0.438 (from EDSS Stage 4)

3 Results

3.1 Base-case analysis

As described above, the base-case analysis incorporated a 36% AAR reduction for prophylactic haem arginate vs BSC, a hemin prophylaxis effect amortisation period of 5 years, and a waning effect period of 23 years. The resulting lifetime costs, life-years (LYs), and QALYs in the NHS/PSS direct medical perspective are presented in Table 12. Givosiran yielded a substantial increase in discounted QALYs of 8.76 vs hemin prophylaxis and 9.26 vs BSC. Discounted costs for givosiran were approximately [redacted] higher than for hemin prophylaxis and [redacted] higher than for BSC.

Table 12. Base-case effectiveness and cost results

Technology	LYs	Disc LYs	QALYs	Disc QALYs	Costs (£)	Disc Costs (£)
Givosiran	39.63	21.33	24.26	13.32	[redacted]	[redacted]
Hemin prophylaxis	39.63	21.33	7.83	4.55	[redacted]	[redacted]
BSC	39.63	21.33	7.07	4.05	[redacted]	[redacted]
Difference, givosiran vs.						
Hemin prophylaxis	0.00	0.00	16.43	8.76	[redacted]	[redacted]
BSC	0.00	0.00	17.18	9.26	[redacted]	[redacted]

BSC: best supportive care; Disc: discounted; ICER: incremental cost-effectiveness ratio; LY: life-year; QALY: quality-adjusted life-year

Table 13 presents the resulting incremental cost-effectiveness ratios (ICERs) in terms of cost per life-year gained and per QALY gained for givosiran compared with hemin prophylaxis and BSC. The discounted ICER for givosiran vs hemin prophylaxis was £[redacted]/QALY, which was 14% higher than the ICER for givosiran vs BSC (£[redacted]/QALY).

Table 13. Base-case cost-effectiveness results

	Undiscounted		Discounted	
ICER	Cost/LY	Cost/QALY	Cost/LY	Cost/QALY
Givosiran vs. hemin prophylaxis	NA	[redacted]	NA	[redacted]
Givosiran vs. BSC	NA	[redacted]	NA	[redacted]

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life-year; NA: not applicable; QALY: quality-adjusted life-year

Proportion of the model cohorts in each health state over time

Figure 2 presents the health-state distributions of the model cohorts over time in the givosiran, hemin prophylaxis, and BSC arms. The model predicts that most patients receiving givosiran rapidly move to the Asymptomatic health state (within 5 years) and remain Asymptomatic until death. In the hemin prophylaxis arm, the model predicts that over time most patients are in the Recurrent health state until death, with a decrease from baseline until year 5 in the proportion of patients in the Severe health state accompanied by an increase in the proportion in the other three health states, after which the proportion in the Severe health state increases. Patients on BSC remain within the health states they were in upon freezing of their transitions following cycle 1 (based on the 6-month double-blind period in ENVISION), until death.

Figure 2. Health-state distributions of the patient cohorts over time (Markov traces)

BSC: best supportive care

Disaggregated QALYs by health state

The QALYs accrued in the different health states are summarised in Table 14. Givosiran yielded an approximately three-fold higher number of QALYs than either hemin prophylaxis or BSC, and 98% of QALYs for givosiran were accrued in the Asymptomatic health state, compared with 43% and 48% for hemin prophylaxis and BSC, respectively.

Table 14. Distribution of QALYs in the patient cohorts across health states

QALYs	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Undiscounted					
Givosiran	23.86	0.34	0.07	-0.01	24.26
Hemin prophylaxis	3.34	2.15	2.43	-0.10	7.83
BSC	3.41	1.62	2.08	-0.04	7.07
Difference, givosiran vs.					
Hemin prophylaxis	20.51	-1.82	-2.36	0.09	16.43
BSC	20.44	-1.29	-2.01	0.03	17.18
Discounted					
Givosiran	12.99	0.25	0.07	0.00	13.3
Hemin prophylaxis	1.76	1.32	1.49	-0.01	4.55
BSC	1.88	0.91	1.22	0.04	4.05
Difference, givosiran vs.					
Hemin prophylaxis	11.23	-1.07	-1.42	0.01	8.76
BSC	11.11	-0.66	-1.15	-0.04	9.26

BSC: best supportive care; QALY: quality-adjusted life-year

Disaggregated costs by category of cost

Overall costs per patient in the givosiran, hemin prophylaxis, and BSC arms disaggregated by category of cost are shown in Table 15. The majority of costs were attributable to drug acquisition cost for givosiran; in contrast, acute attack treatment was the main cost component for hemin prophylaxis and BSC. Acute attack treatment costs were an order of magnitude higher for hemin prophylaxis and BSC than for givosiran.

Table 15. Summary of costs per patient by category of cost

Costs (£)	Drug	Admin	Chronic symptoms	Attacks	AEs	Opioid addiction	EOL	Total
Undiscounted								
Givosiran	[redacted]	3,973	[redacted]	[redacted]	149	1,791	5,198	[redacted]
Hemin prophylaxis	[redacted]	138,369	[redacted]	[redacted]	6,739	33,205	5,198	[redacted]
BSC	[redacted]	0	[redacted]	[redacted]	171	34,691	5,198	[redacted]
Difference, givosiran vs.								
Hemin prophylaxis	[redacted]	-134,396	[redacted]	[redacted]	-6,590	-31,414	0	[redacted]
BSC	[redacted]	3,973	[redacted]	[redacted]	-22	-32,901	0	[redacted]
Discounted								
Givosiran	[redacted]	3,163	[redacted]	[redacted]	112	1,186	1,493	[redacted]
Hemin prophylaxis	[redacted]	75,807	[redacted]	[redacted]	3,692	17,665	1,493	[redacted]
BSC	[redacted]	0	[redacted]	[redacted]	94	18,663	1,493	[redacted]
Difference, givosiran vs.								
Hemin prophylaxis	[redacted]	-72,644	[redacted]	[redacted]	-3,580	-16,479	0	[redacted]
BSC	[redacted]	3,163	[redacted]	[redacted]	18	-17,477	0	[redacted]

Admin: administration; AE: adverse event; BSC: best supportive care; EOL: end of life

Disaggregated costs by health state

Costs disaggregated by health state are presented in Table 16. Costs were primarily accrued in the Asymptomatic health state for givosiran, but in the Recurrent and Severe health states for hemin prophylaxis and BSC.

Table 16. Summary of costs per patient by health state

Costs (£)	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Undiscounted					
Givosiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hemin prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference, givosiran vs.					
Hemin prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discounted					
Givosiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hemin prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference, givosiran vs.					
Hemin prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care

3.2 Threshold analyses

3.2.1 Two-way threshold analysis: AAR reduction × amortisation period

A two-way threshold analysis was performed to explore the impact on the ICER of varying AAR reduction and amortisation period for hemin prophylaxis, holding waning of effect for hemin prophylaxis fixed at the base-case value of 23 years. As shown in Table 17 and Figure 3, the ICER for givosiran vs hemin prophylaxis increased with increasing AAR reduction for hemin prophylaxis and with lengthening duration of amortisation of hemin prophylaxis effectiveness. The ICER ranged from £[redacted]/QALY for a 10% AAR reduction amortised over 18 months to £[redacted]/QALY for a 51% AAR reduction amortised over 7 years.

Table 17. ICERs (£/QALY) for givosiran vs hemin prophylaxis in two-way threshold analysis

Amortisation of effect	Hemin prophylaxis AAR reduction (total effect) vs BSC			
	10%	26%	36%	51%
18 months	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]
4 years	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]
6 years	[redacted]	[redacted]	[redacted]	[redacted]
7 years	[redacted]	[redacted]	[redacted]	[redacted]

Figure 3. Results of two-way threshold analysis, givosiran vs hemin prophylaxis

AAR: annualised attack rate; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year
Note: assumes 23-year waning effect for hemin prophylaxis effectiveness

3.2.2 Three-way threshold analysis: AAR reduction × amortisation period × waning effectiveness

A three-way threshold analysis was performed to explore the impact on the ICER of varying AAR reduction, amortisation period, and waning of effect for hemin prophylaxis. As shown in Table 18 and Figure 4, for any combination of AAR reduction × amortisation period, the ICER was highest with no waning of hemin prophylaxis effectiveness and intermediate with 23-year waning per Schmitt et al. (2018)[9]; the ICER was similar for waning over 3 years or 7 years (the same duration as the base-case effect amortisation period). The ICER ranged from [redacted]/QALY for a 10% AAR reduction amortised over 18 months with waning over 3 years to [redacted]/QALY for a 51% AAR reduction amortised over 18 months with no waning of hemin prophylaxis effectiveness.

Table 18. ICERs (£/QALY) for givosiran vs hemin prophylaxis in three-way threshold analysis

Hemin prophylaxis AAR reduction vs BSC	Amortisation of effect	Waning of effect (time from when total effect is reached)			
		No waning of effect	3 years	7 years (maximum effect amortisation period)	23 years (Schmitt et al. 2018[9])
10%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]

Hemin prophylaxis AAR reduction vs BSC	Amortisation of effect	Waning of effect (time from when total effect is reached)			
		No waning of effect	3 years	7 years (maximum effect amortisation period)	23 years (Schmitt et al. 2018[9])
26%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]
36%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]
51%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]

AAR: annualised attack rate; BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

Figure 4. Results of three-way threshold analysis

[redacted]

AAR: annualised attack rate; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

3.3 Scenario analyses

As shown in Table 19, of the six scenario analyses performed for this resubmission, the largest change compared with the base-case scenario was seen with the scenario in which starting age was set at 37 years, which resulted in a 34% increase in the ICER for givosiran vs hemin prophylaxis. The ICER for givosiran vs hemin prophylaxis increased by approximately 10% relative to the base case for both alternative menopause scenarios, and by approximately 12% when using RRMS utility values. The ICER was insensitive to using the piecewise method to model givosiran ToT, and to the exclusion of opioid addiction costs.

