NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Givosiran for treating acute hepatic porphyria [ID1549]

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from Alnylam

2. **Company clarification response**

3. **Consultee submissions** from:
   a. British Porphyria Association:
      i. Submission
      ii. Supporting document on patient case studies
   b. Global Porphyria Advocacy Coalition submission
   c. National Acute Porphyria Service, Cardiff and Vale UHB
   d. National Acute Porphyria Service, King's College Hospital NHS Foundation Trust
   e. NHS England and Improvement

4. **Evidence Review Group report** prepared by PenTAG

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

6. **Evidence Review Group addendum**

Please note that the appendices to the company's submission and company model will be available as a separate file on NICE Docs for information only.

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Givosiran for treating acute hepatic porphyria [ID1549]

Version: 24 November 2020

Submitted by: [redacted]

Alnylam Pharmaceuticals

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Abbreviations

Abbreviation	Definition
AAR	Annualised attack rate
ADP	ALA dehydratase deficient porphyria
AE	Adverse event
AHP	Acute hepatic porphyria
AIC	Akaike information criterion
AIP	Acute intermittent porphyria
ALA	Delta aminolevulinic acid
ALAS1	Delta aminolevulinic acid synthase 1
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BMI	Body mass index
BSC	Best supportive care
CEA	Cost-effectiveness analysis
CI	Confidence interval
CKD	Chronic kidney disease
CO	Cross-over
DB	Double blind
eGFR	Estimated glomerular filtration rate
EPNET	European Porphyria Network
EQ-5D-3L	EuroQol 5-dimensions questionnaire (3-level version)
EQ-5D-5L	EuroQol 5-dimensions questionnaire (5-level version)
FAS	Full analysis set
HCC	Hepatocellular carcinoma
HCP	Hereditary coproporphyria
HCRU	Healthcare resource use
HR	Hazard ratio
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IRS	Interactive response system
ITT	Intent to treat; LS:
IV	Intravenous
LS	Least square
LY	Life-year
LYG	Life-years gained
MAD	Multiple-ascending dose
MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
NAPS	National Acute Porphyria Service
NRS	Numeric rating scale
OLE	Open-label extension
OWSA	One-way sensitivity analysis
PBG	Porphobilinogen
PCS	Physical component summary
PGIC	Patient global impression of change questionnaire
PPEQ	Porphyria patient experience questionnaire
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
QoL	Quality of life

RCT	Randomised controlled trial
RDI	Relative dose intensity
SAD	Single ascending dose
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-12	Short Form-12 Health Survey
siRNA	Small interfering ribonucleic acid
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
SOC	System organ class
ToT	Time on treatment
UK	United Kingdom
ULN	Upper limit of normal
VAS	Visual analogue scale
VP	Variegate porphyria
WTP	Willingness-to-pay

Executive Summary

Overview of the proposed technology

Givosiran (Givlaari®), is an EMA and FDA approved medication in the ribonucleic acid interference (RNAi) therapeutic class.[1,2] Givosiran is indicated in Europe for the treatment of acute hepatic porphyria (AHP) in patients aged 12 years or older.[2] In 2017, givosiran received a priority medicines assessment (PRIME) designation from the EMA for the prevention of acute attacks of AHP,[3] and was reviewed under the EMA's accelerated assessment procedure, which is reserved for medicines expected to offer therapeutic innovation and that are of major public health interest.[4] The European Commission (EC) approved givosiran in March 2020.[4] Similarly, givosiran achieved Breakthrough Therapy designation from the United States (US) Food and Drug Administration (FDA) for the same indication,[5] and was approved by the FDA in November 2019 for the treatment of adults with AHP.[5]

Alnylam has specifically engineered givosiran to treat acute hepatic porphyria (AHP), a group of rare inherited metabolic disorders of haem biosynthesis in which specific patterns of overproduction of haem precursors occur in the liver.[6,7] AHP is characterised by excruciatingly painful acute attacks (which are potentially life-threatening if not treated) and, for many patients, chronic debilitating symptoms that negatively impact daily functioning and health-related quality of life (QoL).[8-11]

Givosiran targets the gene transcript of delta aminolevulinic acid synthase 1 (ALAS1) for the treatment of the AHP variants acute intermittent porphyria (AIP), ALAD porphyria (ADP), hereditary coproporphyria (HCP) and variegate porphyria (VP).[12,13] Administration of givosiran significantly lowers liver ALAS1 protein levels in a sustained manner and thereby decreases levels of the toxic haem intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG) to near-normal levels.[13,14] By reducing the accumulation of these intermediates, givosiran significantly reduces or prevents the occurrence of porphyria-related attacks and also decreases other aspects of AHP disease burden.

In the double-blind, placebo-controlled, phase 3 trial ENVISION, where AHP patients with a history of repeated acute attacks were randomly assigned to receive either givosiran or placebo, givosiran demonstrated the ability to significantly reduce levels of ALA and PBG, reduce the frequency and severity of AHP attacks, and improve QoL in patients with AHP compared with placebo treated patients.[14]

Nature of the condition

Disease background

AHP is a rare disease, with a prevalence of ~10 cases per million in the UK.[15] Approximately 5% of symptomatic patients experience recurrent acute porphyria attacks,[15] and according to the National Acute Porphyria Service (NAPS), there are currently 35 people with severe recurrent AHP attacks in the UK, the majority of whom would be candidates for treatment with givosiran.

In AHP, the toxic porphyrin precursors ALA and PBG accumulate in the liver due to increased liver ALAS1 gene transcription, increased haem consumption, and mechanisms related to hormonal fluctuation during menstruation and pregnancy.[9,16,17] QoL in AHP is not assumed to be constant over time, as continuous and relentless accumulation of ALA and PBG, which are central to the pathophysiology of AHP disease, drive both acute porphyria attacks and chronic-porphyria related symptoms.[18]

Acute attacks are accompanied by high excretion of ALA and PBG in the urine.[19-21] The clinical manifestations of AHP differ between the four subtypes. In addition to the association of AHP attacks with widespread dysfunction across the autonomic, central, and peripheral nervous systems, the majority of patients with repeated acute attacks also experience chronic symptoms and long-term complications.[11,19,22]

Acute porphyria attacks

AHP attacks manifest as episodes of potentially extreme incapacitation characterised by a combination of non-specific symptoms.[23] Attacks start with intense and usually diffuse abdominal pain and muscle weakness, followed by nausea and vomiting, constipation or diarrhoea, hypertension, tachycardia, limb, head, neck or chest pain, fever, mental symptoms (including confusion and hallucinations), convulsions, and seizures.[7,16,24] Neurovisceral symptoms are generally indistinguishable across AHP subtypes, but may vary substantially between patients.[17,25] AHP attacks are extremely painful, with one AHP patient describing the level of pain as "not compatible with life".[23] Severe attacks require hospital admission and prompt treatment.

Chronic symptoms and long-term complications of AHP

Chronic, ongoing signs and symptoms, outside those found in attacks, are common in AHP patients with repeated attacks, and their prevalence is higher among patients who experience attacks more frequently.[19] A recent British Porphyria Association patient survey reported that 94% of patients surveyed experienced chronic symptoms between attacks, including pain (87%), fatigue and tiredness (83%), emotional distress (80%), and trouble sleeping (60%).[26] AHP patients may develop chronic pain associated with axonal motor polyneuropathy,[27] and chronic non-attack pain persists regardless of use of hemin or opioids during an attack.[11] Chronic pain symptoms can lead to severe depression and anxiety, which may necessitate psychiatric care.[8] Notably, a 370-fold higher rate of suicide (3.7% vs 0.01%), has been reported in AHP patients compared with the general population, particularly among individuals experiencing repeated AHP attacks.[19,28,29] Other frequent chronic AHP symptoms include fatigue, nausea, anxiety and fear of the symptoms of an attack.[11,22,23] Additionally, long-term complications such as chronic kidney disease, hypertension, hepatocellular carcinoma, and anaemia are associated with AHP, and their occurrence frequently increases with higher rates of acute porphyria attacks.[19,21,30,31]

Current treatment options

Prior to givosiran there were no therapies licensed for the prevention of repeated AHP attacks in the UK, and there remains a high unmet medical need for a safe and effective therapy that addresses the underlying cause of AHP to prevent attacks and improve the QoL of patients with this condition. Current AHP treatment options focus on the control and symptomatic relief of acute attacks and the management of repeated attacks and include the identification and elimination of lifestyle triggers and symptomatic therapies for pain, hypertension, tachycardia, nausea, vomiting, and convulsions. The only specific treatment for acute attacks is infusion of hemin, which usually improves the symptoms of an AHP attack within a few days.[17,24]

Impact of the new technology

Givosiran represents a step-change in the management of AHP; however, it is not expected the technology will require significant changes to the way current services are organised or delivered. Since givosiran is the only disease-modifying therapy that treats the underlying AHP disease process, thereby preventing the occurrence of attacks and addressing ongoing chronic pain,[2,14] it addresses an important unmet need for patients with a history of AHP attacks. Furthermore, AHP predominately affects women in their reproductive years, and is associated with opioid use and the potential for dependence, mental health issues, and a social care burden such that the performance of daily activities, including childcare and maintaining employment, may become impossible.[11,26,32,33] The introduction of givosiran in the UK is therefore expected to reduce the burden of AHP on patients, caregivers, and society.

Outcomes from the pivotal phase 3 study ENVISION, which included patients from the UK, demonstrate that patients who receive givosiran experience fewer debilitating AHP attacks and improvements in symptoms, which translate into improved QoL.[14] Givosiran treatment leads to pain reduction and an improved ability of AHP patients to function physically and socially.[14] Clinical experts have highlighted the

positive impact of givosiran on their patients' QoL, including life-altering changes in their patients' experience of debilitating symptoms, ability to carry out activities of daily living, and social and family interactions, and a documented lowering of caregiver burden.[34-37] Some UK ENVISION study participants stated that thanks to givosiran, they 'got their life back'.[35] Givosiran is also expected to improve the ability of AHP patients to work (and to return to work after extended sick leave), and to allow them to meet new professional milestones not previously possible.[34-37]

Impact on the NHS—costs and health effects

Value for money

Alnylam Pharmaceuticals developed a *de novo* Markov model to estimate the impact of treatment with givosiran on AHP patients in terms of costs and effects (quality-adjusted life-years; QALYs). The model compared best supportive care (BSC) consisting of established clinical management without givosiran vs givosiran with BSC. For each six-month cycle, the AHP cohort transitioned across five health states corresponding to the four mutually exclusive categories of AHP disease severity based on the frequency of acute attack (i.e., Asymptomatic, Symptomatic, Recurrent, and Severe), plus death. After a five-year time horizon, the cohort was assumed to remain stable. To ensure alignment with clinical practice in the UK, the model design and assumptions made were developed in consultation with established clinical experts on AHP including expert clinicians from NAPS, the highly specialised service supporting UK patients with porphyria.

The cost-effectiveness analysis (CEA) considers patients with recurrent severe attacks of AHP, per the final NICE scope.[38] This target population is consistent with the patient population in ENVISION, which exclusively enrolled patients with a history of repeated acute attacks. Demographic data inputs to the CEA were obtained from the baseline characteristics of the population in the ENVISION trial.[14] Givosiran compared with BSC yields a discounted incremental cost-effectiveness ratio (ICER) of [redacted]. After five years, the model predicts that 95% of givosiran-treated patients will be asymptomatic compared with only 13% of BSC-treated AHP patients.

Budget impact

[redacted]

Impact of the technology beyond direct health benefits

The introduction of givosiran is expected to lead to savings of healthcare resource usage, as treatment with givosiran has been demonstrated to reduce the accumulation of the toxic porphyrin precursors ALA and PBG—and consequently the burden of acute attacks—across patients over time. As such, the NHS is expected to benefit from a disinvestment in resources and symptomatic treatments associated with management of acute attacks and AHP-related comorbidities.

Conclusions

In the largest trial of AHP to-date, measuring a comprehensive range of outcomes that reflect the multi-systemic nature of the disease, and in a population representative of the NHS setting, givosiran was shown to limit the frequency and severity of AHP attacks, reduce pain and improve the ability of AHP patients to function physically and socially.[14] Clinician testimonials highlight life-altering changes in their AHP patients' experience of debilitating symptoms, ability to carry out activities of daily living, social and family interactions, and ability to work.[34-37]

Crucially, the management and treatment of AHP patients will be coordinated by NAPS with no major adaptations required to existing care infrastructure, to ensure the appropriate use of givosiran. The value for money estimates are in the range of those for medicines previously approved under the NICE HST process,[39] and the estimated budget impact of givosiran is expected to be controlled by the limitation of disease management and treatment exclusively to highly specialised NAPS centres, and remains below [redacted] in each of the first five years. The introduction of givosiran for the treatment of AHP represents a unique opportunity to treat the underlying disease-causing mechanism behind this rare and burdensome genetic disease.

Section A – Decision problem

1. Statement of the decision problem

Table 1. Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	Adults and young people aged 12 years or older with recurrent severe attacks of acute hepatic porphyria	None	N/A
Intervention	Givosiran	None	N/A
Comparator(s)	Established clinical management without givosiran, which may include: • haem arginate • gonadotrophin analogues • liver transplantation	Liver transplantation has not been included as a comparator in the economic model.	Due to its extreme rarity, liver transplantation is not considered a relevant comparator.
Outcomes	The outcome measures to be considered include: • Numbers of acute attacks • Porphyrin precursor concentrations in urine • Neurological impairment • Autonomic function • Mortality • Adverse effects of treatment • Health-related QoL (for patients and carers).	None	N/A
Subgroups to be considered	If the evidence allows, subgroups based on the subtype of acute hepatic porphyria (i.e., AIP, ADP, HCP, VP) will be considered. • Guidance will only be issued in accordance with the marketing authorisation. • Guidance will consider any Managed Access Arrangements	None	N/A
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	None	N/A
Cost to the NHS and PSS, and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life-year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	None	N/A
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise.	None	N/A
Special considerations, including issues related to equality	• Guidance will only be issued in accordance with the marketing authorisation • Guidance will consider any Managed Access Arrangements	None	N/A

ADP: delta aminolevulinic acid dehydratase deficiency porphyria; AIP: acute intermittent porphyria; HCP: hereditary coproporphyria; NHS: National Health Service; QoL: quality of life; VP: variegate porphyria

2. Description of technology under assessment

2.1. Brand name, approved name and therapeutic class

Brand name: Givlaari®[2]

Approved name: givosiran[2]

Therapeutic class: ribonucleic acid interference (RNAi) therapeutic (ATC code not yet assigned[2])

2.2. Principal mechanism of action of the technology

Givosiran is an EMA approved medicine in the RNAi therapeutic class.[4] RNAi is a natural process of gene silencing that occurs in organisms ranging from plants to mammals.[40] Small interfering RNA (siRNA) bind sequentially to specific target messenger RNA (mRNA) sequences in a way that leads to the degradation of those targeted mRNA strands, thereby inhibiting the synthesis of the corresponding protein. RNAi therapeutics use the same mechanism of action to inhibit the production of specific disease-causing proteins.[41] The discovery of RNAi was awarded the 2006 Nobel Prize in Physiology or Medicine.[42] Alnylam's drug discovery platform exclusively focuses on developing RNAi medicines to target the cause of diseases by potently silencing specific mRNAs.