Table 19. Results of scenario analyses

Scenario	Givosiran vs hemin prophylaxis		Givosiran vs BSC	
	ICER (£/QALY)	% change	ICER (£/QALY)	% change
Base case	[redacted]	–	[redacted]	–
Starting age = 37 years	[redacted]	34.0%	[redacted]	39.4%
10% Asymptomatic women continue treatment after menopause onset	[redacted]	9.4%	[redacted]	10.3%
Time of menopause: normal distribution fitting average age of menopause onset in UK (UK Women's Cohort Study[70])	[redacted]	9.5%	[redacted]	10.4%
ToT givosiran: Piecewise, KM + log-logistic	[redacted]	0.04%	[redacted]	0.04%
Opioid addiction costs excluded	[redacted]	1.4%	[redacted]	1.6%
Health-state utilities based on RRMS proxy values (Hawton et al. 2016[5])	[redacted]	11.6%	[redacted]	3.2%

ICER: incremental cost-effectiveness ratio; KM: Kaplan–Meier; QALY: quality-adjusted life-year; RRMS: relapsing-remitting multiple sclerosis; ToT: time on treatment

4 Conclusions

The revised analyses presented here represent Alnylam's effort to address the uncertainties raised by the Committee and ERG. In view of the inadequate evidence base for haem arginate prophylaxis, we believe the approach we have taken to evaluate givosiran versus this comparator is the only available option that may be helpful to inform the Committee's decision-making. We have modelled the effectiveness of hemin prophylaxis based on our review of the totality of the available evidence, guided by the expert opinion of Dr. Penny Stein, as summarised in Table 20. A key point is that expert opinion does not support the effectiveness of hemin potentially being higher than the maximum 51% scenario we modelled, or being close to the effectiveness of givosiran.

Table 20. Summary of hemin prophylaxis effectiveness settings

Parameter	Base case	Additional scenarios	Source(s)	Clinical expert input*
Effectiveness (AAR reduction vs BSC, %)	36	10, 26, 51	Proportion of patients experiencing clinical improvement from Marsden et al. (2015)[8] × AAR reduction from Neeleman et al. (2018)[4]	50% AAR reduction is absolute best-case scenario for hemin prophylaxis
Amortisation period (years)	5	1.5, 3, 4, 6, 7	Marsden et al. (2015)[8] Neeleman et al. (2018)[4]	Maximum effect of hemin prophylaxis in first year, plateauing to ~5 years before waning
Waning of effectiveness (years)	23	3, 7, no waning	Schmitt et al. (2018)[9]	Hemin prophylaxis effectiveness takes ~20 years to taper off

AAR: annualised attack rate; BSC: best supportive care
*Dr. Penny Stein, 27 July 2021

In the revised base-case analysis, the ICER for givosiran vs hemin prophylaxis was £[redacted]/QALY, which was not substantially different from the ICER for givosiran vs BSC in the original submission.

ICERs in the threshold analyses varied over a relatively narrow range, from £[redacted]/QALY to £[redacted]/QALY, indicating that under clinically plausible conditions givosiran is predicted to offer clinical benefit over hemin prophylaxis at an incremental cost that should be regarded as acceptable for a disease-modifying therapy in this target population with high unmet medical need.

Our revised analyses also address the Committee's request to explore the sensitivity of the model to key parameters. Model results were relatively sensitive to cohort starting age, but it is expected that it will be many years before the age distribution of patients starting givosiran might shift substantially below the base-case value in the CEA, due to the low incidence of AHP and the facts that only a small proportion of incident patients will have "recurrent severe" disease according to the NAPS definition and not all patients who are newly treated will be younger. Model results changed only on the order of 10% with alternative menopause assumptions, and were relatively insensitive to the use of utilities for RRMS instead of our base-case approach.

Taking the clinical and pharmacoeconomic considerations into account, it is most likely that hemin prophylaxis should not be regarded as a viable treatment option now that givosiran is available. Nevertheless, we hope that by modelling hemin prophylaxis to the best of our ability we have provided the Committee with the basis to render an informed decision on givosiran.

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6 Appendix 1

Excel file with July 2021 targeted literature search:

132 ALN Givo Hemin Prophylaxis in AHP TL

London, 13 August 2021

Acute hepatic porphyria - givosiran [ID1549]: ENVISION 36-month data update

Jasdeep Hayre
Associate Director, Technology Appraisals
National Institute for Health and Care Excellence

Dear Jasdeep,

Further to our submission on 30 July of the revised cost-effectiveness model (CEM) for Givlaari® (givosiran) for the treatment of acute hepatic porphyria (AHP), we are providing NICE with this concise update on the preliminary end-of-study data from the pivotal phase 3 trial, ENVISION, capturing results from the trial's open-label extension (OLE) out to 36 months. In their report, the ERG noted, "Longer term clinical data, for example from more recent data cuts of the ENVISION OLE, would address uncertainty surrounding the extrapolation of givosiran and BSC treatment effect over time." We hope that this data summary will be helpful to the ERG and the Committee in their appraisal of the revised CEM.

1. Introduction

Alnylam wishes to provide the HST Committee and ERG with the most up-to-date evidence available from the ENVISION trial. Database lock for final, 36-month ENVISION OLE data occurred on 30 July 2021. However, due to ongoing data processing, individual patient data (IPD) for these late-breaking data are not yet available for incorporation in the CEM or to share with NICE. Full finalisation and quality control of all outputs are underway with an expected completion date of 20 September 2021.

Nevertheless, preliminary graphs and tables summarising the 36-month data most relevant to the CEM have been prepared and are being shared here in the interest of transparency and to support the key model assumption of sustained and continued givosiran efficacy through 3 years.

2. Efficacy data

2.1. Acute attack rate

As presented in our resubmission document, the ENVISION primary composite endpoint of annualised attack rate (AAR) continued to decline out to final 36-month follow-up (Figure 1 and Table 1). These results confirm the sustained and continuing improvement in acute attack status in patients receiving givosiran across 3 years of follow-up. It is apparent from these data that AAR is trending towards complete cessation of attacks in patients on givosiran, with no signal of waning efficacy.

Figure 1. Attack rate in the ENVISION trial and OLE from baseline to Month 36

Source: Alnylam, ENVISION data on file
DB: double-blind; Givo: givosiran; Pbo: placebo; OLE: open-label extension

Table 1. Summary of attack rate in the ENVISION trial and OLE at baseline and Months 6, 18, and 36

AAR	Placebo/Givosiran (N=46)	Givosiran/Givosiran (N=48)	All Givosiran (N=94)
Historical			
Median (Q1, Q3)*	7.0 (4.0, 14.0)	8.0 (4.0, 18.0)	8.0 (4.0, 16.0)
Mean (SD)*	10.7 (9.2)	12.1 (9.0)	11.4 (9.1)
Month 6 (DB period)			
n	46	48	48
Median (Q1, Q3)*	10.65 (2.24, 25.93)	1.04 (0, 6.35)	1.04 (0, 6.35)
Mean (95% CI)†	12.26 (9.22, 16.29)	3.35 (2.37, 4.74)	3.35 (2.37, 4.74)
Month 18 (OLE)			
n	45‡	48	93‡
Median (Q1, Q3)*	1.62 (0, 2.94)	0.58 (0, 3.24)	0.72 (0, 3.13)
Mean (SEM)§	2.44 (0.49)	2.54 (0.62)	2.50 (0.42)
Month 36 (OLE)			
n	[redacted]	[redacted]	[redacted]
Median (Q1, Q3)*	[redacted]	[redacted]	[redacted]
Mean (SEM)§	[redacted]	[redacted]	[redacted]

Sources: Alnylam, ENVISION Clinical Study Report 2[1]; Alnylam, ENVISION data on file
AAR: annualised attack rate; CI: confidence interval; DB: double-blind; OLE: open-label extension; Q1, Q3: interquartile range; SD: standard deviation; SEM: standard error of mean
Note: Placebo/givosiran includes patients receiving placebo in the DB period and givosiran in the OLE period. In the placebo/givosiran group, AAR in the DB period is calculated from study baseline to Month 6, and AARs in the OLE period are calculated using data only post-givosiran treatment from Month 6 (i.e., Day 1 of receiving givosiran in the OLE) to

Month 18 or Month 36. Givosiran/givosiran includes patients receiving givosiran in the DB and OLE periods. In the givosiran/givosiran group, AARs in the DB and OLE periods are calculated from study baseline (i.e., Day 1 of receiving givosiran in the DB period) to Months 6, 18, or 36.
*Calculated from the individual patient's AAR.
†Derived using the negative binomial regression model with treatment group and stratification factors (prior hemin prophylaxis status and historical attack rates) as fixed effects, and the logarithm of the follow-up time as an offset variable.
‡One patient whose follow-up duration after taking givosiran was <85 days was excluded from the analysis.
§Duration-weighted mean AAR is presented. Standard error of the mean is calculated using Cochran's formula (1977).

2.2. Levels of toxic haem precursors

As described in our original Company Submission (CS), uncontrolled levels of the toxic haem intermediates aminolaevulinic acid (ALA) and porphobilinogen (PBG) drive both the acute and chronic aspects of AHP.[2-4] The latest available data from the ENVISION OLE demonstrate that ALA and PBG levels remained suppressed in patients receiving givosiran out to final 36-month follow-up (Figure 2).

Figure 2. Median urinary (A) ALA and (B) PBG levels in the ENVISION trial and OLE from baseline to Month 36

A) ALA

B) PBG

Source: Alnylam, ENVISION data on file
ALA: aminolaevulinic acid; DB: double-blind; Givo: givosiran; PBG: porphobilinogen; Pbo: placebo; OLE: open-label extension

These findings confirm the durability of ribonucleic acid interference (RNAi) with givosiran, connecting the mechanism of action of givosiran with the observed reduction in AAR and providing the basis for expecting corresponding improvements in chronic symptoms of AHP over time periods longer than the duration of currently available data. As explained in our resubmission document, givosiran treats AHP by silencing expression of the messenger RNA for delta aminolaevulinic acid synthase 1 (ALAS1), thereby reducing levels of ALA and PBG.[5,6] There is no basis to expect that direct silencing of the disease-causal mechanism by givosiran could wear off over time periods longer than the multi-year data currently available—indeed, durable action could be considered an established feature of RNAi therapies like givosiran.[7-12] Synthesis of both ALA and PBG depends on ALAS1,[13] and there are no known alternative biochemical pathways for synthesis of these toxic intermediates that could allow their levels to evade the controlling effect of givosiran. Across the ENVISION trial and OLE, only [redacted] of the 94 patients developed treatment-emergent anti-drug antibodies, which were transient and had no impact on the pharmacokinetics, pharmacodynamics, efficacy or safety of givosiran.[1] Thus, no waning of effectiveness of givosiran over time is anticipated.

In contrast, regular hemin administration induces haem oxygenase 1 in the liver, leading to exacerbation of haem breakdown and increased expression of ALAS1, which in turn promotes overproduction of the toxic intermediates ALA and PBG.[14] Thus repeated administration of hemin as with haem arginate prophylaxis leads to waning effectiveness over time, and may actually promote attack recurrence.

3. Safety data

Adverse events (AEs) reported through to Month 36 of the ENVISION OLE were generally consistent with those up to Month 18 as previously presented in the CS (Table 2, Table 3). By 36 months, [redacted] patients discontinued treatment due to AEs considered related to study drug.

Table 2. Overall summary of AEs in the ENVISION trial and OLE from baseline to Month 36

N (%) patients with ≥1:	Placebo/Givosiran (N=46, PY=[redacted])	Givosiran/Givosiran (N=48, PY=[redacted])	All Givosiran (N=94, PY=[redacted])
AE	[redacted]	[redacted]	[redacted]
Study drug–related AE	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]
Study drug–related SAE	[redacted]	[redacted]	[redacted]
Severe AE	[redacted]	[redacted]	[redacted]
Study drug–related severe AE	[redacted]	[redacted]	[redacted]
AE leading to discontinuation	[redacted]	[redacted]	[redacted]
Study drug–related AE leading to discontinuation	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]

Source: Alnylam, ENVISION data on file
AE: adverse event; OLE: open-label extension; PY: patient-year; SAE: serious adverse event

Table 3. AEs reported in ≥10% of patients in the ENVISION trial and OLE from baseline to Month 36

	Patients, n (%)		
AE	Placebo/Givosiran (N=46, PY=[redacted])	Givosiran/Givosiran (N=48, PY=[redacted])	All Givosiran (N=94, PY=[redacted])
Nausea	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Source: Alnylam, ENVISION data on file
AE: adverse event; OLE: open-label extension; PY: patient-year; URTI: upper respiratory tract infection

Serious AEs (SAEs) reported in ≥2 patients up to Month 36 of the ENVISION OLE are presented in Table 4. [redacted]

[redacted]

Table 4. SAEs reported in ≥2 patients in the ENVISION trial and OLE from baseline to Month 36

SAE	Patients, n (%)		
	Placebo/Givosiran (N=46, PY=[redacted])	Givosiran/Givosiran (N=48, PY=[redacted])	All Givosiran (N=94, PY=[redacted])
≥1	[redacted]	[redacted]	[redacted]
Chronic kidney disease	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Source: Alnylam, ENVISION data on file
OLE: open-label extension; PY: patient-year; SAE: serious adverse event

[redacted]

4. Conclusions

The summary of preliminary end-of-study data from ENVISION presented above confirm that continuing givosiran treatment to 36 months yielded further improvements in efficacy compared with the 18-month data incorporated in the CEM. These results support the extrapolation of health-state transitions in the givosiran arm of the CEM out to 3 years.

In addition, givosiran continued to demonstrate an acceptable safety profile with ongoing treatment. AE-related discontinuations continued to be rare up to Month 36, supporting the favourable tolerability profile of givosiran.

Overall, the 36-month data from the ENVISION OLE increase confidence in the revised CEM we have submitted, and in the favourable benefit/risk profile of givosiran in the target patient population.

Alnylam would be pleased to answer any questions that NICE may have about these data. We wish to note that this document contains data not previously disclosed that will require redaction, as indicated by academic-in-confidence highlighting.

Kind regards,
Patrick Barry
Associate Director Market Access Europe/Canada/MEA (CEMEA)

5. References

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Givosiran for treating acute hepatic porphyria [ID1549]

Consultation on the evaluation consultation document – deadline for comments 5pm on Friday 2 July 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Evaluation Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example 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 provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The British Porphyria Association
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Best supportive care**: ECD (p3) 'Clinical trial evidence shows that givosiran reduces the frequency of attacks compared with best supportive care without haem arginate'. We are concerned that there remains a level of confusion over what best supportive care means, and would like to take this opportunity to reiterate that best supportive care **does** include haem arginate. This is essential because if porphyria attacks are not treated with haem arginate, they can well become fatal. There is a very fine line between haem arginate used reactively to treat attacks ("best supportive care") and haem used "prophylactically" to try to prevent attacks. The practice in the UK is to minimise the amount of haem arginate given in prophylactic treatment, so the haem is given just before attacks are expected, rather than just after the attacks have started. In order to be reassured that the committee has fully captured this understanding, we illustrate an example of typical best supportive care during the trial run-in period. Patient A • Haem prophylaxis prior to trial: **receives haem at days 7, 14, 21 and 28** in an attempt to reduce the frequency and severity of attacks. Patient has frequent/continual pain, but escalations into full blown attacks that require multiple haem doses are avoided some of the time. • Best supportive care during trial run-in period (no haem prophylaxis): during the first 10 days, the patient manages without any haem, although pain starts to increase slowly from day 6. By day 10 it is evident that they are in a full-blown attack and require three doses of haem to treat the attack. This is repeated later in the month: patient **receives haem at days 10, 11, 12, then 23 and 24.**
2	**Long-term data:** ECD (p3) 'It is uncertain how effective givosiran is in the long term'. In the UK and internationally, numerous patients have received givosiran on the open label extension for 3+ and 4+ years and for some of these patients, their conditions are continuing to improve. Phase 1 / 2 Part C open label extension may provide useful data here. If this is not sufficient, what does NICE mean by long term? What time frame would NICE be looking at to answer any uncertainties here?
3	**Age at model entry** ECD (p15): The ECD reveals some level of confusion between the age of diagnosis of acute porphyria (often in a patient's 20s) and the age at which recurrent attacks are more likely to start (more often in a patient's 30s and 40s). Therefore, although anyone newly diagnosed might become eligible to receive givosiran if they started recurrent attacks, this is unlikely to be until their 30s or 40s. Dr Eliane Sardh from Sweden presented data on 15 Swedish patients at the British and Irish Porphyria Network (BIPNET) symposium on 14 June 2021, which detailed the Swedish experience as being similar to the UK experience, and commented on 2 patients who had recently started having recurrent attacks.
4	**Stopping treatment / Time on treatment** ECD (p13): An important factor that we would like to expand upon, to ensure the NICE committee have a full understanding, is that if a patient starts givosiran soon after a pattern of recurrent attacks commences, effect of the givosiran on biochemistry and symptoms is rapid. International research is suggesting that treatment may be able to be stopped, or a treatment break offered, after a short period of treatment with givosiran.

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	This is in contrast to those who have had established recurrent attacks for many years and may require a longer spell of treatment before the biochemistry reduces to nearer normal levels – even if attack symptoms stop rapidly. These patients might need longer periods of treatment. The French and Swedish experiences may offer a wider perspective of this aspect.
5	**Quality of life** The ECD highlights that quality of life data from the ENVISION trial does not fully capture the profound impact that acute porphyria has on quality of life, nor does it demonstrate the immense changes that givosiran can make to patients. Standard instruments fail to reveal the enormity of the benefit arising from treatment with givosiran. In the absence of strong data, and with the utilities from relapsing-remitting multiple sclerosis having some similarities, but also a number of differences with acute porphyria, the BPA would like to re-draw the committee's attention to the following sources of information on quality of life: • An article relating to quality of life, which was initially submitted as academic in confidence, but is now peer reviewed and published: Gill, L., Burrell, S., Chamberlayne, J. *et al.* Patient and caregiver experiences of living with acute hepatic porphyria in the UK: a mixed-methods study. *Orphanet J Rare Dis* **16,** 187 (2021). https://doi.org/10.1186/s13023-021-01816-2 • Qualitative testimonials from patients experiencing recurrent attacks (as submitted with the BPA submission). Three of the seven patients were able to directly compare life on haem arginate and life on treatment with givosiran. Haem arginate has been noted by patients to be an effective treatment that stops them from dying, but it does not provide the immense improvements to every aspect of a patient's life that givosiran does.
6	**Additional expertise** It would be valuable to invite either Dr Eliane Sardh from Sweden, or Dr Laurent Gouya from France to the subsequent evaluation committee meetings. Both are expert porphyria consultants, who are each managing 20 or more patients on Givosiran through the Envision open label extension, or the Early Access Program. Their experience of givosiran on patients would be valuable to the discussion. See, for example comments in 3 and 4 above.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Global Porphyria Advocacy Coalition (GPAC)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

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Comment number	Comments
1	GPAC were disappointed to hear the recommendation of 'minded not to recommend' givosiran as an option for the treatment of acute hepatic porphyria patients. GPAC really feel there is an unmet need for those seriously affected by AHP and hope the questions identified can be addressed in a constructive and timely manner in order to make this treatment available to the small number of patients that are in great and urgent need.
2	GPAC has worked with the British Porphyria Association and fully supports the information provided in their ECD response form for all points they have made, including: - Best supportive care - Long-term data - Age at model entry - Stopping treatment/time on treatment - Quality of life
3	**Additional international clinical expertise:** GPAC would encourage further input from other international clinicians who have seen larger numbers of patients and for a longer-term. Their insight will further corroborate the experiences presented by the UK clinician expertise. Specifically, Professor Eliane Sardh from the Porphyria Centre, Karolinska University Hospital, Stockholm, Sweden and Professor Laurent Gouya from the Centre Français des Porphyries CRMR – Porphyries in Paris, France. Professor Sardh has treated a large number of patients for over 4 years from the Phase 1/2 Part C givosiran trials, the open label extension and through the early access program. Professor Gouya was heavily involved in the trials and is also currently treating more than 20 patients in France in a flexible manner. Their input should be sought as it would be invaluable in providing more data and insight into 'long-term data', 'age at model entry', 'stopping treatment/time on treatment' and 'quality of life'.