The porphyrias are rare inherited metabolic disorders of haem biosynthesis in which specific patterns of overproduction of haem precursors are associated with characteristic clinical features.[6] Acute hepatic porphyria (AHP) comprises a group of porphyrias in which the major site of excess production of haem precursors is the liver (Table 2).[6,7]

Table 2. Classification of porphyria

Classification	Main manifestation	AHP subtype
Hepatic	Acute, neurologic	**Acute intermittent porphyria (AIP)**
		ALAD porphyria (ADP)
	Acute, neurologic and cutaneous	**Hereditary coproporphyria (HCP)**
		Variegate porphyria (VP)
	Cutaneous	Porphyria cutanea tarda (PCT)
		Hepatoerythropoietic porphyria (HEP)
Erythropoietic	Cutaneous	Congenital erythropoietic porphyria (CEP)
		Erythropoietic protoporphyria (EPP)
		X-linked protoporphyria (XLP)

Note: The four AHP types that can be treated with givosiran are indicated with bold typeface and grey shading. Givosiran is not indicated for the other types of porphyria listed in this table. ALAD: delta aminolevulinic acid dehydratase. Source: Ramanujam (2015)[6]

AHP is characterised by the occurrence of acute neurovisceral attacks in which patients experience debilitating symptoms, including abdominal pain, nausea, vomiting, constipation, seizures, and neuropsychiatric symptoms.[43] Women are more likely to have AHP attacks, with the majority presenting when they are between 20 and 40 years of age.[44] This has been linked to changes in ovarian physiology.[7,45]

Acute attacks are accompanied by high excretion of the porphyrin precursors aminolevulinic acid (ALA) and porphobilinogen (PBG) in the urine.[19-21] ALA is neurotoxic and may exert its effect either via oxidant or genotoxicity properties.[17,46] Thus, ALA seems to be directly responsible for the symptoms of acute porphyria.[10,47]

Givosiran is a small interfering ribonucleic acid (siRNA) therapeutic targeting delta aminolevulinic acid synthase 1 (ALAS1) for the treatment of AHP.[12,13] Administration of givosiran significantly lowers induced liver ALAS1 levels in a sustained manner and thereby decreases levels of the toxic haem intermediates ALA and PBG to near-normal levels.[13,14] By reducing accumulation of these intermediates, givosiran significantly reduces or prevents the occurrence of porphyria-related attacks and also decreases other aspects of disease burden.

2.3. Dosing Information of technology being evaluated

Table 3. Dosing Information of technology being evaluated

Pharmaceutical formulation	Solution for injection[2]
Method of administration	Subcutaneous injection[2]
Doses	2.5 mg/kg body weight[2]
Dosing frequency	Once monthly[2]

Average length of a course of treatment	It is expected that patients will be treated with givosiran for the duration of their lives, subject to the clinical judgement of the treating physician; however, female patients who achieve asymptomatic status by menopause onset are expected to be able to discontinue givosiran treatment without incurring risk of further acute attacks. [redacted]
Anticipated average interval between courses of treatments	1 month[2]
Anticipated number of repeat courses of treatments	It is expected that patients will be treated with givosiran for the duration of their lives, subject to the clinical judgement of the treating physician.
Dose adjustments	No dose adjustment is required.[2]

3. Regulatory information

3.1. UK marketing authorisation status

A positive CHMP opinion was published on 30 January 2020.[4] Givosiran received marketing authorisation valid throughout the European Union (EU) on 2 March 2020.[48]

3.2. Anticipated launch date in the UK

It is anticipated that givosiran will be launched in the UK shortly after NICE approval.

3.3. Regulatory approval of the technology outside the UK

Givosiran is approved for use in the USA and the EU.[1,49]

3.4. Current use of technology in England

N/A

4. Ongoing studies

4.1. Completed and ongoing studies on the technology from which additional evidence relevant to the decision problem will be available in the next 12 months

ENVISION (NCT03338816) is a phase 3 randomised, double-blind, placebo-controlled multicentre study with an ongoing, 30-month open-label extension to evaluate the efficacy and safety of givosiran in patients with AHP.[14,50] The primary endpoint, reduction in annualised rate for porphyria attacks requiring hospitalisation, an urgent healthcare visit, or intravenous (IV) hemin (haem arginate) administration at home, was reached in ENVISION, and AHP patients who received givosiran had a significantly lower rate of composite porphyria attacks (73% lower rate; $p<0.001$) than those who received placebo. Givosiran treatment also resulted in lower levels of urinary ALA and PBG, fewer days of hemin use, and better daily scores for pain than placebo. A manuscript based on a 12-month ENVISION OLE data cut will be submitted for publication in the next 12 months, and a poster of a 24-month ENVISION OLE data cut may be presented at the 2021 International Congress on Porphyrins and Porphyrias. The ENVISION OLE study (6-month double-blind period and 30 month OLE) will complete within the next 12 months, but the results will not be published within this timeframe.

Other ongoing studies include a phase 1/2 multicentre, open-label extension (OLE) study (NCT02949830) to evaluate the long-term (up to 42 months) safety and clinical activity of givosiran in patients with acute

intermittent porphyria who have completed a previous givosiran clinical study,[51,52] and an expanded access protocol of givosiran for patients with AHP (NCT04056481).[53]

Additional natural history data from part B of the EXPLORE study are anticipated to be available within the next 12 months.

4.2. Summary of other planned assessments of technology in the UK

ELEVATE, a global observational longitudinal prospective AHP patient registry, will start enrolling AHP patients from the UK and other countries from Q2 2021. ELEVATE is a disease registry with study objectives including to characterise the long-term real-world safety of givosiran in patients with all types of AHP; to characterise the long-term real-world effectiveness of givosiran in patients with all types of AHP; and to describe the natural history and real-world clinical management of patients diagnosed with AHP.[54]

5. Equality

5.1. Equality considerations

A timely HST review would support NICE's commitment to promoting equality. Givosiran targets a hereditary progressive, debilitating, and potentially fatal disease (in the absence of treatment),[33] for which there are no other disease-modifying treatment options that treat the underlying AHP disease process. AHP is found in all ethnic and racial groups.[7] The fact that AHP is a hereditary disease amplifies the burden it places on affected families, as revealed in a recent survey of patients and caregivers in the UK.[26]

Furthermore, AHP predominantly affects women in their reproductive years, and is associated with often excruciating pain, opioid use and the potential for dependence, mental health issues and a social care burden such that the performance of daily activities, including childcare and maintaining employment may become impossible.[11,26,32,33]

5.2. How the submission will address equality issues

Availability of givosiran would fill an unmet need for patients with AHP as well as families impacted by the hereditary nature of the disease.

Section B – Nature of the condition

6. Disease morbidity

- Acute hepatic porphyria (AHP) comprises a family of rare genetic metabolic disorders characterised by repeated severe attacks and debilitating chronic manifestations between attacks that negatively impact daily functioning and quality of life.
- AHP attacks primarily manifest as severe abdominal pain accompanied by nausea, psychiatric manifestations, fatigue, and muscle weakness.
- AHP patients can experience residual disability after an attack subsides that may result in long-term disability.
- Pain is the cardinal chronic symptom associated with AHP.
- Chronic symptoms are frequently neurological (paraesthesia, motor weakness, paralysis) or psychiatric (anxiety, depression, psychosis/hallucinations, insomnia, and suicidality).
- Long-term AHP complications include hypertension, renal impairment, hepatocellular carcinoma, and anaemia.
- AHP disproportionately impacts female patients in their prime productive years.

6.1. Disease overview

6.1.1. Pathophysiology

AHP consists of the four rare, metabolic disorders ADP, AIP, HCP and VP (Table 2), caused by genetic mutations in the haem synthesis pathway enzymes ALA dehydratase (ALAD), hydroxymethylbilane synthase, coproporphyrinogen oxidase and protoporphyrinogen oxidase, respectively (Figure 1).[10] AIP, HCP and VP are autosomal dominant disorders, whereas ADP is an autosomal recessive disorder.[11,24]

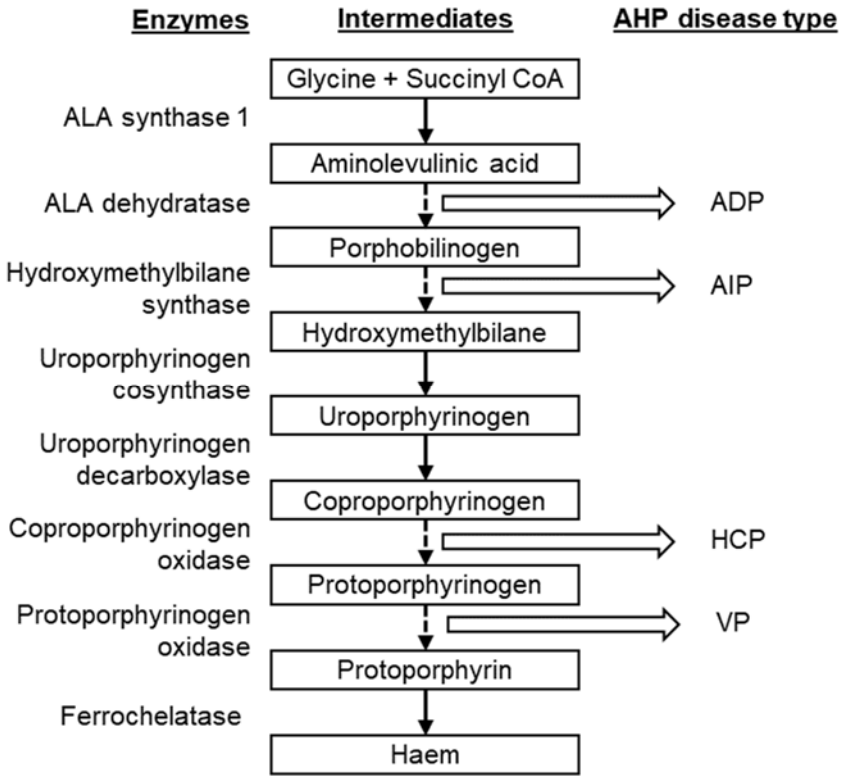


Figure 1. Pathophysiology of AHP

ADP: ALA dehydratase-deficient porphyria; AHP: acute hepatic porphyria; AIP: acute intermittent porphyria; ALA: aminolevulinic acid; CoA: coenzyme A; HCP: hereditary coproporphyria; VP: variegate porphyria. Source: Adapted from Bissell et al. (2017)[10]

In AHP, the haem intermediates ALA and PBG accumulate in the liver due to increased liver ALAS1 gene transcription, increased haem consumption, and mechanisms related to hormonal fluctuation during menstruation and pregnancy.[9,16,17] Acute attacks are accompanied by high excretion of the porphyrin precursors ALA and PBG in the urine.[19-21] ALA is neurotoxic and may exert its effect either via oxidant or genotoxicity properties.[17,46] Thus, ALA seems to be directly responsible for the symptoms of acute porphyria.[10,47]

AIP – acute intermittent porphyria

AIP, the most common of the AHP subtypes, is caused by mutations in the hydroxymethylbilane synthase (HMBS) gene, resulting in partial HMBS deficiency (Figure 1).[9,11,24]

VP – variegate porphyria

VP is due to mutations leading to partial loss-of-function (i.e., 50% of normal function) of the PPOX gene encoding the enzyme protoporphyrinogen oxidase (Figure 1).[9,24]

HCP – hereditary coproporphyria

HCP is caused by mutations in the CPOX gene, which encodes the enzyme coproporphyrinogen oxidase (Figure 1).[9,24]

ADP – ALAD porphyria

ADP, the rarest AHP subtype, is due to a substantial deficiency of ALAD (Figure 1), and usually manifests in childhood with ALAD activity of 1%–5% of normal.[24] Heterozygous individuals are generally clinically asymptomatic.[11,24]

6.1.2. Clinical features

AHP is characterised by acute attacks (which may be severe and potentially life-threatening if not promptly treated; see Section 8.2.1) and, for many patients, chronic debilitating symptoms that negatively impact daily functioning and quality of life (QoL).[8-11] The clinical manifestations of AHP differ between the four subtypes: AIP and ADP typically present as acute neurovisceral (i.e., affecting the viscera and the autonomic nervous system that innervates them) attacks alone, whereas patients with HCP or VP may experience acute attacks with cutaneous phototoxicity due to a build-up of porphyrins in the skin or dermal blood vessels occurring apart from or along with attacks.[24] AIP and ADP are the only types of porphyria that are not generally associated with cutaneous phototoxicity, as the causative enzyme deficiencies occur prior to porphyrin formation in the haem biosynthetic pathway, although cutaneous symptoms may occur in patients with AIP if the disease is complicated by advanced renal disease.[24] Skin lesions in HCP are less common than in VP but more common than in AIP.[11]

In addition to the association of AHP attacks with widespread dysfunction across the autonomic, central, and peripheral nervous systems, the majority of patients who experience repeated acute attacks also experience chronic symptoms and long-term complications.[11,19,22]

AHP disease severity

While there is no standard classification to define disease severity in AHP, a long-term (50-year) study by Neeleman et al. (2018) proposed a categorisation based on the frequency of occurrence of attacks as follows:[19]

- Recurrent: >4 attacks per year
- Symptomatic: ≥1 porphyria attack in any year but does not meet the Recurrent attack criteria
- Asymptomatic: mutation carriers who have never experienced a proven acute porphyria attack

Data from this large, long-term observational study demonstrated a strong association between acute attack frequency and the number of AHP-related manifestations, including acute symptoms (e.g., gastrointestinal [GI] symptoms, fatigue, malaise), pain, neurological and psychiatric symptoms, seizures, and long-term complications.[19] The classification of AHP severity described in Neeleman et al. was subsequently used as a basis for development of the health states in the economic model, as described in 12.1.3. However, based on findings from the ENVISION phase 3 study of givosiran, categorising all patients with more than four attacks per year as part of one singular health state is an overly broad and crude consideration of patients' disease severity. The ENVISION study revealed high variation in the number of attacks patients could experience in a given year, ranging from 0 to 52.[55] The addition of a "Severe" disease health state for patients with more than 24 attacks per year allows for more granular estimation of patients' disease severity. Expert UK clinicians considered a four-level categorisation of AHP health states to be appropriate, so this categorisation is used to define health states in this submission.[56]

Acute attacks

AHP attacks manifest as episodes of potentially extreme incapacitation characterised by a combination of non-specific symptoms.[23] Attacks start with intense and usually diffuse abdominal pain and muscle weakness, followed by nausea and vomiting, constipation or diarrhoea, hypertension, tachycardia, limb, head, neck or chest pain, mental symptoms (including confusion and hallucinations), convulsions, and seizures.[7,16,24] Neurovisceral symptoms are generally indistinguishable across AHP subtypes, but may vary substantially between patients.[17,25]

The frequency of symptoms during AHP attacks as reported by patients in the natural history study EXPLORE, which included 112 patients in Europe (n=63, including 6 in England and Wales[22]) and North America (n=49), are presented in Figure 2.[11] The most debilitating and frequent AHP attack symptom was

severe, diffuse neurovisceral pain in the abdomen, limbs, or back. Overall, 98% of AHP patients reported pain during an acute attack, including abdominal pain (92%), limb pain (77%), back pain (72%), muscle pain (66%), and headache (51%).[22]