Insert extra rows as needed

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- If you have received agreement from NICE to submit additional evidence with your comments on the evaluation consultation document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**International Porphyria Patient Network (IPPN)**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[The IPPN has no direct or indirect links to, or is and was funded from, the tobacco industry]
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The Evaluation consultation document (ECD) on page 3 ¶ 1.2 states: "Clinical trial evidence shows that givosiran reduces the frequency of attacks compared with best supportive care without haem arginate." This statement is inaccurate. The protocol for the ENVISION trial required the patients "to discontinue or not initiate prophylactic hemin during the trial" but that during the trial "Investigators treated attacks according to the local standard of care, which could include intravenous administration of hemin." (Balwani et al. 2020, NEJM, DOI: 10.1056/NEJMoa1913147)
2	On ECD page 4¶ 2.2, the prevalence of AHP is given as 1 in 100,000 people in Europe. Current publications estimate the prevalence of acute intermittent porphyria which is the most frequent form of AHP in Europe to be 1 in 1,700: "The prevalence of mutations among patients with acute intermittent porphyria (the most common subtype of acute hepatic porphyria) is approximately 1 in 1700 in Western countries, [9,10] although disease penetrance is low, with less than 10% of patients ever having disease symptoms develop.[1]" (Sardh et al. 2019, NEJM DOI: 10.1056/NEJMoa1807838) The ECD should either correct the number or specify that the reported prevalence refers to symptomatic AHP.
3	Inconsistent information: On page 4 ¶ 2.2, the ECD states that there are currently 35 patients with acute porphyria having treatment for recurrent acute attacks in the UK. The presentation that was shown at the committee meeting 1 (13 May 2021, document: ID1540 givosiran part 1 slides to PM for public [redacted], p. 3) states that "currently 26 people are treated for recurrent attacks in the UK".
4	Pricing remains opaque: On page 5 ¶ 3 of the ECD, the price of givosiran is given as 41,884.43 GBP per 189-mg vial, with a recommended dose of 2.5 mg per kg body weight once a month. However, the paragraph also states that the company has a commercial arrangement, i.e., a simple discount patient access scheme. This means that the actual price is not accessible to the stakeholders or the public, which prevents these stakeholder groups form providing meaningful feedback regarding the cost effectiveness.
5	The implications of the current treatment options are not comprehensively discussed: On page 7 ¶ 4.2, the clinical experts explained that liver transplant is performed when haem arginate is no longer an option. While a liver transplantation cures AHP, it is connected to accompanying lifelong adverse consequences, symptoms of different nature and health risks. We miss the discussion on the fact that givosiran could prevent these adverse effects in people with AHP while at the same time saving valuable donor organs for other groups of patients.
6	Experience with givosiran in the clinical practice: On page 7-8 ¶4.4, the ECD describes the experience with givosiran in the clinical practice. The description in our opinion does not capture the full benefit as detailed by the clinical and patient experts, i.e., the degree of freedom from acute attacks and other insights provided at the committee meeting on 13 May 2021 and in the submissions of the patient organisations.

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	Side note: The presentation that was shown at the committee meeting 1 (13 May 2021, document: ID1540 givosiran part 1 slides to PM for public [redacted], p. 10) on the patient and carer organisation submissions states that submission were received from 2 organisations – the British Porphyria Association (BPA), Global Advocacy Coalition (GPAC). As a clarification, the International Porphyria Patient Network (IPPN) and the BPA made a joint submission, with the IPPN forgoing an own submission but supporting the BPA's.
7	Comment on comparators (ECD p. 8 ¶ 4.5): The ECD states that: "The company submission only included evidence comparing givosiran with best supportive care. This was different to the NICE scope, which specified haem arginate, GnRH analogues and liver transplant as comparators. […] The committee agreed that all treatment options currently used in NHS clinical practice should have been considered. It concluded that prophylactic haem arginate is the most appropriate comparator for this appraisal." The clinical experts at the committee meeting (13 May 2021) explained that there is no clear distinction between prophylactic haem arginate and haem arginate to treat an acute attack in people with recurrent severe attacks. Further, as outlined above (point 1), haem arginate was used in the clinical trial (ENVISION) to treat acute attacks if deemed necessary by the treating physician. The opinion of the clinical experts should be given more weight for this decision.
8	The ECD on p. 11 ¶ 4.10 describes the quality-of-life results obtained by the EQ-5D-5L instrument in the ENVISION trial and states: "The committee noted that fewer attacks did not lead to improved health-related quality of life and considered this to be unexpected. It was aware that health-related quality of life is affected by many factors including chronic symptoms and psychological factors. It recalled that chronic symptoms may not reduce as quickly as the frequency of attacks and that 6 months might be too short to capture givosiran's full benefits." The EQ-5D-5L is not validated for acute porphyrias and its sensitivity for capturing disease characteristics and treatment effects in acute porphyria is not known. During the HST committee meeting for givorsiran held on 13 May 2021, the clinical and patient experts explained that the EQ-5D-5L instrument asks about the quality-of-life of the present day. The acute porphyrias however are characterised by intermittent symptoms. The HST committee in previous appraisal procedures accepted that the EQ-5D instrument is not suitable for capturing intermittent symptoms (e.g., HST13: volanesorsen for treating familial chylomicronaemia syndrome). In order to be consistent with previous appraisal procedures and to reflect the full discussion of the committee meeting, the inputs provided by the clinical and patient experts should be included in the paragraph describing quality-of-life in the ECD.
9	Comment: The ECD describes the company's model which contains 4 health states defined by the number of attacks in the last 12 months (p.11 ¶ 4.11): "The company's economic model compared givosiran with best supportive care. The Markov model contained 4 health states and 1 absorbing state (death). The health states were defined by the number of severe attacks (attacks needing hospitalisation, an urgent healthcare visit or intravenous haem arginate) in 12 months: - asymptomatic (0 attacks) - symptomatic (4 or less attacks) - recurrent (4 to 14 attacks) - severe (more than 24 attacks)."

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	Therefore, people having 4 attacks per year can be either in the “symptomatic” or “recurrent” state which is ambiguous.
10	Comment: On p. 12 ¶ 4.12-4.13, the assumptions of the economic model are given. A 60-years time horizon is adopted, with a starting age of 42 years. Taken the starting age and the time horizon together, this would imply a very long life-time of 102 years.
11	Comment on stopping the treatment and time on treatment (ECD p. 13-14 ¶ 4.16 and 4.17): In the Swiss experience (n=3 patients receiving givosiran), patients who do not experience a benefit decide to stop the treatment (Anna Minder MD, presentation Netzwerk Metabolik 20 October 2020). Therefore, no costs should be expected from people not sufficiently benefitting from the treatment.
12	Stakeholders of the appraisal proceeding had the opportunity to request access to the economic model produced by Alnylam Pharmaceuticals. However, the HST committee based their discussion on cost effectiveness of givosiran on “the ERG’s approach of using utilities from relapsing–remitting multiple sclerosis as the best available proxy for the chronic symptoms.” (ECD p. 14-15 ¶ 4.19). The stakeholder did not have access to the ERG’s model.

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**National Acute Porphyria Services at Cardiff and Vale University Hospital and at King's College Hospital**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	As clinical experts we are very disappointed that givosiran will not be available to treat patients with severe acute porphyria straight away. We have a small number of patients whose illness has progressed to a critical stage where haem arginate has limited benefit and the necessary central venous access can no longer be maintained. It is highly likely that givosiran would be effective in these patients, but their disease is progressively worsening, and as a consequence we have had to restart referrals for liver transplantation. Our clinical experience, and that of porphyria specialists in Europe, is that givosiran is extremely effective in carefully selected and managed patients with severe acute porphyria and can transform the lives of these typically young patients. Givosiran is recognised by porphyria experts all over the world as a huge step change in the management of this small but very severely affected group of patients. All 5 UK patients currently being treated with givosiran stopped having attacks and stopped needing haem arginate within 6 months of starting the drug. They have now been on givosiran for between 3 and 4+ years with no loss of treatment efficacy. Chronic pain and fatigue had either disappeared or greatly improved within 12 months, with none of the patients currently requiring regular analgesia. 4 of the 5 patients are now in full time or part time employment having previously been unable to work. Givosiran is a far more effective treatment than haem arginate, with far fewer side effects. We understand that published evidence is limited given that givosiran is so new, and we encourage the committee to seek additional clinical opinion from experts in other countries where the drug is being used and experience is being rapidly gained (such as Sweden and France).
2	The evaluation consultation document notes that there are 35 patents in the UK receiving treatment for recurrent acute attacks. We currently have only 27 patients (21 being managed with haem arginate infusions in various regimes, 6 on givosiran provided by the company through their post-trial Expanded Access Program, and none on gonadotrophin analogues). However it is wrong to assume that all 21 patients currently being managed with haem arginate would switch to givosiran. It is likely that those who have been stable on haem arginate, without an acute attack in the past 2-years, would stop this treatment to determine whether attacks recurred and if further therapy was needed. In addition, some patients may not want to change to givosiran for a variety of reasons.
3	Best supportive care for recurrent porphyria attacks is not “without haem arginate”. It involves using haem arginate “on demand” as a reactive treatment for attacks, rather than giving it regularly to try to prevent attacks. However in practice the difference between these two approaches is blurred. Patients with severe recurrent attacks of porphyria have daily pain and other symptoms, and they typically need a haem arginate infusion every 6-10 days as treatment, which is very similar to the standard prophylactic regime of a regular haem arginate infusion every 7 days.
4	We would like to reiterate the limited effectiveness and acceptability of the current treatment options for this patient group: Gonadorelin analogues are not suitable for males and have limited efficacy in a minority of female patients in whom recurrent attacks are clearly premenstrual. This treatment effectively induces a chemical menopause in young women, with all of the attendant symptoms and complications. For these reasons it is rarely used in the UK, and not considered as an option in most other European countries. Liver transplantation has been used in a few patients when medical therapies are no longer effective or when acute attacks are associated with recurrent life threating complications. However this

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	remains a treatment of last resort and is associated with a new set of health problems. Many patients also develop impaired renal function, which then requires a combined liver and kidney transplant with additional risks and complications. The committee is correct that the main management strategy for patients with severe recurrent attacks of porphyria is to administer haem arginate infusions regularly at a frequency of 1-4 infusions per month. However there is no evidence base for this treatment and it provides limited clinical benefit. Although prophylactic haem arginate has some effect on reducing attack frequency, patients remain very unwell. They continue to have disabling pain and other chronic symptoms, together with breakthrough attacks requiring extra haem arginate infusions and hospital admissions. These patients are highly dependent on haem arginate and also on maintaining central venous access. Delays in their regular treatment can result in life threatening attacks. In the past year, a young patient with acute intermittent porphyria whose infusion was delayed for two days had a very severe attack complicated by paralysis and respiratory arrest. This delay occurred because of difficulties with venous access, which is a particular problem associated with frequent haem arginate infusions.
5	Age at model entry: It seems unlikely that the majority of patients will need to continue givosiran until the menopause. Younger patients who start givosiran as soon as they are diagnosed with recurrent attacks have fewer chronic symptoms and co-morbidities and are expected to respond better than patients who switch to givosiran after being managed with haem arginate for many years. Experience from other European centres already using givosiran suggests that patients with a shorter duration of recurrency respond more quickly and completely to givosiran and do not relapse when the drug is stopped. In addition some patients can tolerate less than monthly dosing. Tachyphylaxis has not been seen in patients on givosiran, and if anything response improves over time, with gradually improving urine biochemistry (falling urine porphobilinogen concentrations) and fewer chronic symptoms. All this suggests that patients who are started on givosiran early in the natural history of their disease are likely to need only short periods of treatment, perhaps for a few years.

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ERG Review of Company's Response to ECD

23 August 2021

Produced by	**Peninsula Technology Assessment Group (PenTAG)** **University of Exeter Medical School** **South Cloisters** **St Luke's Campus** **Heavitree Road** **Exeter** **EX1 2LU**
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This document is linked to ERG report	Farmer, C., O'Toole, B., Muthukumar, M., Robinson, S., Kiff, F., Trigg, L., Gardiner, T., Newsome, P.N., Crathorne, L., Melendez-Torres, G. J. Givosiran for treating acute hepatic porphyria [ID1549]: A Highly Specialised Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2021.
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1. SUMMARY

In their evaluation consultation document (ECD), the committee raised a number of concerns regarding the company's economic evaluation of givosiran for the treatment of acute hepatic porphyria. In this document, the evidence review group (ERG) review additional evidence provided by the company to address these concerns, in advance of a second committee meeting. This evidence includes an updated data cut from the ENVISION open-label extension (OLE) trial ([redacted]). These data were provided in a letter to NICE submitted subsequent to the company's ECD response, but not included in the economic model.

2. KEY ISSUES

2.1. Updated clinical efficacy data for givosiran

The company presented updated clinical data from the ENVISION OLE at 36 months for patients who received givosiran from baseline, and at 30 months for those who received placebo during the initial 6-month double-blind phase. These data were limited to the annualised attack rate (AAR; median [Q1-Q3] and adjusted mean [SEM]) and graphical representations of aminolaevulinic acid (ALA) and porphobilinogen (PBG) levels. It should be noted that these data were not used to inform the company's revised economic analysis post ECD. The ERG understood that whilst updated data were available, the company were unable to analyse, quality assess and include these data within the model, given time constraints.

AAR data reported at the final cut-off [redacted]. As with earlier follow-up, variance data surrounding effects indicate some uncertainty in the precise effect of givosiran, which may reflect the small sample size and/or variation in effect in a known heterogeneous population. Nevertheless, consistent with the advice of clinicians during its original appraisal, the ERG consider that the overall effect of givosiran on AAR [redacted].

The company did not provide a breakdown of AAR according to resource need (e.g. attack leading to hospitalisation); this is something the ERG requested from the company at clarification due to known imprecision in the measurement of attacks, and the potential for different health and cost impacts according to the severity of the attack. At earlier cut-offs for ENVISION and ENVISION OLE, the data appeared to suggest that [redacted], and further data would be informative for understanding whether this is a true and sustained effect.

No subgroup data were reported for AAR at this timepoint to evaluate potential variation in effect across the treated population. As noted in its original report, the ERG considered that the sample size of ENVISION/ENVISION OLE is potentially too small to identify conclusive differences, however the ERG would have been interested to see whether potential differences in effect between patients with and without chronic symptoms and prior opioid use noted at earlier cut-off were consistent at the final follow-up.

During its original appraisal, the ERG noted that there is some uncertainty about the value of ALA and PBG for understanding the clinical efficacy of givosiran. Overall, the new evidence provided by the company showed that

[redacted]. As with earlier follow-up the company did not report variance data for ALA and PBG levels, and these were presented in graphical form only.

2.2. Updated safety data for givosiran

A comparison of summary safety data reported in the CS and at the new data cut is reported in Table 1 below. The new data appear to show [redacted]. The nature of drug-related serious and severe AEs was not reported, though the company did provide breakdown of AEs occurring in ≥10% of participants and severe AEs occurring in ≥2 people. The ERG was unclear why rates of CKD and elevated ALT levels, both outcomes of interest, did not appear in the former of these data tables, considering that more than 10% of participants experienced these outcomes at 18-months. [redacted]. Moreover, the company do not report if [redacted], which was of concern to a stakeholder on the appraisal.

The ERG noted in its original report that the heterogeneous nature of AHP and the complex medical history of people with AHP make the interpretation of AE data challenging. However, the ERG considered the data to suggest that there is a moderate risk of serious and severe adverse events associated with givosiran, which does not diminish over time. As potentially the risk of these events could continue to increase over time, this is a new area of uncertainty for this appraisal. The ERG therefore considers the safety evidence to be consistent with proposals from UK stakeholders that givosiran should initially be administered in a specialist centre, and may benefit from proposals to introduce breaks in treatment (although the ERG note that the clinical efficacy of this approach has not been evaluated).

Table 1: Summary risk of adverse events between 18- and 36- months

N (%) patients with ≥1:	[redacted]	[redacted]
AE	[redacted]	[redacted]
Study drug–related AE	[redacted]	[redacted]
SAE	[redacted]	[redacted]
Study drug–related SAE	[redacted]	[redacted]
Severe AE	[redacted]	[redacted]

N (%) patients with ≥1:	[redacted]	[redacted]
Study drug–related severe AE	[redacted]	[redacted]
AE leading to discontinuation	[redacted]	[redacted]
Study drug–related AE leading to discontinuation	[redacted]	[redacted]
Death	[redacted]	[redacted]

Abbreviations: AE, adverse event; NR, not reported

2.3. Estimating the effectiveness of the base case comparator, prophylactic haem arginate

The company updated a systematic literature review (SLR) to identify clinical effect evidence for prophylactic haem. The original SLR was reported in the CS and identified evidence for prophylactic haem published up until September 2020.The update conducted by the company searched for new evidence published between August 2020 and 02 July 2021. The search did not identify any new evidence. An appraisal of the methods used for this SLR is summarised in **Error! Reference source not found.**.

Table 2: ERG appraisal of company's updated SLR to identify clinical effects of prophylactic haem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Company response Appendix 1 and Section 2.1.2.3.	The searches for clinical and cost effectiveness are an update of the original searches by the company with a focus on hemin prophylaxis. They are well conducted using a variety of sources and a good range of search techniques. The same strategy is used for all searches, but as no study type filters are used this is not an issue.
Inclusion criteria	Original CS Document B, Table 10.	Since the inclusion criteria are not provided in the company response, the ERG assumes that the inclusion criteria were comparable with those in the original CS and were therefore appropriate to the decision problem.
Screening	Original CS SLR report.	The ERG assumes that screening was comparable with that in the original CS. Therefore, screening was assumed to have been conducted to appropriate standards.
Data extraction	Company response Section 2.1.2.3.	No new evidence was identified by the SLR. Data extraction was therefore not completed.
QA of included studies	Original SLR report8, original CS, Document B, Section 11.2.2 and company response Appendix 1.	No evidence was identified by the SLR. Critical appraisal was therefore not completed. The company had referenced the Drummond checklist as the critical appraisal tool that would be used in the original CS, the ERG assumes this would be the same in this SLR.
Studies identified	Company response Section 2.1.2.3.	No new evidence was identified by the SLR.

Abbreviations: CS, company submission; ERG, Evidence Review Group; SLR, systematic literature review

In their ECD response, the company used non-randomised evidence relating to the effectiveness of prophylactic haem arginate to model a range of plausible effectiveness estimates for prophylactic haem arginate. As described above, the ERG was confident that all relevant evidence was considered. The ERG agreed with the company's conclusion that a 'formal' network meta-analysis or indirect treatment comparison using e.g. the method of Bucher would not have been appropriate given the poor quality of available evidence. Instead, the company's approach could be best described as an unanchored indirect comparison, in which plausible estimates for reduction in AAR with prophylactic haem arginate were applied to the comparator arm findings for AAR in the ENVISION study.

The company selected two of the five evidence sources to generate a range of effectiveness estimates. The remaining three evidence sources were deprioritised due to concerns over generalisability and suitability, which the ERG regarded as broadly appropriate. Of the two sources used, one (Marsden et al. 2015)[1] was interpreted by the company as providing an estimate of the proportion of patients with AHP who experienced clinical improvement from prophylactic haem arginate (between 50% and 70%, according to the publication), while the other (Neeleman et al. 2018)[2] was interpreted by the company as providing an estimate of AAR reduction *conditional* on treatment response (estimated as a 51.3% reduction). The ERG agreed with the interpretation of Marsden et al. (2015)[1] but was not convinced that the interpretation of Neeleman et al. (2018)[2] as providing an estimate of effectiveness conditional on response was as straightforward as presented. The basis for this interpretation was that patients were resistant to weaning due to acute attacks being 'triggered', but it is unclear whether such a direct causal link can be drawn. In addition, any number of factors could influence the success or acceptability of weaning that do not relate to treatment response.

The company's base case estimate of the effectiveness of prophylactic haem arginate was based on multiplying an estimate of 70% response against a reduction of 51.3% in AAR. This followed clearly from the company's interpretation of the two evidence sources. A number of scenarios were generated including a lower bound estimate of response (50%) multiplied by a 51.3% reduction, a scenario that essentially assumed the estimate from Neeleman et al. (2018)[2] was the unconditional estimate of AAR reduction, and a scenario assuming a 10% AAR reduction. Scenarios drew extensively on expert opinion which, while not generally considered a high-quality form of evidence, was appropriate given the circumstances and was well documented. While the ERG agreed that all the generated scenarios were reasonable, the ERG regarded that there was some basis to consider the scenario of an absolute AAR reduction of 51.3% as plausible as the base case estimate.

Subsequent to this, the company explored several scenarios for the ‘amortisation period’ of this effect, defined as the time taken for prophylactic haem arginate to reach maximum effect plus the time over which this effect was sustained. In practice and as operationalized by the company, the amortisation period is the time at which the state distribution of patients ‘peaks’ in terms of utility benefits for distribution of patients by health state. This is discussed further below.

3. COMPANY MODEL FOLLOWING ECD

For clarity,

below outlines NICE preferences as stated in the ECD, ERG preferences as stated in the ERG report and company changes post ECD. The final two columns outline how the company's revised base case deviates from both NICE and ERG preferences.