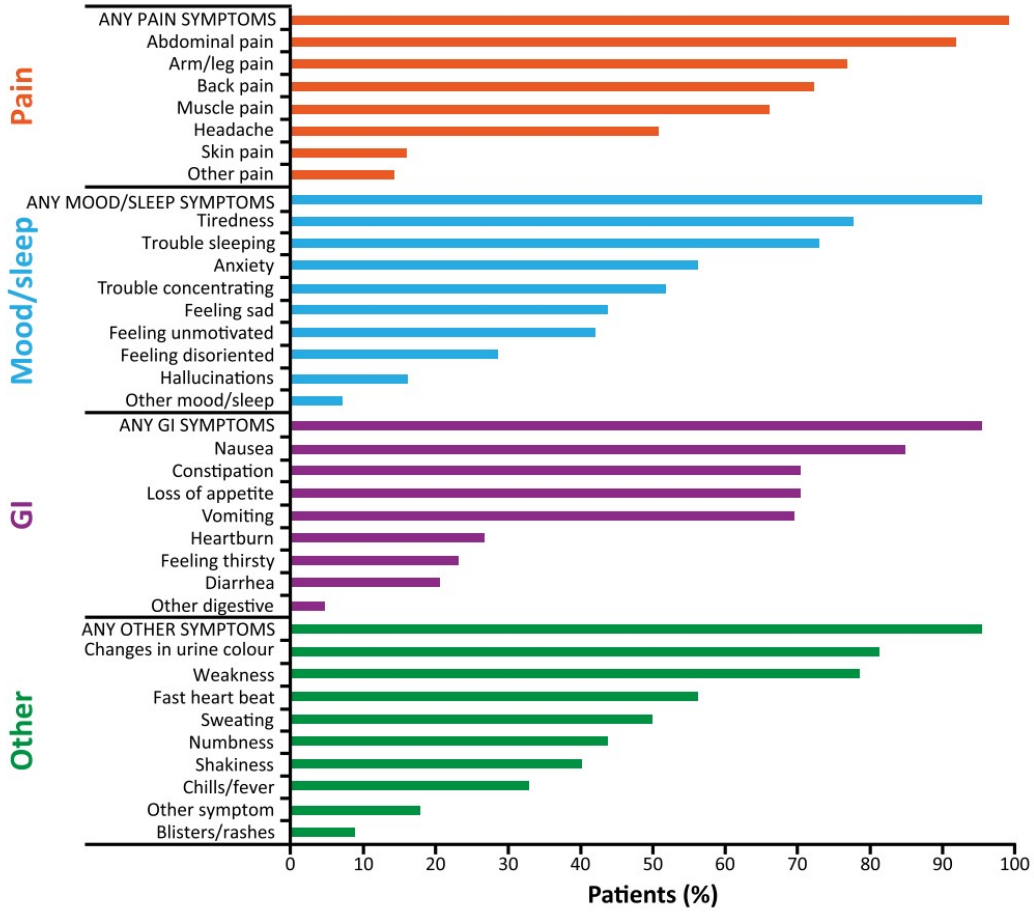


Figure 2. Frequency of symptoms during AHP attacks
GI: gastrointestinal. Source: EXPLORE study, Gouya et al. (2020)[11]

The intensity of abdominal pain is typically high (>7 cm on the visual analogue scale [VAS; scale from 0–10 cm])[17] and severely debilitating, as reported in AHP attack patient testimonials (Table 4).

Table 4. Patient testimonials of their experience during AHP attacks

Pain
"So, they present always the same way, they present with, for me, excruciating stomach pain, pain in my back and pain down my inner thighs. When I say pain, its off the score – its off the 0–10 score, its way over that."[26,32]
"…the fear that my body would sort of break from the pain, because I couldn't, in my head I'm thinking there is only so much I can deal with, at some point you're going to snap."[26,32]
"I'm more than in tears, like I am literally like crying, crying, because the pain is just, it's so bad, it's like a stabbing, it's a burning, it's a pulling and a twisting, it's everything you could imagine, it's the absolute worst pain in the world."[23]
"not compatible with life".[23]
"…there is no pain like porphyria pain. There can be no comparison (to other pain). It is not of this world".[57]
"I describe mine as having the worst flu you ever had in your life, that whole body ache and everything else that goes along with it and multiply that by about a hundred times."[23]
Nausea
"unbearable"; "uncontrollable"; "The nausea is what just knocks me out. I mean it just—literally, I cannot do anything."[23]
"You're like throwing up to the point where like you want to die, and you're spitting up bile, and even though your stomach is completely empty and you're like, 'where is this coming from? I haven't eaten in hours. I've been throwing up for half a day'. I'm vomiting foam at that point." [23]
Neurological symptoms
"I'll lose feelings in my hands and my stomach will be – it feels like someone's kicking me in the stomach. It's very, very sore and very tender. And then my liver area will start burning really badly. I can't eat because anything that I eat will come back up. And, I'm dizzy at times and disoriented and the biggest thing is that it robs me of my quality of life." [23]

"I had like paralysis also in my legs, and I couldn't walk. I mean like I was dragging a leg. And also I had difficulty breathing. I almost got put on the ventilator."[23]
"I had seizures after seizures … about three of them within about four hours."[23]
Fatigue
"It will take me a couple of days just to lay in bed and sleep trying to recover."

Source: American Porphyria Foundation (2017)[57]; BresMed Health Solutions 2019[32]; Gill 2019[26]; Simon 2018[23]

GI symptoms during an acute attack were reported in 95% of patients in EXPLORE, with nausea (85%) being the most common, followed by loss of appetite (71%), constipation (71%), and vomiting (70%).[11,22] The experience of nausea (and vomiting) during an acute attack is especially debilitating, which has been described by patients as constant or unrelenting.[32,57]

Mood and sleep disorders were reported in 94% of patients experiencing an acute attack in EXPLORE.[11,22] Specific symptoms included tiredness (78%), trouble sleeping (73%), anxiety (56%), trouble concentrating (52%), and feeling sad (44%).[11,22] Accounts from patients and their caregivers describe a range of psychiatric symptoms experienced during an acute attack. In a UK survey of 46 patients and their caregivers, respondents recounted their experiences with mood changes, loss of memory, psychosis and hallucinations, confusion, fear and anxiety.[32] The impact of AHP on psychological well-being is described further in Section 7. Other acute attack symptoms reported by patients in the EXPLORE study included weakness (64%), sweating (48%), shakiness (39%), rapid heart-beat (35%), numbness (36%) and chills or fever (36%).[11]

Most acute attacks last no more than 1 or 2 weeks.[58] The mean duration of acute attacks requiring hemin administration and/or treatment at a healthcare facility in EXPLORE was 7.3 days (standard deviation [SD]=6.0 days).[11] This average duration of acute attack has been validated by three UK physicians as being representative of their experience with AHP patients.[56]

Most patients recover from acute attacks;[17] however, the extent of muscle weakness, the need for mechanical ventilation, bulbar palsy, consciousness impairment, and the development of hyponatraemia are correlated with poorer outcome.[59] Permanent quadriplegia may also rarely occur as a result of severe attacks.[60]

Recurrent acute attack

European Porphyria Network (EPNET) guidelines report the definition of recurrent acute attacks as >4 attacks per year, and NAPS and the majority of studies align with this definition.[6,19,29,61] Approximately 3-5% of symptomatic AIP patients experience recurrent acute attacks.[15] According to NAPS, there are currently N=35 people with severe recurrent AHP in the UK. Of them, N=6 patients are included in givosiran trials/compassionate use. According to expert opinion, it is assumed that there will be approximately N=2 new (incident) patients with severe recurrent acute attacks each year.

AIP patients in the EXPLORE study who experienced repeated attacks had a mean rate of 9.4 attacks per year, and a mean of 6.3 attacks were severe enough to require treatment (hemin) or hospitalisation in the past year.[22] Patients in EXPLORE who experienced repeated attacks were hospitalised overnight an average of 4.5 times in a year.[11]

Chronic disease manifestations

Chronic, ongoing signs and symptoms, outside those found in attacks, are common in AHP patients with repeated attacks, and their prevalence is higher among patients who experience attacks more frequently.[19] Chronic manifestations include pain, neurological, and psychiatric symptoms (Table 5).[19]

A recent patient survey conducted in collaboration with the British Porphyria Association (Gill et al., 2019) reported that 94% of patients surveyed experienced chronic symptoms between attacks, including pain (87%), fatigue and tiredness (83%), emotional distress (80%), and trouble sleeping (60%).[26]

Pain, neurological and psychiatric symptoms in chronic porphyria patients generally increase with higher AHP attack frequency (

Table 6, Table 86 [in Appendix 5]), highlighting the significant impact of chronic manifestations in AHP and the association between attack frequency and frequency of reported symptoms.[19]

Table 5. Patient testimonials of their experience of chronic AHP

Pain
"… pain level is probably like at a six out of 10, um, on a daily basis… I would say it feels like you—like I said, you have like little people in there with barbed wires, just like fighting."[23]
"I have pain disassociation so that my level of pain is at a five all the time, which is probably someone else, a normal person's 10, because I'm so used to the pain."[23]
"I would say 80% of the time I'm symptomatic."[23]
"On a pain scale from zero to 10 where you know zero is no pain and 10 is the worst, um, a typical day you know the headaches are probably around a four to a five."[23]
"I don't really sleep well at night at all from the porphyria because, um, my back hurts and, uh, my feet hurt and my legs, they hurt a lot."[23]
Nausea
"You know, I don't really get a whole lot of relief in between attacks. I still experience severe, severe nausea, especially in the morning when I first wake up."[23]
"I was nauseated every day and it was like a six to a seven on the scale."[23]
Fatigue
"It definitely affects me. I get tired very easily and have to take one, two naps a day."[23]
"… it's so frustrating. You know, you shouldn't be that tired. You know, you should be able to live a normal life."[23]
Neuropathy
"I haven't been able to – off and on I haven't been able to feel my hands since November of 2011. Um, I, I have less or more numbness in my fingers and tingling in my fingers and hand."[23]
"Nerve pain and nerve sensations because when you get numbness sometimes there's nerves that are kind of alive and other parts that are dead. And it feels like something is crawling on you. And it's like a bug is on your arm or something touches you on the middle of the night. It wakes you up. I get woken up a lot because of nerve sensation."[23]

Source: Simon 2018[23]

Table 6. Chronic symptoms in AIP

Symptom	Recurrent cases (n=11) (%)	Symptomatic cases (n=24) (%)	Asymptomatic controls (n=53) (%)	Linear-by-linear Chi^2 association test
Pain	100.0	91.7	30.2	P<0.001
Neurological	81.8	45.8	17.0	P<0.001
Psychiatric	81.8	33.3	18.9	P<0.001

Note: Recurrent cases were defined as having >4 attacks per year, Symptomatic cases had at least one attack in any year that they were followed but did not meet that criteria for a Recurrent case, and Asymptomatic controls were mutation carriers who did not experience attacks. AIP: acute intermittent porphyria. Source: Neeleman et al. (2018)[19]

Chronic symptoms were reported by 65% of EXPLORE patients, and of these, 71% reported having daily symptoms.[11,22] Severe, chronic pain, defined as persistent or recurrent pain lasting >3 months,[62] was experienced by 63% of patients with chronic non-attack symptoms in EXPLORE (Figure 3).[22]

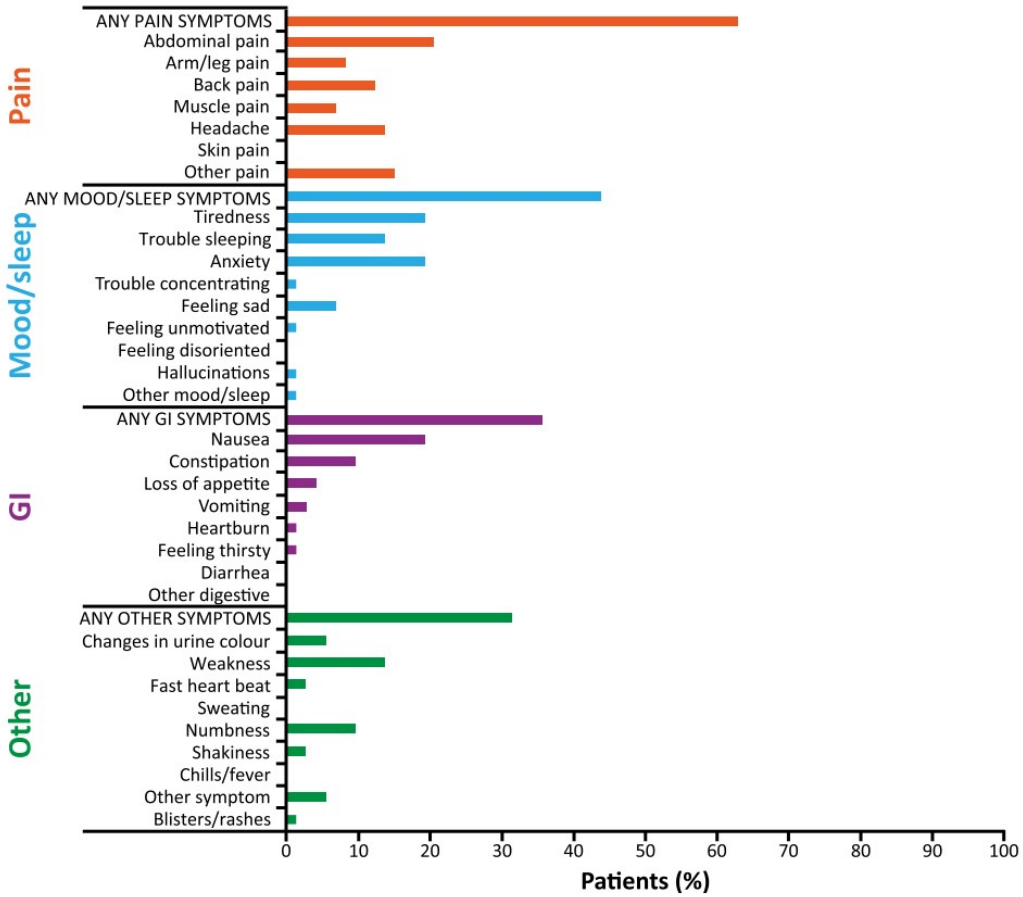


Figure 3. Frequency of chronic symptoms in EXPLORE
GI: gastrointestinal. Source: EXPLORE study, Gouya et al. (2020)[11]

AHP patients may also develop chronic pain associated with axonal motor polyneuropathy,[27] and chronic pain symptoms can lead to severe depression and anxiety, which may necessitate psychiatric care.[8] Chronic non-attack pain persists regardless of use of hemin or opioids during an attack.[11] Other frequent chronic AHP symptoms include fatigue, nausea, anxiety and fear of the symptoms of an attack.[11,22,23]

Long-term complications

Long-term complications associated with AHP include chronic kidney disease (CKD), hypertension, hepatocellular carcinoma (HCC), and anaemia, and their occurrence frequently increases with higher rates of acute attack (Table 7).[19,21,30,31]

Table 7. Long term complications in AIP

Long-term complication	Recurrent cases (n=11) (%)	Symptomatic cases (n=24) (%)	Asymptomatic controls (n=53) (%)	Linear-by-linear Chi^2 association test
CKD	63.6	45.8	13.2	P<0.001
Hypertension	72.7	70.8	26.4	P<0.001
HCC	9.1	8.3	1.9	P=0.15
Anaemia	63.6	16.7	5.7	P<0.001

*p-value is for Chi-squared or Fisher's Exact Test comparisons of recurrent vs asymptomatic, and symptomatic vs asymptomatic. Note: Recurrent cases were defined as having >4 attacks per year, Symptomatic cases had at least one attack in any year that they were followed but did not meet that criteria for a Recurrent case, and Symptomatic controls were mutation carriers who did not experience attacks. AIP: acute intermittent porphyria; CKD: chronic kidney disease; HCC: hepatocellular carcinoma. Source: Neeleman et al. (2018)[19]

Chronic kidney disease

CKD and renal impairment are potential long-term complications of AHP.[17,30,63,64] High levels of the toxic metabolite ALA induce vascular injury, and repeated attacks may cause acute kidney injury and progression to irreversible CKD.[21] Although no data are available on the increase in mortality due to CKD in

UK patients with AHP specifically, CKD Stage 3 or 4 is associated with mortality hazard rate 7.6 times higher than in the general UK population.[65]

Hypertension

AHP may lead to an increased long-term risk of chronic sustained hypertension,[8,21,30,66] and deaths due to complications of hypertension in AIP patients have been reported.[30]

HCC

An estimated 10% of patients with AHP die from cancer of the liver,[31,67] and HCC has been reported as a long-term complication of AHP, occurring in approximately 1.5% of AHP patients.[30,31,68-72] HCC may occur in AHP patients who do not experience attacks or show signs of cirrhosis,[17,30] and may be due to direct carcinogenicity of ALA, reduction in free radical scavenging due to reduced haem-containing antioxidant enzymes, or tumour suppressor genes being directly or indirectly affected by mutations in the HMBS gene.[30,46]

Other life-long porphyria-related symptoms

Epilepsy has been reported in patients with AHP,[73] and epileptic seizures have been reported in both symptomatic patients and in asymptomatic gene cariers.[74] Although no data are available on the increase in mortality due to epileptic seizures in patients with AHP specifically, the United Kingdom National General Practice Study of Epilepsy has reported a 2.5 fold increase in annual mortality due to epileptic seizures compared with the general population.[75]

Hyponatraemia is an electrolyte abnormality that occurs during an acute attack. Hyponatraemia becomes increasingly prevalent as patients experience more frequent attacks[19] and is a risk factor for seizures.[76]

Anaemia is most prevalent in patients with repeated AHP attacks, and is often accompanied by kidney disease.[19,77] Although no data are available on the increase in mortality due to anaemia in patients with AHP specifically, it has been associated with a 70% increase in 8-year mortality.[78]

6.1.3. Diagnosis

For most AHP patients, symptom onset is between the second and fourth decades of life, with a median age at diagnosis of 33 years.[15,73] AHP is often initially overlooked or misdiagnosed. Factors that may contribute to a delayed or missed diagnosis include: (1) lack of awareness of the rare porphyria disorders among some clinicians; (2) presentation with complex and non-specific symptoms; (3) patients may be followed and treated by multiple different clinicians for individual symptoms; and (4) certain precipitating factors such as menstruation/pregnancy and infections may confound symptom assessment.[17,25,29,79] For 61% of patients included in the EXPLORE natural history study, accurate diagnosis took over 5 years.[11]

Accuracy and speed are vital in diagnosing AHP patients during attacks, as delaying treatment can lead to neurologic damage and possibly death.[43] Under- and misdiagnosis also put patients at risk of receiving porphyrinogenic medications with a potentially fatal outcome.[16,17] The first-line biochemical testing for AHP is a urine test for PBG +/- ALA. Testing is ideally carried out during a suspected attack, when PBG and ALA levels are substantially elevated, but urinary testing can also be performed outside of attacks since patients in remission may also have elevated levels. Porphyrins in urine should not be tested without also including testing for ALA or PBG. Additional biochemical tests, including tests for plasma or faecal porphyrins, can be performed to confirm diagnosis and AHP type but are not specific for AHP when tested alone.[17,43] Once a diagnosis of AHP is biochemically confirmed, genetic testing allows the identification of the specific mutation and the AHP type (especially if the PBG test results are not definitive for a type), and can be useful for identifying at-risk family members.[17,33]

6.1.4. Survival

In recent years, improvements in disease recognition and the prompt treatment of acute attacks with hemin have dramatically reduced attack-related mortality, making it a rare event.[8,80]

Although there has been a decline in attack-related mortality, the overall life expectancy of patients with AHP may be affected by several long-term complications (i.e., CKD, hypertension, HCC, anaemia, and epilepsy) that are associated with reductions in survival (see Section 6.1.2 for mortality in long-term complications, and Section 6.3 for a discussion on life expectancy). A real-world study by Baravelli et al. (2020) reports a mortality HR of 1.3 (HR 1.3, 95% CI 1.0, 1.8) for AHP patients compared with the general population.[81]

Additionally, a higher rate of suicide has been reported in AHP patients compared with the general population (3.7% vs 0.01%), particularly among individuals experiencing repeated AHP attacks.[19,28,29]

6.1.5. Specific patient needs addressed

Prior to givosiran there were no therapies licensed for the prevention of repeated AHP attacks available in the UK (see Section 8 for details). Severe attacks require hospital admission and prompt treatment. Following recovery from an acute attack, chronic symptoms and long-term complications can continue to cause significant morbidity and mortality. There remains a high unmet medical need for a safe and effective therapy that addresses the underlying cause of AHP and improves the QoL of patients with this condition. Since givosiran is the only disease-modifying therapy that treats the underlying AHP disease process, thereby preventing the occurrence of attacks and addressing ongoing chronic pain,[14] it meets an important unmet need for patients with a history of recurrent attacks in the UK.[2]

6.2. Number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year

6.2.1. Epidemiological data

AIP is the most common of the AHP types, with an annual incidence in the UK estimated to be eight times that of HCP and twice that of VP.[24,82] Only a handful of ADP cases have been reported globally,[6] and the incidence of ADP in the UK is unknown.

Incidence rates of AIP, HCP, and VP in the UK have been estimated using data collected from EPNET[15] (Table 8). Based on an estimated 2019 UK population of 66.9 million,[83] the combined annual incidence of AIP, HCP, and VP in the UK would be 17.4 new cases per year, including both acute and non-acute diagnoses.[15] This estimated total incidence assumes that the rate for HCP in the UK is comparable to that of the rest of Europe.

Prevalence rates for AIP, HCP, and VP in the UK have been estimated using data from EPNET[15] and Whatley et al. (2013)[84] (Table 8). Estimates of the combined prevalence of all severity levels of AIP, HCP and VP in the UK range from 763 to 1739 cases in 2019.

Table 8. Incidence and prevalence of AHP subtypes in the UK

Porphyria Type	Incidence rate and estimated cases	Prevalence rate(s) and estimated cases
AIP	0.16 per million[15] or 10.7 cases	• 7.2 per million[15] or 482 cases • 1–2 per 100,000[84] or 669–1338 cases
HCP	EU*: 0.02 per million[15] or 1.4 cases	• 1–2 per million[15] or 67–134 cases
VP	0.08 per million[15] or 5.4 cases	• 3.2 per million[15] or 214 cases • 1 per 250,000[84] or 268 cases

*UK-specific incidence rate not available. AHP: acute hepatic porphyria; AIP: acute intermittent porphyria; HCP: hereditary coproporphyria; VP: variegate porphyria. Sources: Elder (2013)[15] and Whatley (2013)[84]

6.2.2. Data from the National Acute Porphyria Service (NAPS)

An estimated 5% of prevalent cases of AIP experience recurrent attacks (i.e., defined as >4 attacks/year).[6] NAPS has identified 35 patients, including 6 patients currently being treated with givosiran through clinical trials, as severe recurrent AHP patients[31] qualifying for treatment with givosiran. The total severe recurrent AHP population size in the UK (since 2012) appears to be stable at approximately 35 patients, with a

maximum recorded annual case fluctuation of no more than 5 new severe recurrent AHP patients in any one year.

6.3. Life expectancy of people with the disease in England

Due to improvements in disease recognition and the prompt use of hemin to treat attacks, AHP attack-related mortality has become a rare event (see Sections 6.1.2 and 6.1.4). However, chronic symptoms and long-term complications of AHP may have an impact on survival and therefore negatively affect the life expectancy of AHP patients.[31] Life expectancy in AHP is discussed in detail in Section 6.1.4, and there is no prevailing evidence suggesting that the life expectancy of AHP patients in England is different.

7. Impact of the disease on quality of life

- AHP patients have a reduced QoL, particularly with regard to pain and discomfort, anxiety and depression, and the ability to function normally.
- AHP attacks are emotionally traumatic for patients, and impact core needs such as relationships and employment; suicidality is not uncommon and has been noted as a significant contributor to AHP patient mortality.
- The ENVISION trial demonstrated givosiran significantly decreased the occurrence of AHP attacks and improved health-related QoL
- Givosiran reduces number of attacks, which leads to a reduction in chronic symptoms and reduced negative impact on QoL
- Givosiran reduces the intensity and severity of AHP attacks when they do occur.
- The reduced functional status of AHP patients constitutes a substantial caregiver burden, which may be alleviated through givosiran therapy.
- The significant improvement on patient QoL as shown in the ENVISION trial has been further supported by expert physicians in clinical practice.

7.1. Impact on the quality of life of patients, their families and carers

Patients with AHP experience debilitating attacks and disabling chronic symptoms between attacks resulting in a reduced QoL, particularly with regard to pain/discomfort, anxiety/depression, and the ability to function normally.[11] Patients in the EXPLORE study reported experiencing substantial problems with pain, anxiety/depression, everyday activities, and mobility (Figure 4), and 25% of AHP patients required assistance in activities of daily living.[85]

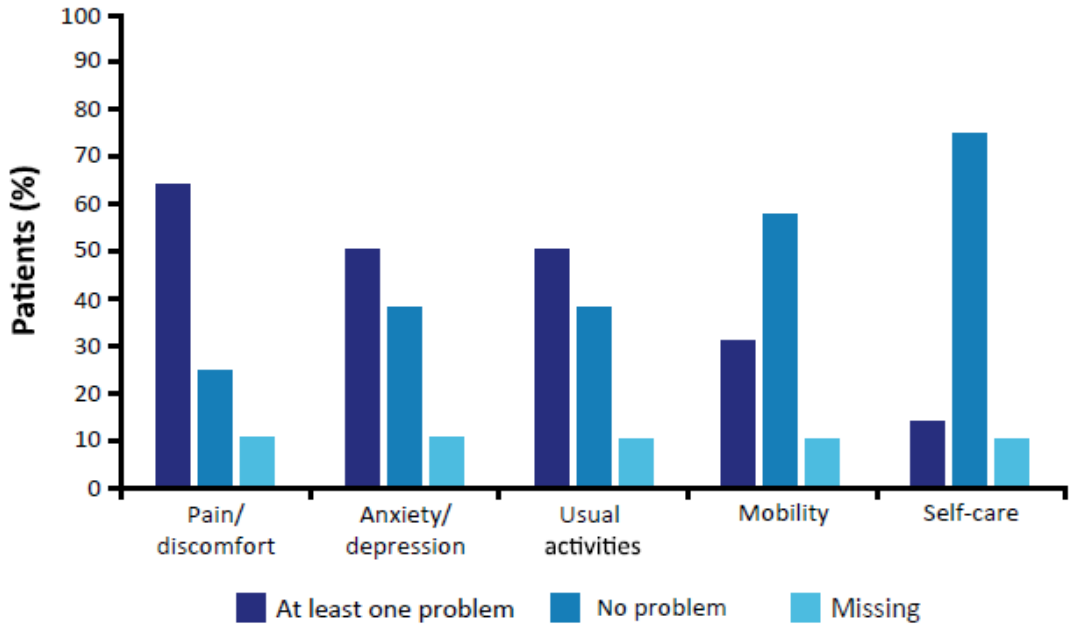


Figure 4. Symptomatic patients with AHP reporting at least some problem in specific domains of the EQ-5D-5L

EQ-5D-5L: 5-level version of the EuroQol five-dimensional health status questionnaire. Source: EXPLORE study, Gouya et al. (2020)[11]

For AHP patients, quality of life is negatively affected not only during attacks but also between attacks. AHP patients who have experienced acute attacks report high rates of anxiety and depression.[19,86,87] The mental toll that AHP takes on patients is significant, affecting personal relationships, causing feelings of isolation, and increasing the risk of suicide (Section 6.1.4)

AHP patients describe feelings of isolation, not only due to a lack of understanding about the disease by friends, family, and healthcare professionals, but also due to the intensity of the pain they experience (Table 4, Table 5).[29]

Patients with AIP in particular experience serious life consequences, such as limitation in family size.[86] Some AHP patients have even reported that the excruciating porphyria-related pain and concerns regarding receiving appropriate diagnosis and care have led to the loss of spouses and the custody of their children.[57]

With a peak occurrence in the third decade of life,[58] AHP disproportionately impacts patients in their prime productive years, and negatively impacts self-sufficiency and employment prospects.[86,88] The EXPLORE study reported that 67% of AHP patients were not able to work full time, and that 85% of AHP patients in employment had lost on average 54 workdays in the past year due to AHP.[85]

The reduced functional status of AHP patients also constitutes a substantial caregiver burden, with employed AHP caregivers reporting an average of 17 workdays lost in order to care for AHP patients.[22,85]

A UK survey of AHP patients revealed that the acute and chronic nature of AHP combined with a lack of effective treatments result in feelings of frustration, fear, anxiety, and depression that affect both patients and their caregivers. Frequently mentioned concerns among patients and carers included coping with pain, a range of other symptoms experienced (e.g., nausea, fatigue, and seizures), and the cognitive and psychiatric symptoms that often accompany this disease (Table 4, Table 5, Table 9).[26,32]

Table 9. First-person accounts of the impact of AHP on patient QoL

Category	Impact
Pain	Acute: 'In actual fact, it's the worst pain I've ever experienced. I wouldn't want anyone to go through the same kind of pain as that. And when you're in that kind of pain, you just want it to stop […] I mean when you're in a lot of pain, your mind's not thinking straight, if you don't want to be there, you don't want to be here because it is just so painful. It's really severe.' Chronic: "the main problem that I experience with the acute attacks, was that I was getting chronic pain in between the acute severe attacks… because I was in too much pain, but yes that's the chronic pain was the worst because it never ever stopped. It didn't end."'
Paralysis and muscle weakness	'It's re-occurred several times now. In my 20 attacks, it's happened more recently in my last five, where I've ended up waking up one morning and I can't move my leg or I can't, or I get out of bed to go to the toilet and I fall. And that's just where the nerves have been attacked obviously, during the porphyria attack.'
GI symptoms	Acute: 'I have terrible nausea; I can't even keep water down at that point, so I had to be hydrated on a drip in hospital.' Chronic: "there are other days where I wake up and I just feel very nauseous."
Fatigue	'I mean even, for the year after my five attacks, I could do one thing a day. So the only thing that in-between attacks that was the killer is the energy levels.'
Seizures	"they [consultants] said [seizures/convulsions] damaged part of, the memory part of my brain. So I have to write things a lot."
Anxiety and	'Psychological depression I suppose because it completely and utterly ruins your life, well it ruined my life.'

Category	Impact
Depression	
Confusion and psychosis	Acute: 'I suffer with hallucinations, confusion, I don't really know what's going on, I don't really know where I am, I'm not safe to be alone.' Chronic: 'I can't concentrate enough now to read – I'll start reading something and basically, I don't know where I am, I sort of lose track before I get to the bottom of the page.'
Daily living	'I didn't work for […] 18 months I didn't work at all. I was on benefits. I was a sick person at home on benefits. Couldn't work, then I went back, the doctors said don't be a nurse forget about it. but I didn't want to do that, life isn't worth living if I can't do what I want to do.'
Social life	'I really felt not part of society' 'It's very difficult to plan anything long term, like I said, holidays, family holidays, wedding attendance. Socially, it really has impacted, we have to live everyday really day to day.'
Impact on personal relationships	"Early in our relationship, when she was having an attack every 2 weeks or so, she would become furious and I wouldn't really know how best to deal with that. And she would break down into tears and bounce between periods of elation and periods of weeping, and she wouldn't sleep so I would stay up with her…"

AHP: acute hepatic porphyria; GI: gastrointestinal; QoL: quality of life. Sources: UK Burden of Illness of Acute Hepatic Porphyria in Patients and Caregivers (2019),[32] Gill et al. (2019)[26]

7.2. Impact that the technology will have on patients, their families and carers

Since givosiran is the only disease-modifying therapy that treats the underlying AHP disease process, thereby preventing the occurrence of attacks and addressing ongoing chronic pain,[2,14] it meets an important unmet need for patients with a history of AHP attacks. The introduction of givosiran in the UK is therefore expected to reduce the burden of AHP on patients, caregivers, and society. Longer-term clinical data and patient-reported outcomes will help define the long-term benefits of givosiran for AHP patients and their carers.