As noted in

- , the company presented an updated base case including the following amendments in response to the ECD:
  - Extrapolation of givosiran efficacy reduced from five years to three years, with transition probabilities 'frozen' at three years: In the company's original base case, givosiran treatment efficacy was assumed to continue until Year 5 before transition probabilities were frozen. This assumption was considered to be inappropriate due to the lack of supporting clinical evidence. As noted previously, [redacted]. The ERG therefore consider this revision (whereby transition probabilities from month 12 to 18 are recycled up to Year 3) to be broadly appropriate.
  - Inclusion of prophylactic haem arginate as comparator: NICE considered the most appropriate comparator to be prophylactic haem arginate. As such, the company included prophylactic haem arginate as a comparator in the revised base case analysis. Although the ERG initially had concerns surrounding the inclusion of an off-label treatment with limited long term effectiveness data in the model, the ERG agreed with NICE that prophylactic haem arginate better reflected clinical practice within the UK, and therefore may be considered an appropriate comparator within the economic analysis.
  - Updated costs for chronic conditions: The company conducted an updated literature search (June 2021) to identify more relevant costs for chronic conditions within the model. The ERG considered that the updated sources (which were based on published UK studies) appeared more robust, as several costs for chronic conditions i.e. back pain, advanced neuropathy, motor weakness were originally derived from unconventional sources such as article publications from The Guardian. Due to time constraints the ERG were unable to fully appraise each individual study; however it should be noted that the updated costs were not considerably different to those reported the original model. Furthermore, chronic costs were not considered a key driver of cost effectiveness.

The ERG considered the company's three main revisions to be broadly acceptable.

Table 3: NICE preferences, ERG preferences and company changes post ECD

Model parameter	Committee preferences (from ECD)	ERG preferences (from ERG report)	Company's changes/new base case (post ECD response)	Deviations from committee preferences (Company's changes/new base case vs. committee preferences)	Deviations from ERG preferences (Company's changes/new base case vs. ERG preferences)
Givosiran treatment efficacy	Allowing people to move between health states in the first 18 months after which they remain in the same health state in the givosiran arm	Givosiran transition probabilities based on OLE data (frozen at 18 months).	Givosiran efficacy frozen at 3 years.	Company revised base case assumes givosiran efficacy continues for 3 years before freezing (NICE prefer freezing at 18 months).	Company revised base case assumes givosiran efficacy continues for 3 years before freezing (ERG prefer freezing at 18 months)
BSC treatment efficacy	Allowing people to move between health states in the first 6 months after which they remain in the same health state in the best supportive care arm	N/A	As per original base case	N/A	N/A
ToT extrapolation	Using the log-logistic model to extrapolate time on treatment	ToT extrapolated using piecewise approach (KM curve + log Normal cure).	As per original base case	N/A	Company revised base case extrapolates ToT by applying log logistic curve (fully parametric)
Utility values	Using utilities from relapsing–remitting multiple sclerosis	AHP utilities based on RRMS values in Hawton et al.(2016)[3]	As per original base case	Company revised base case does not incorporate utilities from RRMS patients	Company revised base case does not incorporate utilities from RRMS patients
Menopause assumption	Continuing treatment until menopause for most women and throughout the time	N/A	As per original base case	N/A	N/A

Model parameter	Committee preferences (from ECD)	ERG preferences (from ERG report)	Company's changes/new base case (post ECD response)	Deviations from committee preferences (Company's changes/new base case vs. committee preferences)	Deviations from ERG preferences (Company's changes/new base case vs. ERG preferences)
	horizon of the model for men and some women				
Opioid addiction costs	Including the costs of opioid dependency	Opioid dependency costs removed.	As per original base case	N/A	Company's revised base case includes opioid addiction costs
Comparator	The committee noted that the most appropriate comparator was prophylactic haem arginate	N/A	Prophylactic haem arginate included as comparator (36% total AAR reduction vs BSC with effect amortisation period of 5 years. Waning of effect period, 23 years)	N/A	N/A
Costs associated with chronic conditions	N/A	N/A	Updated chronic cost sources based on June 2021 literature search (also applied latest inflation index)	Company revised base case includes updated costs for chronic conditions (NICE did not state a preference for these costs to be updated)	Company revised base case includes updated costs for chronic conditions (ERG did not state a preference for these costs to be updated)
Probability of menopause onset	N/A	The per cycle probability of menopause onset based on mean age from UK Women's Cohort study (fitting a normal distribution).	As per original base case	N/A	Company revised base case uses Greer et al[4] to inform probability of menopause onset

Abbreviations: AAR, annualized relapse rate; AHP, Acute Hepatic Porphyria; BSC, best supportive care; KM, Kaplan Meier; N/A, not applicable; NICE, National Institute for Health and Care Excellence; OLE, open-label extension; RRMS, relapsing remitting multiple sclerosis; ToT, time on treatment

The company's revised base case results are presented in Table 4 below. The company also reproduced 4 of the ERG's scenario analyses and two new scenarios (see Table 5 for results).

It should be stated that the revised base case results do not fully align with NICE preferences i.e. NICE stated a preference for using RRMS utility values, though the company did not use these in their revised base case; and therefore the ERG do not consider these to be suitable for decision making. The ERG conducted additional analyses (Base case A and B). Both analyses used the full set of NICE committee preferences as the base case, incorporated the three revisions made by the company post-ECD and based the per cycle probability of menopause on mean age from UK Women's cohort. The only variation between base case A and B was the use of alternative health state utility values (see Section 4 for these results).

The ERG would like to highlight that the company's revised results are not based on the updated data cut from the ENVISION open-label extension (OLE) trial (36-month final follow-up, at [redacted]). This is because the company was unable to incorporate these data into the revised model.

In the revised model, the company estimated transition probabilities for prophylactic haem arginate by applying a 36% reduction relative to BSC AAR. The ERG noted that the company's approach to estimating per cycle transition probabilities within the model was broadly appropriate, while acknowledging the uncertainty surrounding the use of a 36% reduction in AAR (as noted above, data from Neeleman et al. (2018)[2] estimated an AAR reduction of 51%). As such NICE may wish to consider scenario analyses whereby a 51% reduction in AAR is used to model the effectiveness of prophylactic haem arginate.

Table 4: Revised base case cost effectiveness results (post ECD)

ICER	Undiscounted		Discounted	
	Cost/LY	Cost/QALY	Cost/LY	Cost/QALY
Givosiran vs. hemin prophylaxis	NA	[redacted]	NA	[redacted]
Givosiran vs. BSC	NA	[redacted]	NA	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life-year; NA: not applicable; QALY: quality-adjusted life-year

Table 5: Revised scenario analyses results (post ECD)

Scenario	Givosiran vs hemin prophylaxis		Givosiran vs BSC	
	ICER (£/QALY)	% change	ICER (£/QALY)	% change
Base case	[redacted]	[redacted]	[redacted]	–
Starting age = 37 years	[redacted]	[redacted]	[redacted]	39.4%
10% Asymptomatic women continue treatment after menopause onset	[redacted]	[redacted]	[redacted]	10.3%
Time of menopause: normal distribution fitting average age of menopause onset in UK (UK Women's Cohort Study[70])	[redacted]	[redacted]	[redacted]	10.4%
ToT givosiran: Piecewise, KM + log-logistic	[redacted]	[redacted]	[redacted]	0.04%
Opioid addiction costs excluded	[redacted]	[redacted]	[redacted]	1.6%
Health-state utilities based on RRMS proxy values (Hawton et al. 2016[3])	[redacted]	[redacted]	[redacted]	3.2%

Abbreviations: ICER: incremental cost-effectiveness ratio; KM: Kaplan–Meier; QALY: quality-adjusted life-year; RRMS: relapsing-remitting multiple sclerosis; ToT: time on treatment

3.1. Additional sensitivity analyses (post ECD)

In the company's revised base case AAR reduction was estimated to be 36% vs BSC, amortisation was assumed to be five years and treatment waning 23 years.

The company acknowledged that there is uncertainty surrounding the long-term effectiveness of prophylactic haem arginate and therefore provided additional threshold analyses (two way and three way), which simultaneously tested uncertainty with respect to AAR reduction, amortisation and waning of treatment effect. During communication between the ERG, NICE and the company, it was agreed that such scenario analyses would help to capture uncertainty surrounding the modelled long term treatment effect of prophylactic haem arginate, and present NICE with a range of possible ICERs. The ERG note that is challenging to identify a 'most plausible' ICER from the company's scenario analyses presented in Table 6 and Table 7, due to the lack of robust long term effectiveness data for prophylactic haem arginate.

The lowest ICER reported in the company's threshold analysis was [redacted]. In this scenario prophylactic haem arginate was associated with a 10% reduction in AAR, 18 month amortisation and three-year waning. The highest ICER reported in the company's threshold analysis was [redacted] In this scenario prophylactic haem arginate was associated with a 51% reduction in AAR, 18-month amortisation and no waning in effect.

Table 6: Two way threshold analysis (AAR reduction x amortisation period)

	Hemin prophylaxis AAR reduction (total effect) vs BSC			
	10%	26%	36%	51%
18 months	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]
4 years	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]
6 years	[redacted]	[redacted]	[redacted]	[redacted]
7 years	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AAR, annualized relapse rate; BSC, best supportive care; vs, versus

Table 7: Three way threshold analysis (AAR reduction x amortisation period x waning effectiveness)

Hemin prophylaxis AAR reduction vs BSC	Amortisation of effect	Waning of effect (time from when total effect is reached)			
		No waning of effect	3 years	7 years (maximum effect amortisation period)	23 years (Schmitt et al. 2018)
10%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]
26%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]
36%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]
51%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]

Hemin prophylaxis AAR reduction vs BSC	Amortisation of effect	Waning of effect (time from when total effect is reached)			
		No waning of effect	3 years	7 years (maximum effect amortisation period)	23 years (Schmitt et al. 2018)
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AAR, annualized relapse rate; BSC, best supportive care; BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life; vs, versus

4. ERG MODEL FOLLOWING ECD

In this section, the ERG presents the following updated analyses:

- Base case A: Committee base case results (Table 8 and Table 9)
- Base case B: Committee base case results- using alternative utilities (Table 10 and Table 11)
- Updated ERG scenario analyses (Please note that the scenarios considered in Base case A and Base case B are not included here.