AHP has a disproportionate impact on female patients because it predominately affects women in their reproductive years, and is associated with often excruciating pain, opioid use and the potential for dependence, mental health issues, and a social care burden such that the performance of daily activities, including childcare and maintaining employment may become impossible.[11,26,32,33]

Outcomes from the ENVISION study demonstrate that patients who receive givosiran experience fewer debilitating attacks of AHP which will in turn favourably impact QoL.[14] Givosiran treatment leads to pain reduction and improves the ability of AHP patients to function physically and socially.[14] Clinical experts have described the positive impact of givosiran on their patients' QoL and have noted significant and life-altering changes in their patients' experience of debilitating symptoms, ability to carry out activities of daily living, and social and family interactions.[34,35,37]

As demonstrated in the ENVISION study, givosiran is also expected to improve the ability of AHP patients to work and to return to work after extended sick leave, and to allow AHP patients to meet new professional milestones not previously possible.[34-37] Treatment with givosiran also results in a documented lowering of caregiver burden, and clinical experts who have treated patients with givosiran have described improvements in family and social relationships.[34-36]

A clinical expert from the UK who treated six patients with givosiran described how, prior to treatment, the unpredictable health problems associated with porphyria effectively dominated all aspects of the patients' lives (e.g., family and social life, education and employment, mental health, and excessive medicalisation). Following treatment with givosiran, the six patients experienced positive changes and dramatically improved aspects of their lives, including:[35]

- A reduction in, or complete elimination, of acute attacks
- Almost immediate improvements in pain for half of the treated patients, which has resulted in no further requirement for analgesia

- Efficacious alternatives to hemin prophylaxis (see section 9.7.1 for details on hemin efficacy and safety)
- Improved mobility and reversal of neuropathy
- Weight stabilisation
- Increased work productivity
- Cessation of antidepressant and other medication
- Positive personal life events
- Feeling stronger and fitter
- Patients reporting that they 'got their life back'

8. Extent and nature of current treatment options

- Normosang® (hemin [haem arginate]) is the only treatment approved in the UK for the management of AHP attacks.
- Prior to givosiran there were no licensed therapies for the prevention of repeated AHP attacks in the UK.
- There remains a high unmet medical need for a safe and effective therapy that can be used to prevent AHP attacks, improve the QoL of AHP patients, and reduce long-term AHP complications.
- Givosiran addresses this unmet need with a demonstrated reduction in the rate of AHP attacks, sustained reductions in pain, improvements in physical function, a reduced requirement for hemin and opioids, and an acceptable safety profile.
- In the UK, givosiran would be administered exclusively within the existing NAPS highly specialised service.

8.1. Relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used

Guidelines for the evaluation and management of AHP were published in 2013 by the British and Irish Porphyria Network (BIPNET)[89] and most recently updated in 2017.[24] The guidelines describe best practice in the clinical assessment, investigation, and management of acute porphyria attacks and their complications, including severe attacks with neuropathy. As these guidelines were published before the availability of givosiran, they do not include any disease-modifying therapies, and should now be updated.

The BIPNET guidelines recommend general measures for avoiding repeated attacks and note that hemin has been used off-label in some patients with AHP with the intention of being a prophylactic treatment. Due to its off-label status and complications related to venous access, iron overload, and difficulty withdrawing treatment, prophylactic hemin is not considered as a comparator to givosiran.[24]

8.2. Description of the clinical pathway of care that includes the proposed use of the technology

Current AHP treatment options focus on the control and symptomatic relief of acute attacks and the management of repeated attacks.[24]

8.2.1. Management of AHP attacks

A crucial part of managing AHP attacks is to identify and eliminate any triggers in the patient's lifestyle, including new medications, underlying infections, smoking, drug use, and alcohol consumption.[14,17,24]

Symptoms of an acute attack may be severe and require hospitalisation. Present symptomatic therapy includes treatment for pain, hypertension, tachycardia, nausea, vomiting, and convulsions.[17,24] The EXPLORE natural history study reported that treatment for AHP attacks included opioids in 54% of patients, carbohydrates and non-steroidal anti-inflammatory drugs in up to 45% of patients, and hemin in 67% of patients.[22]

The only specific treatment for acute attacks in the UK is hemin (haem arginate),[10] which is approved under the brand name Normosang® and is indicated for the treatment of acute attacks of hepatic porphyria (AIP, PV, HCP).[90] Hemin suppresses the activity of the ALAS1 enzyme, thereby reducing the production of toxic haem precursors (Figure 1).[7] Symptoms of an AHP attack usually improve within a few days of starting hemin and most patients recover within 1–2 weeks.[24]

8.2.2. Prophylaxis of future AHP attacks

Before givosiran, there were no approved therapies in the UK for prophylaxis of future AHP attacks. Therapies that have been used in the UK with the intention of avoiding future AHP attacks include off-label use of hemin prophylactically, gonadotropin-releasing hormone (GnRH) analogues for women whose attacks are related to menstruation and, as a last resort, liver transplant.[24] All of these therapies have a limited evidence base with regards to their applicability, effectiveness, and/or safety,[24] thus leaving a significant unmet need for a safe and effective treatment to prevent AHP attacks.

Hemin

In the UK, Normosang® (haem arginate) is only licensed for the treatment of acute attacks. It may be used for the amelioration of symptoms and speeding the resolution of an attack once it has occurred.

Given the lack of approved treatment options and in light of urgent patient need, off-label prophylactic use of hemin has been reported in the UK. A retrospective study in the UK (N = 22) has reported that 64% of AHP patients receiving hemin prophylaxis still had AHP attacks requiring hospitalisation, 50% were using opioid medications regularly, and 65% noted no improvements in their work capacity since before they started hemin prophylaxis. Instances of occlusion of the central catheter, long-term vascular damage, thrombus formation and loss of central and peripheral venous access (required for future access for hemin as rescue therapy) were also reported.[91]

Prophylactic use of hemin is off-label and there are no robust data demonstrating efficacy. Given the limited evidence of efficacy and the explicit caution in the product label that advises against use of Normosang® as a preventative option, prophylactic hemin is not considered a relevant, mainstay treatment option for the prevention of future AHP attacks.

Orthotopic liver transplantation

Orthotopic liver transplantation is an irreversible, high-risk procedure associated with severe complications,[92] including death. It is therefore considered to be a treatment of last resort for patients with severe, disabling, unmanageable attacks that do not respond to hemin therapy.[33] In the UK, liver transplantation is indicated only after the failure of medical therapies in AHP patients who meet the very specific criteria of ‘recurrent refractory attacks or a severe attack with neurological deficit despite medical therapy’.[93] These stringent criteria, along with considerations regarding the appropriateness of transplant in individual patients due to the risks of the procedure, have resulted in only ten liver transplants being performed for AHP in the UK until 2011.[92] As a consequence, this procedure is so rarely used in this population that it should be regarded as experimental. Access to the procedure is also restricted by organ availability and patient eligibility. Transplantation places a burden on the healthcare delivery system, and donor livers could be used for other patient groups. It can be successful in some patients, as it results in immediate correction of abnormal haem biosynthesis and cessation of attacks and chronic pain; however, it requires life-long immunosuppression and is associated with an increased risk of mortality due to infection.[17]

GnRH analogues

Fluctuating sex hormone concentrations, particularly increased progesterone, constitute a precipitating factor for AHP attacks in women during the luteal phase of the menstrual cycle.[24] GnRH analogues may be administered to prevent AHP attacks associated with the menstrual cycle in women.[24,89] A recent audit reported that 50% of female AHP patients treated with GnRH in the UK experienced some degree of subjective clinical benefit. However, GnRH renders females post-menopausal and predictable side effects include oestrogen deficiency symptoms such as hot flushes, bone demineralisation and reduced libido.[94] The EXPLORE study found that only 6% of AHP patients were taking GnRH analogues for AHP attack prophylaxis.[11]

Givosiran

Before the introduction of givosiran, management options for AHP were focused on avoiding attack triggers, managing chronic pain, and the use of rescue therapy to speed the resolution of symptoms and reduce hospital length of stay during acute attacks. Givosiran is the only product that treats the underlying AHP disease process, thereby significantly reducing the occurrence of attacks and addressing ongoing chronic pain.[2,14]

Although givosiran is indicated for the treatment of AHP in adults and adolescents aged 12 years and older,[2] we expect eligible patients to be those with severe recurrent disease as defined by NAPS (i.e., annualised attack rate [AAR] >4). NAPS has identified 35 severe recurrent AHP patients currently qualifying for treatment with givosiran in England and Wales, including 6 receiving givosiran in clinical trials.

8.3. Issues relating to current clinical practice, including any uncertainty about best practice

As described in Sections 6.1.2, 7.1, and 8.2.2, there remains a high unmet medical need for a safe and effective therapy that can be used to prevent AHP attacks, improve the QoL of AHP patients, and reduce chronic AHP symptoms. Prophylactic use of hemin is off-label and there are no robust data demonstrating efficacy. Givosiran, as described in Sections 2.2 and 8.5, treats the underlying AHP disease process by suppressing to near-normal levels the toxic haem intermediates that drive the symptoms and morbidity in AHP.[13,14]

8.4. The new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

Givosiran treatment will be initiated only by the existing NAPS Highly Specialised Services within the established framework of Kings College and Cardiff (King's College Hospital NHS Foundation Trust; University Hospital of Wales)[95,96] and existing outreach clinics. After initiation, existing homecare provisions could be utilised for continued givosiran administration.

8.5. How the technology is innovative in its potential to make a significant and substantial impact on health-related benefits, and how it is a 'step-change' in the management of AHP

Based on ground-breaking RNAi technology, the givosiran mechanism of action is distinct from all other treatment options for AHP. Givosiran is the first and only disease-modifying therapy in AHP that treats the underlying AHP disease process, thereby significantly reducing the occurrence of attacks and addressing ongoing chronic pain.[14] AHP patients in the givosiran arm of ENVISION experienced a significant 73% mean reduction in AAR relative to placebo, and median reductions from baseline to month 6 in urinary levels of ALA and PBG of 85% and 90%, respectively. Patients receiving givosiran across all pre-specified subgroups experienced similar reductions in porphyria attacks relative to placebo.[14,55] This finding was consistent with the observation from the OLE period of the phase 1 study that patients on givosiran showed sustained attack reduction for up to 3 years at the latest data-cut of 16 October 2019.[97]

In 2017, givosiran received a priority medicines assessment (PRIME) designation from the EMA for the prevention of acute attacks of AHP,[3] and Breakthrough Therapy designation from the United Stated (US) Food and Drug Administration (FDA) for the same indication.[5] PRIME designations are awarded to medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options.[98] Breakthrough Therapy designation is awarded to drugs that treat a serious or life-threatening disease or disorder, and are supported by preliminary clinical evidence of a substantial improvement over current treatment.[99]

8.6. Changes to the way current services are organised or delivered as a result of introducing the technology

We do not believe that use of givosiran will require significant changes to the way current AHP services are organised or delivered.

8.7. Additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice

Liver function tests should be performed prior to initiating treatment with givosiran, and these tests should be repeated monthly during the first 6 months of treatment, and as clinically indicated thereafter.[2] Notably, monthly liver function tests after the first 6 months of treatment are not a standard requirement for givosiran.

8.8. Additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised

No additional facilities, technology, or infrastructure are required.

8.9. Tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology

Based on a survey of clinical experts that estimated healthcare resource use among patients with AHP in the UK, the reduction in acute attacks is expected to result in a decrease in the use of other medications (i.e., opioids, antiemetics, hemin), health care provider services (i.e., nurse practitioner, physician, pain specialist, physiotherapist), ambulance transportation, admissions tests, hospitalisations and intensive care unit stays.[56] Treatment with givosiran is also expected to avoid the use of central venous catheters required for venous access for hemin administration.

Section C – Impact of the new technology

9. Published and unpublished clinical evidence

9.1. Identification of studies

- Givosiran is an effective therapy with a favourable safety profile, and has demonstrated a mean 74% reduction in the primary endpoint (composite AAR) in the pivotal, phase 3 RCT, ENVISION; this significant reduction in acute attacks was consistent within numerous subgroups of patients and has been shown to be sustained over the long term in subsequent OLE studies.
- Treatment with givosiran resulted in a significant reduction in the experience of pain, the cardinal symptom of AHP.
- Patients treated with givosiran showed significantly improved physical function as measured by the Physical Component Summary (PCS) of the SF-12 and reported important and consistent

improvement in QoL as measured by the Patient Global Impression of Change (PGIC) questionnaire and the Porphyria Patient Experience Questionnaire (PPEQ).
- Givosiran was shown to have a favourable safety profile in a phase 1 trial and in the ENVISION RCT, which has been confirmed with long-term data from two OLEs.
- Treatment with givosiran reduces the requirement for the use of on-label rescue hemin and both opioid and non-opioid analgesics.

9.1.1 Strategies used to retrieve relevant clinical data from the published literature

A comprehensive systematic literature review (SLR) was conducted to identify randomised controlled trial (RCTs) and observational studies reporting the safety and efficacy of givosiran and standard of care in patients being treated for AHP. The SLR was conducted in accordance with the requirements of NICE and the Centre for Reviews and Dissemination (CRD) guidance. The detailed search strategy used is listed in Appendix 1.

9.1.2 Strategies used to retrieve relevant clinical data from unpublished sources

A search of the grey literature was conducted and included Embase, ClinicalTrials.gov, the World Health Organisation's International Clinical Trials Registry Platform (WHO ICTRP), websites, including those published by NICE, the US FDA Advisory Committees, the European Public Assessment Reports (EPARs), the Scottish Medicines Consortium (SMC), the All Wales Medicines Strategy Group (AWMSG), and the Canadian Agency for Drugs and Technologies in Health (CADTH).

For the Embase search, the following meetings were included:

- American Society of Hematology (ASH)
- American College of Gastroenterology (ACG)
- American Academy of Neurology (AAN)
- European Academy of Neurology (EAN)
- European Association for the Study of the Liver (EASL)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) International and European Meetings

The proceedings of the following conferences were not indexed in EMBASE at the time of the search, and their abstracts and presentations were searched manually:

- International Congress on Porphyrins and Porphyrias (ICPP) 2019
- German Society for Interdisciplinary Emergency and Acute Medicine (DGINA) 2019
- German Association for Gastroenterology, Digestive and Metabolic Diseases (DGVS) 2019
- European Association for the Study of the Liver (EASL) 2020

Five selected literature reviews were also manually searched to validate the study selection and to identify any additional relevant publications.

9.2. Study selection

The SLR selection criteria for published studies are summarised in Table 10.

Table 10. Selection criteria used for published studies

Inclusion criteria	
Population	Patients ≥12 years of age with a diagnosis of AHP (including AHP subtypes ADP, AIP, HCP, and VP)
Interventions	Givosiran
Comparators	Any, including placebo and/or standard of care
Outcomes	• From clinical studies (RCTs, single-arm studies, OLEs, observational studies): safety and efficacy/effectiveness outcomes, PROs, caregiver burden • From economic studies: costs, cost effectiveness, utility values, resource use, lost productivity • From QoL studies: PROs, caregiver burden, utility values
Study design	• RCTs and non-RCTs • OLEs • Observational studies (e.g., prospective, cross-sectional, and retrospective, including chart reviews,

	registries and surveys) • Single-arm trials • Cost-effectiveness, cost-utility, or cost-minimisation studies • Healthcare resource use studies • Disease burden (disability and lost productivity) studies • QoL, utility assessments or PRO studies • Systematic literature reviews for hand-search*
Language restrictions	None
Search dates	13 September 2020
Exclusion criteria	
Population	Populations with non-acute hepatic porphyrias (i.e., PCT or HEP) or erythropoietic cutaneous porphyrias (i.e., CEP, EPP, XLP)
Interventions	N/A
Comparator	N/A
Outcomes	Pharmacokinetic studies and non-clinical studies
Study design	Case studies, case reports, letters, commentaries, editorials, non-human studies, in-vitro studies
Language restrictions	None
Search dates	13 September 2020

*Systematic literature reviews were not identified in the search results; selected literature reviews were hand-searched. ADP: ALAD porphyria; AHP: acute hepatic porphyria; AIP: acute intermittent porphyria; ALAD: aminolevulinic acid dehydratase; CEP: congenital erythropoietic porphyria; EPP: erythropoietic protoporphyria; HCP: hereditary coproporphyria; HEP: hepatoerythropoietic porphyria; N/A, not applicable; OLE: open-label extension; PCT: porphyria cutanea tarda; PRO: patient-reported outcome; QoL: quality of life; RCT, randomised controlled trial; VP: variegate porphyria; XLP: X-linked protoporphyria.

9.2.1. Published studies included and excluded at each stage

The PRISMA diagram for the SLR is shown in Figure 5.

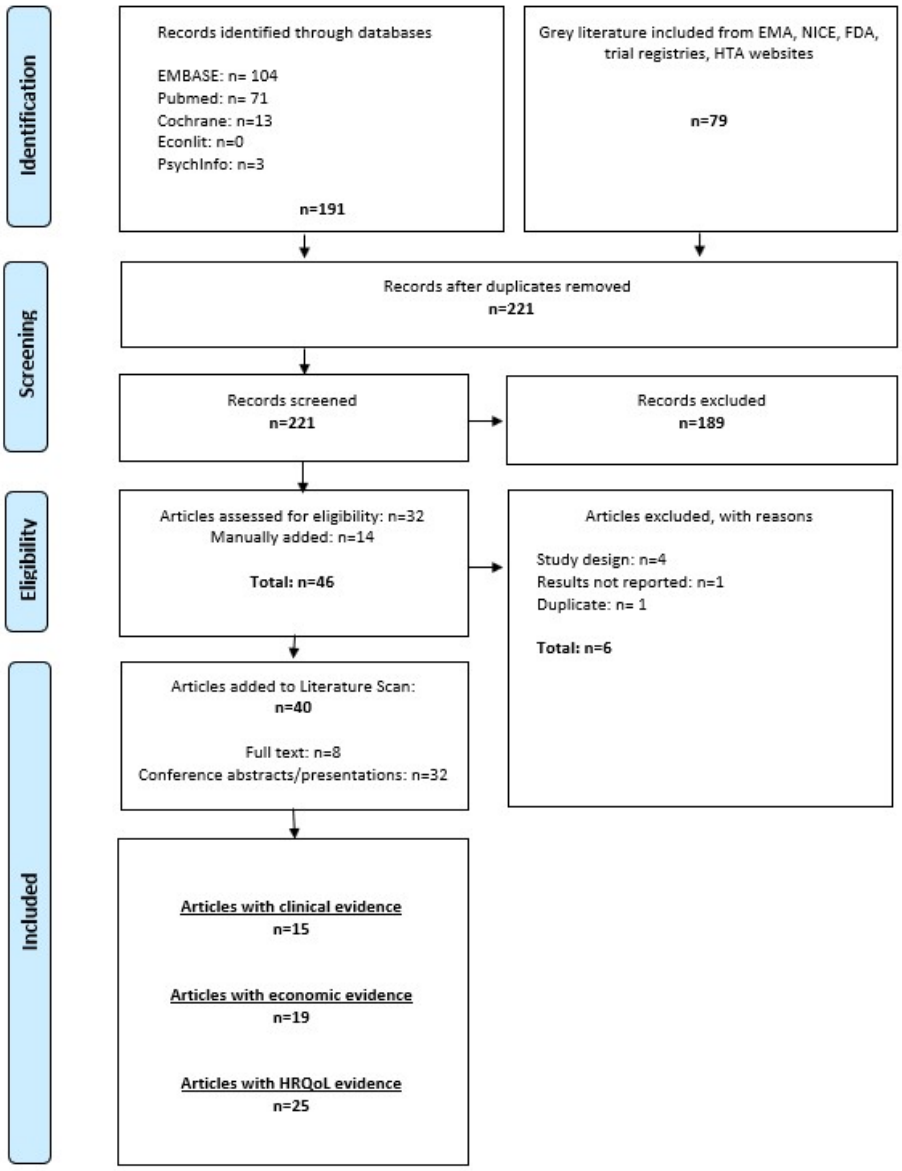


Figure 5. PRISMA flow diagram for clinical evidence in AHP

Note: Natural history studies that did not contain QoL or economic information were excluded from the SLR by amendment. AHP: acute hepatic porphyria; EMA: European Medicines Agency; FDA: Food and Drug Administration; HTA: health technology assessment; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review

9.2.2. Inclusion and exclusion criteria used for the selection of studies from the unpublished literature

The search selection inclusion and exclusion criteria for unpublished studies were the same as the criteria for published studies (Table 10).

9.2.3. Unpublished studies included and excluded at each stage

The grey literature (unpublished) studies are included in the PRISMA diagram for the SLR (Figure 5).

9.3. Complete list of relevant studies

9.3.1. Details of all published and unpublished studies identified using the selection criteria described in Table 10

Table 11 lists the 19 included studies from the SLRs.[36,51,100,101] In cases where there were multiple references for a study, the most complete and/or the most recent publication of that study was selected as the primary study reference in this submission.

Givosiran was evaluated in a phase 3 RCT (ENVISION) in patients with AHP,[14] and interim data from the ENVISION OLE have also been reported.[101,102] A phase 1 randomised, placebo-controlled, safety, tolerability, pharmacokinetics, and pharmacodynamics study was also identified,[13] as well as an OLE of the recurrent attack population of the givosiran phase 1 study.[51]

Hemin was evaluated in one RCT,[103,104] five single-arm interventional studies,[105-109] and nine observational studies.[19,20,91,110-115] Among the 15 hemin studies identified, 11 were in the treatment of acute attacks only,[103,106-115] three assessed patients treated with hemin prophylaxis,[19,20,91] and one study evaluated hemin in both acute attacks and as prophylaxis.[105] The only RCT (N=12) for hemin that was identified was for the treatment of acute attacks.[103] Hemin dosing frequencies were only reported in three of the 15 hemin studies.[14,91,105]

There were no unpublished studies identified as being relevant by the SLR. Excluded studies are listed in Appendix 1.

Table 11. List of included published studies from the SLRs

Primary study reference	Study name NCT number	Population	Intervention	Comparator
Givosiran Trials				
Balwani et al. (2020)[14]	ENVISION NCT03338816	94 participants aged 12 years and older with diagnosis of AHP, who had: • Elevated urinary or plasma PBG or ALA values within the past year • ≥2 attacks within prior 6 months • Willing to discontinue and/or not initiate hemin prophylaxis. Randomised to givosiran: n=48; placebo: n=46	Givosiran	Placebo
Sardh et al. (2019)[13]	Phase 1 NCT02452372	40 adults aged 18–65 years with diagnosis of AIP and confirmed pathogenic mutation in the HMBS gene Part A and B: • Combined (n=23) • Urinary PBG level >4 mmol per mole of creatine (~2x upper limit of normal range) at screening • No attack 6 months before baseline Part C: • Randomised to givosiran (n=13) and placebo (n=4) • Recurrent attacks (≥2 within 6 months before run-in period or receiving scheduled hemin prophylaxis at start of run-in period) Patients required to discontinue scheduled hemin prophylaxis during the run-in and intervention periods.	Givosiran	Placebo
Bonkovsky et al. (2019)[51]	Phase 1/2 OLE NCT02949830	All eligible patients from Part C of phase 1 trial enrolled in the OLE (N=16)	Givosiran	None
Hemin – acute treatment RCT				
Herrick et al. (1989)[103]	-	• 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
Hemin – acute treatment non-randomised studies				
Mustajoki and Nordmann (1993)[106]	-	• 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)[107]	-	• AIP established by quantitative assays of urine, faeces, and erythrocytes (N=8) • Mean age: 38.6 years (range: 22–66 years)	Hemin	None

Primary study reference	Study name NCT number	Population	Intervention	Comparator
Devars du Mayne et al. (1986)[108]	-	• 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)[109]	-	• Clinical evidence of active disease (acute porphyria attack) with elevated ALA and PBG (N=7) • Age not reported	Hemin	None
Herrero et al. (2015)[110]	-	• 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)[111]	-	• 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)[116]	-	• Patients with acute attacks of AIP treated in hospital (N=70) • Age not reported	Hemin	None
Kostrewska et al. (1991)[113]	-	• 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)[114]	-	• Patients with AIP or VP; acute attacks or in remission (N=14) • Age not reported	Hemin	None
Pierach et al. (1980)[115]	-	• Patients with acute attack of AHP (N=57). • Age not reported=57	Hemin	None
Hemin – prophylaxis non-randomised studies				
Gouya et al. (2020)[11]	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)[20]	-	• 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)[19]	-	• 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
Marsden et al. (2015)[91]	-	• 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)[105]	-	• Patients with acute porphyria (AIP, VP, HCP, ADP) • Mean age: 40.3 years (SD:12.3) • Hemin prescribed for acute attacks in (n=90) and for prophylaxis (n=40)	Hemin	None

ADP: ALAD porphyria; AHP: acute hepatic porphyria; AIP: acute intermittent porphyria; ALA: aminolevulinic acid; HCP: hereditary coproporphyria; HMBS: hydromethylbilane synthase gene; OLE: open-label extension; PBG: porphobilinogen; PBGD: porphobilinogen deaminase; SD: standard deviation; SLR: systematic literature review; ULN: upper limit of normal; VP: variegate porphyria

9.3.2. State the rationale behind excluding any of the published studies listed in Table 11

None of the published studies were excluded.

9.4. Summary of methodology of relevant studies

9.4.1. Study design and methodology for each of the published and unpublished studies

Givosiran studies

The clinical development programme for givosiran included the pivotal, phase 3 RCT ENVISION (Table 12), an ENVISION OLE; a randomised, placebo-controlled, multi-dose phase 1 trial (Table 13), and a phase 1/2 OLE. The ongoing givosiran phase 1/2 OLE enrolled 16 of the 17 patients who completed Part C of the phase 1 trial.[13,51]

Hemin studies

The clinical evidence identified for hemin included one RCT, five single-intervention trials, and nine observational studies (See Section 9.3.1). The methodology of the hemin RCT[103] is presented in Table 14.

Four single-intervention trials and six observational studies investigated the use of hemin for the treatment of acute attacks Table 11.[106-111,113-116]

Off-label use of hemin prophylaxis was reported in four observational studies[11,19,20,91] and in one single-intervention trial that described only safety in the use of hemin in acute attacks and as prophylaxis.[105]

Table 12. Summary of methodology for the givosiran Phase 3 ENVISION RCT

Reference	ENVISION, NCT03338816[14]
Study Name	ENVISION: A phase 3 randomised, double-blind, placebo-controlled, multicentre study with an open-label extension to evaluate the efficacy and safety of givosiran in patients with acute hepatic porphyrias
Location	36 study centres in 18 countries. Countries included: UK, Sweden, Netherlands, Germany, Bulgaria, Denmark, Italy, Poland, Finland, France, Spain, US, Canada, Mexico, Australia, Japan, South Korea, and Taiwan
Design	International, multicentre, phase 3, randomised, double-blind, placebo-controlled trial
Duration of study	ENVISION DB period: November 2017 to January 2019, 6-month follow-up ENVISION OLE period: 18 months of follow-up at most recent interim analysis (still ongoing)
Sample size	N=94 (Givosiran=48, Placebo=46)
Inclusion criteria	• Adults and adolescents (≥12 years of age) • Documented diagnosis of AHP (including AIP, HCP, VP, or ADP) based on clinical features, documented evidence of urinary or plasma ALA or PBG elevations ≥4×ULN within the past year prior to or during the screening period and documented genetic evidence of a mutation in a porphyria-related gene • At least two porphyria attacks in the last 6 months prior to screening that required hospitalisation, urgent healthcare visit, or IV hemin treatment at home • Willing to discontinue and/or not initiate hemin prophylaxis
Exclusion criteria	• Clinically significant abnormal laboratory results • Anticipated liver transplantation • History of multiple drug allergies or intolerance to subcutaneous injections • Active HIV, hepatitis C virus, or hepatitis B virus infection(s) • History of recurrent pancreatitis • Females who are pregnant, breast-feeding, or planning to become pregnant during the study • Major surgery planned in first 6 months of study • Had malignancy 5 years prior to screening except for basal or squamous cell carcinoma of the skin, cervical in-situ carcinoma, or breast ductal carcinoma, that has been successfully treated
Method of randomisation	• Patients were randomised 1:1 to study drug or placebo in a double-blind manner. • Treatment groups were stratified at study entry by AHP type: AIP, with genetic evidence of mutation in the HMBS gene, vs HCP, VP, ADP, or any AHP without identified mutation in a porphyria-related gene. • Randomisation for AIP patients was further stratified by each patient's use of hemin prophylaxis regimen at the time of screening and by each patient's historical AAR.
Method of blinding	• Blinded treatment assignment provided and maintained by an IRS • Members of the study team did not have access to the 6-month treatment period unblinded data until the final analysis
Intervention(s) (n=) and Comparator(s) (n=)	• Givosiran, 2.5 mg/kg SC monthly (n=48) • Placebo, sodium chloride 0.9% w/v for SC administration (n=46)
Baseline differences, n (%)	>10% difference in proportion of patients with liver transaminase elevation >ULN Givosiran: 13 (27) Placebo: 3 (7)
Duration of follow-up, lost to follow-up	6-month follow-up

Reference	ENVISION, NCT03338816[14]
information	Only one patient discontinued treatment due to ALT elevation (protocol stopping rule) but completed the 6-month visit.
Statistical tests	The analysis of the primary endpoint was a comparison of the mean AAR for the placebo and givosiran arms using a negative binomial regression model that included fixed effects for the treatment arm and stratification factors (status of hemin prophylaxis use prior to study entry and historical attack rate). The estimated ratio of mean AARs between treatment arms, with its corresponding 95% confidence interval, were estimated from the negative binomial regression model.
Primary outcomes (including scoring methods and timings of assessments)	Composite AAR in patients with AIP, requiring either hospitalisation, an urgent healthcare visit, or IV hemin administration at home over a 6-month treatment period. Occurrence of this outcome was monitored on a daily basis over the 6-month follow-up.
Secondary outcomes (including scoring methods and timings of assessments)	Secondary: • LS mean ALA (mmol/mol Cr) in AIP, at Months 3 and 6 • LS mean PBG (mmol/mol Cr) in AIP, at Month 6 • Mean annualised days on hemin in AIP; monitored on a daily basis from the screening period to Month 6 • AAR in AHP, with AAR requiring either hospitalisation, an urgent healthcare visit, or IV hemin administration at home; monitored on a daily basis over the 6-month follow-up • Daily worst pain intensity was measured with BPI-SF NRS (11-point scale; 0=no pain, 10=pain as bad as you can imagine); monitored on daily basis over 6 months • Daily worst nausea measured with 11-point NRS; monitored on daily basis over 6 months, AUC change from baseline • Daily worst fatigue measured BFI-SF NRS (11-point scale; 0=no fatigue, 10=fatigue as bad as you can imagine); monitored on daily basis over 6 months, AUC change from baseline • The PCS of the SF-12 (range 0=lowest level of health, to 100=highest level of health) Change from baseline • Safety and tolerability of givosiran in patients with any AHP was assessed continuously from baseline to Month 6 Exploratory: • Urinary ALAS1 mRNA levels were monitored at screening, baseline, Week 2 and monthly from Month 1 to Month 6 • Analgesic usage was assessed continuously on a daily basis from screening to Month 6 • Additional QoL measures at screening, Month 3, and Month 6 o SF-12: MCS and PCS are scored on a range 0=lowest level of health, to 100=highest level of health o EQ-5D-5L: 5 health-related QoL dimensions are scored on a 5-point Likert scale which is then used to obtain a value from 0 to 1.0 o Missed days of work/school • PGIC at Month 6, assesses a patient's perceived overall health status change since the beginning of the study using a single-item scale • PPEQ at Month 6, is a set of questions to assess treatment experience and impacts to the patient's life that are not collected by the other QoL assessments