- Table 12 and Table 13)
- Updated ERG two-way sensitivity analysis (incorporating the committee preferences) (

- ERG two-way analyses

The ERG two-way analyses within the original report have been updated to reflect the following:

- Comparison vs prophylactic haem arginate
- Updated costs for chronic conditions
- Committee preferences (Base case B).
- Table 14 to Table 21)
- Updated company two-way and three-way analyses (incorporating the committee preferences) (Company's updated two-way and three-way analyses

The company's two-way and three-way analyses for prophylactic haem arginate have been updated to reflect the committee preferences (Base case B).

- Table 22 and Table 23)

4.1. Base case A

This revised base case analysis incorporates NICE committee preferences as stated in the ECD with the following alterations:

- Extrapolation of givosiran efficacy to three years, the inclusion of prophylactic haem arginate as the relevant comparator and updated costs for chronic conditions. These three revisions made by the company have been accepted by the ERG.
- The per cycle probability of menopause onset based on mean age from UK Women's cohort (fitting a normal distribution). The ERG considered this data source to be more generalisable to the UK.
- Utility values reflect those included in the company's original model.

Table 8. Base case A – Committee base case results (without MAA)

Preferred assumption	Cumulative ICER £/QALY	
	Givosiran vs BSC	Givosiran vs prophylactic haem arginate
Company base-case	[redacted]	[redacted]
Scenario 1: Givosiran transition probabilities based on trial and OLE data until 3 years and frozen thereafter	[redacted]	[redacted]

Scenario 6: The per cycle probability of menopause onset based on mean age from UK Women's cohort study[2] (fitting a normal distribution).	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost effectiveness ratio, OLE, open-label extension; QALY: quality adjusted life year, vs, versus

Table 9. Base case A – Committee base case results (with MAA)

Preferred assumption	Cumulative ICER £/QALY	
	Givosiran vs BSC	Givosiran vs prophylactic haem arginate
Company base-case	[redacted]	[redacted]
Scenario 1: Givosiran transition probabilities based on trial and OLE data until 3 years and frozen thereafter	[redacted]	[redacted]
Scenario 6: The per cycle probability of menopause onset based on mean age from UK Women's cohort study[2] (fitting a normal distribution).	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost effectiveness ratio, OLE, open-label extension; QALY: quality adjusted life year, vs, versus

4.2. Base case B

This revised base case analysis incorporates NICE committee preferences as stated in the ECD with the following alterations:

- Extrapolation of givosiran efficacy to three years, the inclusion of prophylactic haem arginate as the relevant comparator and updated costs for chronic conditions. These three revisions made by the company have been accepted by the ERG.
- The per cycle probability of menopause onset based on mean age from UK Women's cohort (fitting a normal distribution). The ERG considered this data source to be more generalisable to the UK.
- Utility values reflect those preferred by NICE i.e. RRMS utilities.

Table 10. Base case B – Committee base case results using alternative utilities (without MAA)

Preferred assumption	Cumulative ICER £/QALY	
	Givosiran vs BSC	Givosiran vs prophylactic haem arginate
Company base-case	[redacted]	[redacted]
Scenario 1: Givosiran transition probabilities based on trial and OLE data until 3 years and frozen thereafter	[redacted]	[redacted]
Scenario 6: The per cycle probability of menopause onset based on mean age from UK Women's cohort study[2] (fitting a normal distribution).	[redacted]	[redacted]

Preferred assumption	Cumulative ICER £/QALY	
	Givosiran vs BSC	Givosiran vs prophylactic haem arginate
Scenario 4: AHP utilities based on RRMS values in Hawton et al. (2016)[3]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost effectiveness ratio, MAA, managed access agreement; OLE, open-label extension; QALY: quality adjusted life year, RRMS: relapsing remitting multiple sclerosis; vs, versus

Table 11. Base case B – Committee base case results using alternative utilities (with MAA)

Preferred assumption	Cumulative ICER £/QALY	
	Givosiran vs BSC	Givosiran vs prophylactic haem arginate
Company base-case	[redacted]	[redacted]
Scenario 1: Givosiran transition probabilities based on trial and OLE data until 3 years and frozen thereafter	[redacted]	[redacted]
Scenario 6: The per cycle probability of menopause onset based on mean age from UK Women's cohort study[2] (fitting a normal distribution).	[redacted]	[redacted]
Scenario 4: AHP utilities based on RRMS values in Hawton et al. (2016)[3]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost effectiveness ratio, MAA, managed access agreement; OLE, open-label extension; QALY: quality adjusted life year, RRMS: relapsing remitting multiple sclerosis; vs, versus

4.3. ERG scenario analyses

The ERG scenario analyses within the original report have been updated to reflect the following:

- Comparison vs prophylactic haem arginate
- Updated costs for chronic conditions

Please note that the scenarios considered in Base case A and Base case B are not included here.

Table 12. ERG scenarios (without MAA)

Preferred assumption	Givosiran vs BSC		Givosiran vs prophylactic haem arginate	
	£/QALY (ICER)	% change from company base case	£/QALY (ICER)	% change from company base case
Company base-case	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Givosiran efficacy				
Clinical efficacy based on ENVISION and OLE data (TPs frozen after 18 months)	[redacted]	[redacted]	[redacted]	[redacted]
ENVISION efficacy assumed to be maintained up to 18 months (OLE data not considered)	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: BSC efficacy data from ENVISION extended to 18 months	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: ToT extrapolation				
KM curve until 18 months and Log- normal for extrapolation beyond	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: Health state utility values				
Utilities based on EQ-5D data from ENVISION	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent and severe ENVISION utilities adjusted by ERG	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: 10% of patients assumed to require treatment after age of menopause onset	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: Proportion hospitalised for acute attack reduced to 50%	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9: Proportion female reduced to 82%	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 10: Starting cohort mean age reduced to 30 years	[redacted]	[redacted]	[redacted]	[redacted]

Preferred assumption	Givosiran vs BSC		Givosiran vs prophylactic haem arginate	
	£/QALY (ICER)	% change from company base case	£/QALY (ICER)	% change from company base case
Scenario 11: Time horizon reduced to 15 years	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 12: Severe health state 'switched off'	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 13: Patients treated with givosiran require monitoring prior (and once monthly for first 6 months)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AHP, acute hepatic porphyria; BSC, best supportive care; EQ-5D, EuroQol 5-dimensions questionnaire; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; MAA, managed access agreement; NA – Not applicable; OLE, open label extension; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; ToT, time on treatment; TPs, transition probabilities

Table 13. ERG scenarios (with MAA)

Preferred assumption	Givosiran vs BSC		Givosiran vs prophylactic haem arginate	
	£/QALY (ICER)	% change from company base case	£/QALY (ICER)	% change from company base case
Company base-case	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Givosiran efficacy				
Clinical efficacy based on ENVISION and OLE data (TPs frozen after 18 months)	[redacted]	[redacted]	[redacted]	[redacted]
ENVISION efficacy assumed to be maintained up to 18 months (OLE data not considered)	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: BSC efficacy data from ENVISION extended to 18 months	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: ToT extrapolation				
KM curve until 18 months and Log- normal for extrapolation beyond	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: Health state utility values				
Utilities based on EQ-5D data from ENVISION	[redacted]	[redacted]	[redacted]	[redacted]

Preferred assumption	Givosiran vs BSC		Givosiran vs prophylactic haem arginate	
	£/QALY (ICER)	% change from company base case	£/QALY (ICER)	% change from company base case
Recurrent and severe ENVISION utilities adjusted by ERG	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: 10% of patients assumed to require treatment after age of menopause onset	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7: Proportion hospitalised for acute attack reduced to 50%	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 9: Proportion female reduced to 82%	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 10: Starting cohort mean age reduced to 30 years	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 11: Time horizon reduced to 15 years	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 12: Severe health state 'switched off'	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 13: Patients treated with givosiran require monitoring prior (and once monthly for first 6 months)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AHP, acute hepatic porphyria; BSC, best supportive care; EQ-5D, EuroQol 5-dimensions questionnaire; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; MAA, managed access agreement; NA, not applicable; OLE, open label extension; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; ToT, time on treatment; TPs, transition probabilities

4.4. ERG two-way analyses

The ERG two-way analyses within the original report have been updated to reflect the following:

- Comparison vs prophylactic haem arginate
- Updated costs for chronic conditions
- Committee preferences (Base case B).

Table 14 TWSA: Alternative time points for efficacy freezing (without MAA assumptions) – Givosiran vs BSC

		Freeze givosiran efficacy/TPs at					
		6 months	12 months	18 months	24 months	30 months	36 months
Freeze BSC efficacy/TPs at	6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; MAA, managed access agreement; TPs, transition probabilities; WSA, two-way sensitivity analyses; vs, versus

ICER > £100k/QALY	ICER < £100k/QALY

Table 15 TWSA: Alternative time points for efficacy freezing (with MAA assumptions) – Givosiran vs BSC

		Freeze givosiran efficacy/TPs at					
		6 months	12 months	18 months	24 months	30 months	36 months
Freeze BSC efficacy/TPs at	6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; MAA, managed access agreement; TPs, transition probabilities; WSA, two-way sensitivity analyses; vs, versus

ICER > £100k/QALY	ICER < £100k/QALY

Table 16 TWSA: Disease progression post-menopause (without MAA) – Givosiran vs BSC

		Proportion of symptomatic females post-menopause who will receive givosiran treatment					
		0%	5%	10%	15%	20%	25%
Proportion of females	80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	81%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	82%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	83%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	84%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	85%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; MAA, managed access agreement; TWSA, two-way sensitivity analyses; vs, versus

ICER > £100k/QALY	ICER < £100k/QALY

Table 17 TWSA: Disease progression post-menopause (with MAA) – Givosiran vs BSC

		Proportion of symptomatic females post-menopause who will receive givosiran treatment					
		0%	5%	10%	15%	20%	25%
Proportion of females	80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	81%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	82%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	83%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	84%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	85%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; MAA, managed access agreement; TWSA, two-way sensitivity analyses; vs, versus

ICER > £100k/QALY	ICER < £100k/QALY

Table 18 TWSA: Disease progression post-menopause (without MAA) – Givosiran vs haem arginate

		Proportion of symptomatic females post-menopause who will receive givosiran treatment					
		0%	5%	10%	15%	20%	25%
Proportion of females	80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	81%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	82%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	83%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	84%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	85%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement; TWSA, two-way sensitivity analyses; vs, versus