AAR: annualised attack rate; ADA: anti-drug antibodies; ADP: ALAD porphyria; AHP: acute hepatic porphyria; AIP: acute intermittent porphyria; ALA: aminolevulinic acid; ALAS1: aminolevulinic acid synthase 1; ALT: alanine aminotransferase; AUC: area under the curve; BFI-SF: Brief Fatigue Inventory-Short Form; BPI-SF: Brief Pain Inventory-Short Form; Cr: creatinine; EQ-5D-5L: EuroQol 5-Dimension 5-Level Questionnaire; DB: double-blind; HCP: hereditary coproporphyria; HIV: human immunodeficiency virus; HMBS: hydroxymethylbilane synthase gene; IRS: interactive response system; IV: intravenous; kg: kilograms; LS: least square; MCS: Mental Component Summary; mg: milligrams; mmol: millimole: mol: mole; mRNA: messenger ribonucleic acid; n: N: number: sample size; NRS: numeric rating scale; OLE: open-label extension; PBG: porphobilinogen; PCS: Physical Component Summary; PGIC: Patient Global Impression of Change Questionnaire; PK: pharmacokinetics; PPEQ: Porphyria Patient Experience Questionnaire; QoL: quality of life; SC: subcutaneous; SF-12: 12-Item Short Form Health Survey; UK: United Kingdom; ULN: upper limit of normal; US: United States; VP: variegate porphyria. Source: Balwani et al. (2020)[14]; Alnylam (ENVISION PROTOCOL)[117]

Table 13. Summary of methodology for the givosiran Phase 1 RCT

Reference	Phase 1 study, NCT02452372[13]
Study Name	A phase 1, single-ascending dose, multiple-ascending dose, and multi-dose safety, tolerability, pharmacokinetics, and pharmacodynamics study of subcutaneously administered ALN-AS1 in patients with acute intermittent porphyria (AIP)
Location	Six study centres in three countries. Countries included: US, Sweden, UK
Design	International, multicentre, phase 1, randomised, single-ascending dose (single-blind), multiple-ascending dose (single-blind), and multi-dose (double-blind), placebo-controlled trial
Duration of study	May 2015 to September 2017. Part A: 42 days; Part B: 70 days; Part C: 168 days
Sample size	N=40; Parts A and B: n=23; Part C: n=17 (Givosiran=13, Placebo=4)
Inclusion criteria	Parts A, B, and C • Adult male or female patients aged 18 to 65 years • Patients with a diagnosis of AIP, defined as a genetic test showing documentation of a mutation in the HMBS gene • Women of childbearing potential must have a negative pregnancy test, not be nursing, and use effective contraception • Able and willing to provide informed consent

Reference	Phase 1 study, NCT02452372[13]
	Parts A and B only • Patients with a urine PBG level >4 mmol/mol Cr, for at least two measurements during the screening period • Patients who do not have clinically significant health concerns as determined by medical history, physical examination, and 12-lead ECG, and as judged by the investigator Part C only • Patients who have recurrent porphyria attacks defined as one of the following: o A porphyria attack (defined as intense abdominal or back pain requiring hospitalisation, hemin use, treatment consisting of increased carbohydrate intake and/or pain medication use) at least two times during the 6 months before initiation of the run-in period o Patient is on a scheduled regimen of hemin to prevent porphyria attacks at the start of the run-in period and has experienced at least one porphyria attack (requiring unscheduled hemin or opiate use) during the 6 months before initiation of the run-in period and was willing to stop scheduled hemin use during the run-in and treatment periods • Patients are willing to mail urine samples collected during an attack if they are not being treated at the study centre
Exclusion criteria	Parts A, B, and C • Patients with any of the following: ALT and/or TBIL above the ULN confirmed by retest; AST, ALP, or GGT>2×ULN or above the ULN, confirmed by retest, and considered clinically relevant by the investigator • Patients with a history of multiple drug allergies or history of allergic reactions to an oligonucleotide or to GalNAc • Patients with a history of intolerance to SC injections • Patients with a history of alcoholism and/or drug abuse within 2 years of study drug administration • Patients with known HCV or HIV infection; or evidence of current or HBV infection • Patients who have received an investigational agent within 3 months before administration of study drug or who are in follow-up of another clinical study of an investigational agent at the time of study drug administration Parts A and B only • Patients who have experienced an acute porphyria within 6 months of study drug administration • Patients who have started a new chronic prescription medication treatment regimen within 3 months of study drug administration • Patients who have used a GnRH analogue within 30 days of study drug administration • Patients who have active serious mental illness • Patients with chemistry, haematology, and urinalysis safety laboratory test results deemed clinically significant by the Investigator • Any condition (e.g., medical concern), which in the opinion of the investigator, would make the patient unsuitable for enrolment or could interfere with the patient's participation in, or completion of, the study. Part C only • Any condition (e.g., medical concern), which in the opinion of the investigator, would make the patient unsuitable for dosing on Day 0 or could interfere with the patient's participation in, or completion of, the study
Method of randomisation	Parts A, B and C: Patients were randomised 3:1 to receive either givosiran or placebo
Method of blinding	• Parts A and B: single-blind (patients) • Part C: double-blind (patients and study personnel) • Clinical study centre pharmacists maintained the blind according to site-specific procedures and the pharmacy manual. • Because givosiran may be visually distinguishable from placebo, syringes containing dispensed study drug were masked in the pharmacy before transfer to the clinic.
Intervention(s) (n=) and Comparator(s) (n=)	Part A (SAD phase): Givosiran (single injection): 0.035 mg/kg (n=3); 0.10 mg/kg (n=3); 0.35 mg/kg (n=3); 1.0 mg/kg (n=3); 2.5 mg/kg (n=3) Placebo (n=5) Part B (MAD phase): Givosiran (1xmonth for 2 injections): 0.35 mg/kg (n=4); 1 mg/kg (n=4) Part C:Givosiran: 2.5 mg/kg 1xQM for 4 injections (n=3); 2.5 mg/kg 1xQ3M for 2 injections (n=3); 5.0 mg/kg 1xQM for 4 injections (n=3); 5.0 mg/kg 1xQ3M for 2 injections (n=4) Placebo (n=4)
Baseline differences	Part C (givosiran versus placebo) Higher median age in the placebo group (42 years [range:27–60] versus 36 years [range:21–59]) Higher distribution of females in the givosiran group (13/13 versus 2/4) Although some differences were seen in the distribution of race and type of porphyria therapy, because the sample sizes are very small these differences are not likely to be meaningful.
Duration of follow-up, lost to follow-up information	Part A: 42 days Part B: 70 days Part C: 168 days

Reference	Phase 1 study, NCT02452372[13]
	Only one patient did not complete follow-up: fatal haemorrhagic pancreatitis, assessed as unlikely related to study drug due to presence of gallbladder sludge
Statistical tests	• Descriptive statistics were reported for continuous variables, and frequencies and percentages for categorical and ordinal variables. Event count data (numbers of porphyria attacks and doses of hemin administered) were summarised as annualised rates with the standard errors of the mean. A negative binomial regression was fitted to generate statistical inferences on the ratio of • AAR and the annualised number of hemin doses administered in each cohort in Part C.
Primary outcomes (including scoring methods and timings of assessments)	Safety: all AEs were categorised according to the Medical Dictionary for Regulatory Activities, version 17.1, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0
Secondary outcomes (including scoring methods and timings of assessments)	Secondary: Part A: Plasma and urine PK were assessed at Day 0, Day 4, and W1-W4 and W6 Part B: PD effect on plasma and urine ALA (mmol/mol Cr) and PBG (mmol/mol Cr) levels at W0, W1-W6, W8, W10 Part C: Plasma and urine PK were assessed at Day 0 and weekly to W18; PD effect on plasma and urine ALA (mmol/mol Cr) and PBG (mmol/mol Cr) levels at W0 and weekly to W12, then W16 and W18. ALA and PBG monitored during attack throughout study Exploratory • ALA and PBG assessed according to schedule indicated for secondary outcomes • Exploratory biomarkers assessed at all visits in Parts A, B, and C • Attack Symptom Inventory Form used to record attacks throughout the course of Part C • Concomitant medications recorded throughout course of Parts A, B, and C

AAR: annualised attack rate; AIP: acute intermittent porphyria; ALA: aminolevulinic acid; ALP: alkaline phosphatase; ALT: alanine aminotransferase; ASHE: asymptomatic high excreters; Cr: creatinine; ECG: electrocardiogram; GalNAc: N-acetylgalactosamine; GGT: gamma glutamyl transpeptidase; GnRH: gonadotropin-releasing hormone; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HMBS: hydroxymethylbilane synthase gene; kg: kilograms: MAD: multiple-ascending dose; mg: milligrams; mmol: millimole; mol: mole; n: N: number: sample size; PBG: porphobilinogen; PD: pharmacodynamic; PK: pharmacokinetics; Q3M: every 3 months; QM: monthly; SAD: single-ascending dose; SC: subcutaneous; TBIL: total bilirubin; UK: United Kingdom; ULN: upper limit of normal; US: United States; W: week. Source: Sardh et al. (2019)[13]; Clinicaltrials.gov[118]

Table 14. Summary of methodology for hemin RCT

Reference	Herrick et al. (1989)[103]
Study Name	Controlled trial of hemin in acute hepatic porphyria
Objectives	To evaluate the role of hemin in the treatment of clinical attacks of acute porphyria.
Location	Scotland
Design	RCT, DB, CO
Duration of study	Duration of hospital stay
Sample size	N=12
Inclusion criteria	Patients with AIP experiencing recurrent attacks
Exclusion criteria	• Patients who are pregnant • Patients with a history of allergic reaction to exogenous haem
Method of randomisation	Patients were randomised using random number tables to receive either hemin or placebo. Nine of 12 patients who later returned for treatment due to subsequent attacks were given the alternate treatment to the one they were initially randomised to. The distribution of the treatment allocation at randomisation was not described.
Method of blinding	Double-blind
Intervention(s) (n=) and Comparator(s) (n=)	• Hemin 3 mg/kg/24 hr IV for 4 days • Placebo (sterile saline) Numbers at randomisation not reported. Cross-over of 9 of 12 patients
Baseline differences	None reported
Duration of follow-up, lost to follow-up information	Duration of hospitalisation N=3/12 patients did not return for treatment of subsequent attack and could not cross-over treatment.
Statistical tests	Signed rank test was use for all treatment comparisons
Primary outcomes (including scoring methods and timings of assessments)	All assessments were made for the duration of hospital stay • Analgesic requirements (mg) • Pain score (range 0–220) • Duration of hospital stay (days) • Urinary ALA (µmol per 24 h) • Urinary PBG (µmol per 24 h) • Platelet count ($x10^9$/l)
Secondary outcomes (including scoring methods and timings of assessments)	NA

AIP: acute intermittent porphyria; ALA: aminolevulinic acid; CO: cross-over; DB: double-blind; IV: intravenous; kg: kilograms; l: litre; mg: milligrams; n: N: number: sample size; NA: not applicable; NR: not reported; PBG: porphobilinogen; µmol: micromole. Sources: Herrick et al. (1989)[103]

9.4.2. Data from any single study that have been drawn from more than one source, including when trials are linked

Details of the ENVISION trial were drawn from the published phase 3 trial,[14] the unpublished trial protocol,[117] and the unpublished clinical study report.[119] Details from the ENVISION OLE were obtained from a published abstract[101] and unpublished data on file.[102] Details of the givosiran phase 1 and phase 1/2 OLE studies were drawn from a publication,[13] from the clinical study report,[97] and from an abstract (poster).[51] Data from the hemin studies were derived from abstracts and publications.[91,103,105-110,113-116]

9.4.3. Differences between patient populations and methodology in all included studies

The givosiran phase 3 RCT and the small-cohort hemin for acute attacks RCT were published more than three decades apart, and main differences include, but are not limited to, study population size (N=94 versus N=12, respectively), study design (double-blind, placebo-controlled, phase 3 RCT with 0% lost to follow-up versus double-blind cross-over RCT with 3/12 patients [25%] lost to follow-up before the cross-over treatment was initiated, respectively) and differences in best supportive care (BSC) due to the approximately 30 years separating the two studies.[14,103] Furthermore, the hemin for acute attacks RCT looked at the short-term effect of hemin two days into an established AHP attack and did not demonstrate a significant difference for each of the three main indices of the clinical severity of the attack (i.e., analgesic requirement, pain score, and duration of hospital admission).[103]

The givosiran phase 1 RCT study and the hemin for acute attacks RCT were also published more than three decades apart, and main differences include, but are not limited to, study population size, study design and differences in BSC due to the approximately 30 years separating the two studies.[13,103]

Overall, the quality of evidence in the ENVISION and the givosiran phase 1 RCT is vastly superior to that of the small hemin for acute attacks RCT.

9.4.4. Subgroup analyses undertaken in the studies included in section 9.4.1

Pre-specified subgroup analyses of the primary composite endpoint in the ENVISION trial (AAR in AIP) were conducted on the following parameters:[14,119]

- Age at Screening (< or ≥ median age in the overall population)
- Race (White or Non-white)
- Gender (Female or Male)
- Region group 1: North America (United States and Canada) or Other (outside North America)
- Region group 2: Europe or Other (outside Europe)
- Baseline body mass index (BMI) (<25 or ≥25)
- Prior hemin prophylaxis status (Yes or No)
- Historical attack rates prior to randomisation based on the hemin prophylaxis status prior to the study (high or low) screening:
    - High attack rate was defined as AAR ≥7 for patients on a hemin prophylaxis regimen at the time of screening, and AAR ≥12 for patients not on a hemin prophylaxis regimen at screening
- Prior chronic symptoms when not having attacks (Yes or No)
- Prior chronic opioid use when not having attacks (Yes or No)

These analyses were conducted to assess the consistency of the treatment effect for the AIP patients during the 6-month study period. The analyses were also repeated for the entire AHP population.[119] Subgroup analyses by AHP type were also performed on the AAR, on urinary ALA levels at Month 3 and Month 6, and for AEs.[119]

9.4.5. Details of the numbers of patients eligible to enter the studies, randomised, and allocated to each treatment

Givosiran studies

Figure 6 shows the CONSORT diagram for the ENVISION study. Patients (N=94) were randomised 1:1 to the givosiran arm (n=48) or to the placebo arm (n=46).