ICER > £100k/QALY	ICER < £100k/QALY

Table 19 TWSA: Disease progression post-menopause (with MAA) – Givosiran vs haem arginate

		Proportion of symptomatic females post-menopause who will receive givosiran treatment					
		0%	5%	10%	15%	20%	25%
Proportion of females	80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	81%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	82%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	83%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	84%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	85%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement; TWSA, two-way sensitivity analyses; vs, versus

ICER > £100k/QALY	ICER < £100k/QALY

Table 20 TWSA: Start-stop for givosiran (with MAA) – Givosiran vs BSC

		Percentage of patients interrupting givosiran treatment after 1 year of no attack					
		0%	20%	40%	60%	80%	100%
Percentage of patients asymptomatic for 1 entire year	10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; MAA, managed access agreement; TWSA, two-way sensitivity analyses; vs, versus

ICER > £100k/QALY	ICER < £100k/QALY

Table 21 TWSA: Start-stop for givosiran (with MAA) – Givosiran vs haem arginate

		Percentage of patients interrupting givosiran treatment after 1 year of no attack					
		0%	20%	40%	60%	80%	100%
Percentage of patients asymptomatic for 1 entire year	10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MAA, managed access agreement; TWSA, two-way sensitivity analyses; vs, versus

ICER > £100k/QALY	ICER < £100k/QALY

4.5. Company's updated two-way and three-way analyses

The company's two-way and three-way analyses for prophylactic haem arginate have been updated to reflect the committee preferences (Base case B).

Table 22. Company's two-way threshold analysis (incorporating committee preferences)

Amortisation of effect	Hemin prophylaxis AAR reduction (total effect) vs BSC			
	10%	26%	36%	51%
18 months	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]
4 years	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]
6 years	[redacted]	[redacted]	[redacted]	[redacted]
7 years	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AAR, annualised relapse rate; BSC, best supportive care; vs, versus

Table 23. Company's three-way threshold analysis (incorporating committee preferences)

Hemin prophylaxis AAR reduction vs BSC	Amortisation of effect	Waning of effect (time from when total effect is reached)			
		No waning of effect	3 years	7 years (maximum effect amortisation period)	23 years (Schmitt et al. 2018[9])
10%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]

Hemin prophylaxis AAR reduction vs BSC	Amortisation of effect	Waning of effect (time from when total effect is reached)			
		No waning of effect	3 years	7 years (maximum effect amortisation period)	23 years (Schmitt et al. 2018[9])
26%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]
36%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]
51%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AAR, annualised relapse rate; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life; vs, versus

5. ADDITIONAL STAKEHOLDER SUBMISSIONS

Stakeholders for the appraisal expressed disappointment that givosiran was not approved following the first evaluation committee meeting. NAPS clinicians in the UK stated that their experience treating a small group of people (N=5) with givosiran suggests that it may be more effective than prophylactic haem, and results in fewer side effects. Stakeholders suggest proposals from NAPS clinicians that givosian can be administered over short periods, with breaks in treatment to consider whether reductions in ARR are maintained and treatment can be withdrawn indefinitely. NAPS clinicians suggested the potential for givosiran to change patients' biochemistry, which would support a temporary or permanent reduction in attack rate after discontinuing treatment. Accordingly, not all people will require prolonged treatment, such as until menopause in women. This effect may be most relevant for people treated early in the disease. Stakeholders proposed that givosiran be started following diagnosis of recurrent attacks, which may be several years after the condition is originally diagnosed. NAPS clinicians further noted that 27 people in the UK are currently receiving treatment for AHP, including those treated with givosiran, and that not all people would be expected to be treated with givosiran. This may be due to personal preference, or because the condition is stable after withdrawal of prophylactic haem.

Stakeholders confirmed that prophylactic haem is a component of current best supportive care for AHP in the UK. Stakeholders noted that prophylactic haem is not administered regularly, but in response to indications of a forthcoming attack, so as to reduce the potential side effects.

Stakeholders note the limitations in the HRQoL submitted in the company submission, and highlight the potential value of qualitative evidence from people with AHP who have received givosiran, and a mixed methods study (Gill et al. 2021),[5] which in its unpublished form was cited in the original ERG report. Stakeholders further propose that further evidence for the efficacy of givosiran may be identified through dialogue with clinicians in France and Sweden, who have further experience with this treatment.

Stakeholders from IPPN provided a number of further comments on the summary provided in the ECD, which the ERG has summarised and/or responded to in the bullets below:

- The stakeholders suggested that a statement in the ECD (p.3, Section 1.2) is incorrect, however the ERG consider this to be rather a lack of clarity in the statement. The statement is intended to reflect that the comparator used in the company's submission is without prophylactic haem arginate.

- IPPN noted that prevalence rates for symptomatic vs. asymptomatic AHP vary, and that the rate given in the ECD (1 in 100,000) is symptomatic AHP. The rate of AHP is cited to be 1 in 1,700.

- The stakeholders raised concerns that the price discount to the NHS reflected in the PAS is not freely available to stakeholders. Unfortunately, the discount available is provided by the company to the NHS on a confidential basis, and therefore this cannot be published.

- The stakeholders suggested that the benefits of avoiding a liver transplant should have been considered in the company's submission. Based on clinical advice to the ERG and the responses of stakeholders, the ERG agreed with the company's decision to exclude consideration of liver transplant from their analyses, due to the understanding that these are very rarely performed (p.29 of the ERG report).

- The stakeholder is concerned that the summary provided in the ECD does not fully capture the potential benefits of givosiran (p. 7-8). The ERG noted that the views of stakeholder groups and patient representatives were considered by the committee in their decision-making (e.g. section 4.25, p. 17 of the ECD response).

- The ERG thanks the stakeholders for noting that they supported the submission provided by the BPA during the appraisal.

- The stakeholders suggested that more weight be given to clinical opinion that there is a lack of distinction between prophylactic and acute haem in practice. The ERG was aware that administration of haem arginate is directed by clinical need, and that definitions of acute and prophylactic care may be blurred due to a lack of definition about when an attack commences. This means that there is a lack of clarity about the frequency with which haem arginate is used as a prophylactic treatment. The company conducted a SLR to identify evidence for the efficacy of prophylactic haem arginate as used in practice, but as stated earlier in this response, the evidence was of poor quality and not informative for decision-making. However, the committee decision to request further analyses from the company including prophylactic haem arginate as a comparator was consistent with clinical advice that this was necessary to reflect current clinical practice. In the company's revised analysis, the dose for prophylactic haem arginate was 3 mg/kg, used a frequency of 20.7 administrations per cycle based on the average of reported doses per month from Marsden et al.[1] and multiplied by cycle length.

- The stakeholders highlighted a typo in the ECD (p.11) concerning the definition of health states. The health states used in the company's model were defined on the basis of frequency of attacks per year as follows:
  - asymptomatic (0 attacks)
  - symptomatic (4 or less attacks)
  - recurrent (5 to 24 attacks)
  - severe (more than 24 attacks).
- The stakeholders queried the lifetime time horizon (60 years) used given that the starting age of the model is 41.6 years, noting that many people would not live to that age. The ERG noted that the length of the model time horizon is intended to capture the full potential benefits and costs of treatment, and the model accounts for general population mortality during that timeframe.
- The stakeholders suggested that stopping criteria be incorporated in the analysis to account for those patients who do not benefit from treatment. The stakeholders noted that this approach is used by clinicians in Switzerland. As stated above, the committee heard from clinical experts that additional stopping criteria may also be used. However, as the potential use of these criteria is currently unknown (e.g. the number of people who would stop treatment, when they would stop, the potential impact of stopping, and when they would restart), the committee did not feel it was able to consider the use of stopping rules in the economic model.

6. REFERENCES

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Givosiran for treating acute hepatic porphyria [ID1549]

Addendum #1: Additional analyses requested by NICE post AC 2

17 September 2021

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This document is linked to ERG report	Farmer, C., O'Toole, B., Muthukumar, M., Robinson, S., Kiff, F., Trigg, L., Gardiner, T., Newsome, P.N., Crathorne, L., Melendez-Torres, G. J. Givosiran for treating acute hepatic porphyria [ID1549]: A Highly Specialised Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2021.
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1. SUMMARY

The National Institute for Health and Care Excellence (NICE) requested additional analyses incorporating committee preferences, following the second committee meeting. The committee preferences as the ERG have implemented them are outlined below:

- Haem prophylaxis as the appropriate comparator
- Model starting age of 37 years
- Assume 5% asymptomatic women continue after menopause
- Utilities reflect RRMS values
- AAR for haem prophylaxis assumed to be 51%
- Amortisation period for haem prophylaxis assumed to be 18 months
- Treatment waning for haem prophylaxis assumed to be three years

2. ANALYSIS AND RESULTS

The committee did not state a preference with respect to the source used for per cycle probability of menopause onset. Therefore, two analyses are provided in this document. Analysis 1 (Section 2.1) includes the committee preferences outlined above and uses the UK women's cohort to estimate the per cycle probability of menopause onset. Analysis 2 (Section 2.2) includes the committee preferences above and uses Greer et al to estimate the per cycle probability of menopause onset. For completeness, discounted and undiscounted results are presented for each analysis.

2.1. Analysis 1

Table 1: Committee preferences (UK women's cohort), discounted

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained (ICER)
Givosiran	[redacted]	[redacted]	-	-	-
Haem Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALYs, quality adjusted life years

Table 2: Committee preferences (UK women's cohort), undiscounted

	Undiscounted costs	Undiscounted QALYs	Incremental undiscounted costs	Incremental undiscounted QALYs	Cost per QALY gained (ICER)
Givosiran	[redacted]	[redacted]			
Haem Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALYs, quality adjusted life years

2.2. Analysis 2

Table 3: Committee preferences (Greer et al cohort), discounted

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained (ICER)
Company deterministic base case					
Givosiran	[redacted]	[redacted]	-	-	-
Haem Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALYs, quality adjusted life years

Table 4: Committee preferences (Greer et al cohort), undiscounted

	Undiscounted costs	Undiscounted QALYs	Incremental undiscounted costs	Incremental undiscounted QALYs	Cost per QALY gained (ICER)
Givosiran	[redacted]	[redacted]			
Haem Prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALYs, quality adjusted life years