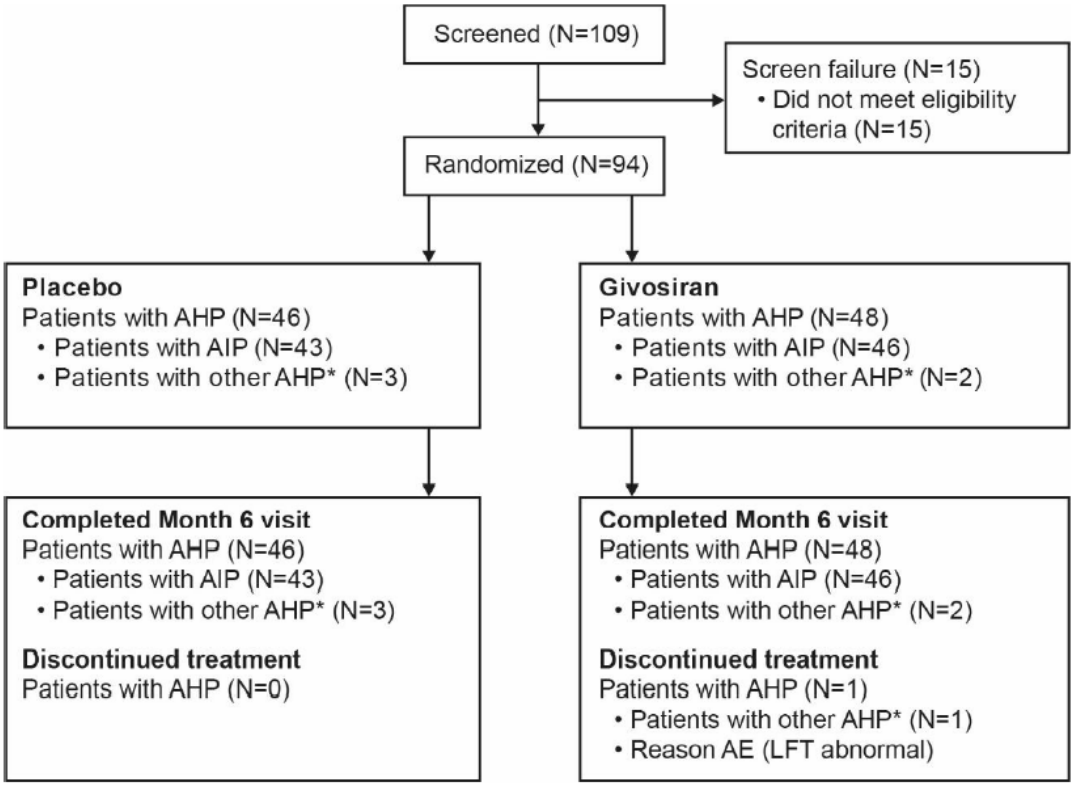


Figure 6. CONSORT flow diagram for the ENVISION RCT

*Patients with other AHP includes patients with HCP, VP, or without an identified AHP mutation. AE: adverse event; AHP: acute hepatic porphyria; AIP: acute intermittent porphyria; ALT: alanine aminotransferase; HCP, hereditary coproporphyria; LFT: liver function test; N: number; RCT: randomised control trial; QM: monthly; VP, variegate porphyria. Source: Balwani et al. (2020)[14]

One treatment discontinuation due to ALT elevation occurred in one patient in the givosiran arm after the 6-month visit.[14] The remaining 93 patients were enrolled in the ongoing ENVISION OLE.[101,102] A CONSORT diagram for the givosiran phase 1 trial is shown in Figure 7.

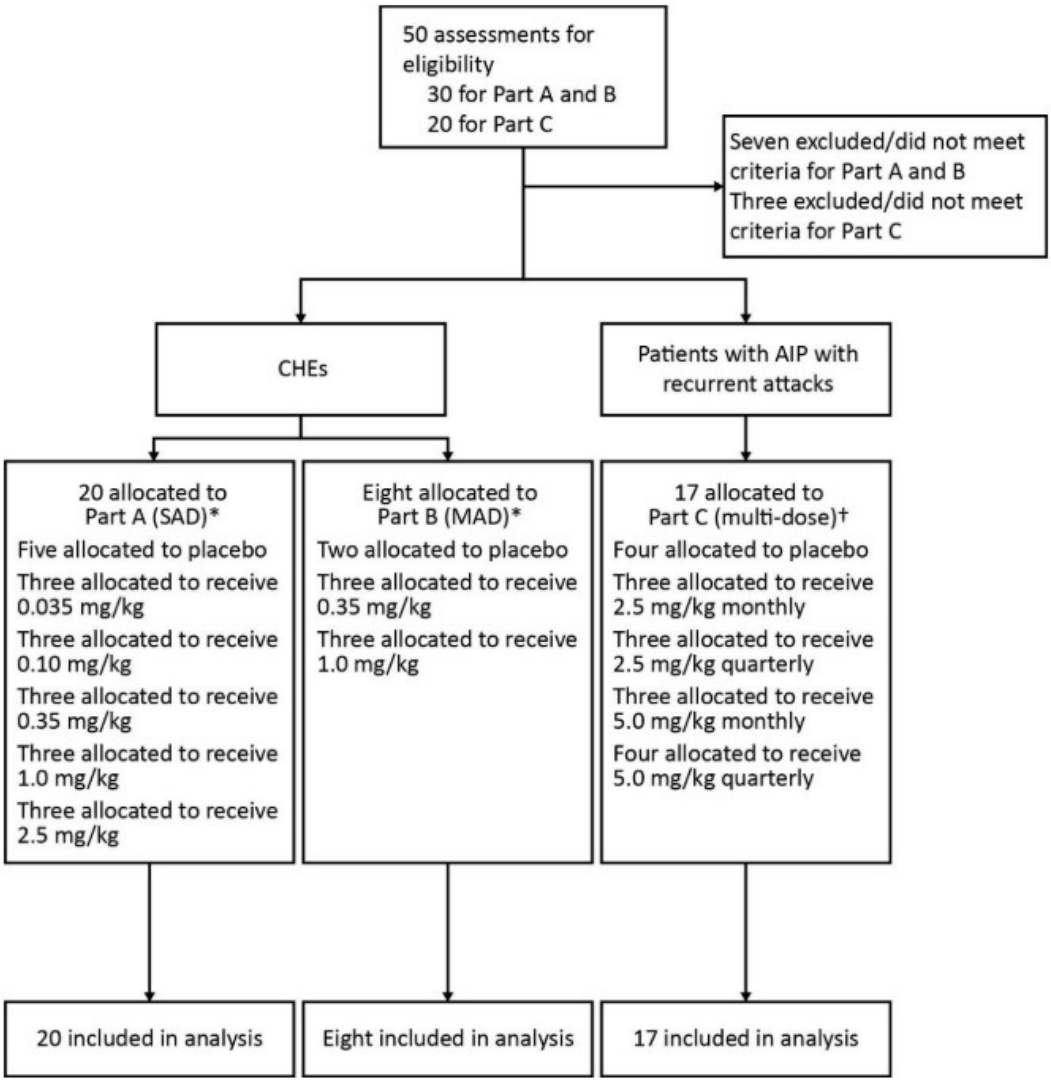


Figure 7. CONSORT flow diagram for the givosiran phase 1 trial

*Two patients in Part A received two injections (either one placebo and one givosiran injection or two givosiran injections at different doses). Three patients were treated in both Part A and Part B. †One patient died after receiving three doses of givosiran at 5 mg/kg monthly but was still included in the analysis. AIP: acute intermittent porphyria; CHE: chronic high excreters; MAD: multiple-ascending dose; SAD: Single-ascending dose. Source: Sardh et al. (2019)[13]

The phase 1/2 OLE included all eligible patients from Part C of the phase 1 trial (i.e., 16 of 17 patients). One patient was not included from the phase 1 trial because they died from causes judged as unlikely to have been due to the study drug.[51] Patient follow-up in the phase 1/2 OLE is currently ongoing.

Hemin studies

The small-cohort hemin-on-demand RCT reported that patients admitted to hospital for an AIP attack were eligible for recruitment;[103] however, the authors did not report the number of patients screened for inclusion in the study. A total of 12 patients were randomised to receive either hemin or placebo (Section 9.6.1 and Table 14), but the number of patients allocated to each treatment was not reported. Three patients (two randomised to hemin and one to placebo) were lost to follow-up and never initiated cross-over treatment. The disposition of patients for the single-intervention trials and observational studies of hemin are summarised in Appendix 1.

9.4.6. Details of and the rationale for, patients that were lost to follow-up or withdrew from the studies

Givosiran studies

In ENVISION, one treatment discontinuation due to ALT elevation occurred in one patient in the givosiran arm after the 6-month visit.[14]

There were no trial regimen discontinuations in the phase 1 trial.[13] One patient in Part C who had received a total of three, once-monthly givosiran injections of 5.0 mg per kilogram, experienced three serious adverse events (SAEs) (i.e., *Staphylococcus epidermidis* bacteraemia, auditory hallucination, and haemorrhagic pancreatitis, which was subsequently fatal). These AEs were considered unlikely to be related to the study drug by the investigator in the context of the patient's medical history. This patient had a complex medical history including monthly hospitalisations for porphyria attacks, quadriparesis from AIP, obesity, hypertension, hypothyroidism, tachycardia, acute kidney injury, increased alkaline phosphatase levels, depression, anxiety, chronic pain with opioid dependence, and Enterobacter bacteraemia.[13]

During the OLE period of ENVISION, one patient discontinued treatment due to a study-drug related non-serious AE of drug hypersensitivity that was moderate in severity. Prior to treatment discontinuation, the patient received placebo during the double-blinded (DB) period and 6 monthly doses of 1.25 mg/kg givosiran during the OLE period.[119]

In the phase 1/2 OLE study (cut-off date 16th October 2019), one patient discontinued treatment and later withdrew from the study due to lack of response to the study drug, and one patient withdrew from the study due to a SAE (anaphylactic reaction).[97]

Hemin studies

Three of the 12 patients (25%) were lost to follow-up prior to receiving their allocated post-cross-over treatment in the hemin RCT, which resulted in missing matched cross-over assessments for a quarter of the study population.[103]

9.5. Critical appraisal of relevant studies

9.5.1. Complete a separate quality assessment table for each study.

Quality assessment of all relevant studies identified in the SLR was conducted independently by two reviewers and disagreements were resolved by a third reviewer. All available publications of a study were used to assess its overall quality. For the ENVISION RCT, the phase 1 trial of givosiran, and the hemin RCT, the quality assessment tables were adapted from the CRD guidance on undertaking reviews in healthcare provided in the NICE HST template. The quality assessments for the RCTs are summarised in Table 15 (ENVISION RCT), Table 16 (givosiran phase 1 RCT), and Table 17 (hemin RCT).

Table 15. Critical appraisal of RCTs – givosiran phase 3 study (ENVISION)

Study question	Response yes/no/not clear/ partially/N/A	How is the question addressed in the study?
Was randomisation carried out appropriately?	Yes	Patients were stratified according to AHP type and use of hemin prophylaxis.
Was the concealment of treatment allocation adequate?	Yes	Patients were assigned study identification numbers via an IRS and once inclusion criteria were confirmed, the IRS assigned a blinded treatment.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Groups were comparable with respect to baseline characteristics including chronic symptoms, previous treatments, and indicators of disease severity.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Participants and outcome assessors were blinded to the allocation of treatment. Treatment assignments were maintained by the IRS and members of the study team did not have access to the 6-month treatment period unblinded data until the final analysis.

Study question	Response yes/no/not clear/ partially/N/A	How is the question addressed in the study?
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No	All but one of the 94 patients went on to participate in the OLE phase of this study.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes were clearly stated a priori and reported accordingly.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Full analysis set included all randomised patients who received at least one dose of study drug. All but one patient that discontinued treatment went on to participate in the OLE phase of the study.

AHP: acute hepatic porphyria; IRS: interactive response system; OLE: open-label extension. Sources: Gouya et al. (2019);[101] Balwani et al. (2020)[14]

Table 16. Critical appraisal of RCTs – givosiran phase 1 study

Study question	Response yes/no/not clear/ partially/N/A	How is the question addressed in the study?
Was randomisation carried out appropriately?	Yes	Randomisation and treatment allocation ratios were clearly described in each part of the study.
Was the concealment of treatment allocation adequate?	Yes	Randomisation lists generated by biostatistician and maintained by dispensing pharmacist.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Group sizes in Parts A and B were too small to assess and not presented. The two treatment groups in Part C of the study appear comparable although sample sizes small.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Partially for Parts A and B Yes, for Part C	Part A and Part B were single-blind only by design (MAD/SAD study in patients that did not experience acute attacks). The risk of bias is low because it was a SAD/MAD study of the same intervention. The study was double-blind in Part C (recurrent attack patients).
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No	All patients were accounted for.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Outcomes were stated a priori and reported accordingly. Exploratory endpoints were clearly identified.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	All randomised patients were included in the analysis and all patients were accounted for. Investigators had stated methodology for handling missing data a priori.

MAD: multiple-ascending dose; SAD: single-ascending dose. Source: Sardh et al. (2019)[13]

Table 17. Critical appraisal of RCTs – hemin RCT

Study question	Response yes/no/not clear/ partially/N/A	How is the question addressed in the study?
Was randomisation carried out appropriately?	Yes	Random numbers table.
Was the concealment of treatment allocation adequate?	Not clear	Hemin is dark in colour and the placebo was a saline solution.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Not clear	Baseline information not clearly reported. The relative treatment allocation of patients was not shown in the individually reported baseline data.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Partially	The clinical outcomes assessor was blind to the treatment code and patients were blindfolded during treatment administration. Both treatment and placebo were administered intravenously. However, the persons administering the treatment may not have been blinded to treatment as hemin is dark in colour (compared with saline solution). Treatment administration and outcome assessment appear to have been conducted by different personnel.
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	Not clear	Only 9 of 12 patients were administered the alternate treatment of hemin or placebo. The three remaining patients did not present with subsequent attacks that would have required additional therapy, and their follow-up was not ascertained.
Is there any evidence to suggest that the	No	

authors measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not clear	Likely, however the treatment of the three patients who did not have paired attacks is not clear.

Source: Herrick et al. (1989)[103]

9.6. Results of the relevant studies

9.6.1. Results tables for studies with all relevant outcome measures pertinent to the decision problem

Givosiran studies

ENVISION phase 3 RCT

The clinical efficacy of givosiran was evaluated in the ENVISION RCT.[14] Table 18 summarises the clinical efficacy outcomes. The endpoints in the ENVISION trial were chosen to measure the effects of givosiran on clinically important and patient-relevant outcomes.[119]

Table 18. Summary of outcomes from the Phase 3 ENVISION study

Reference	Balwani, et al. (2020)[14]				
Study name	ENVISION, NCT03338816				
Size of study groups	Givosiran=48 Placebo=46				
Study duration	6 months				
Type of analysis	ITT				
Outcome name (unit)	**Effect Size**		**Statistical test**		**Comments**
	Value	**95%CI**	**Type**	**p-value**	
Mean composite AAR in AIP (RR)	0.26	(0.16, 0.41)	MMRM	6.04×10^{-9}	This effect was consistent and statistically significant across a wide range of subgroups including age group, race, geographic region, baseline BMI, prior hemin prophylaxis, historical attack rates, and prior chronic symptoms between attacks.
LS mean urinary ALA in AIP at 3 months (mmol/mol Cr)	-18	(-22.3, -14.2)	t-test	8.74×10^{-14}	
LS mean Urinary ALA in AIP at 6 months (mmol/mol Cr)	-19	(-26.0, -12.2)	t-test	6.24×10^{-7}	
LS mean Urinary PBG in AIP at 6 months (mmol/mol Cr)	-36	(-49.7, -22.7)	t-test	8.80×10^{-7}	
Mean annualised days on hemin usage in AIP	0.23	(0.11, 0.45)	t-test	2.36×10^{-5}	
Mean composite AAR in AHP (RR)	0.27	(0.17, 0.43)	MMRM	1.36×10^{-8}	
Daily worst pain (BPI-SF-NRS, range 0–10 points) AUC change from baseline**	-12.680	(-25.526, 0.166)	ANCOVA Wilcoxon	0.0530* 0.0455	
Daily worst nausea (NRS, range: 0–10 points) AUC change from baseline**	-6.940	(-19.837, 5.957)	ANCOVA	0.2876	
Daily worst fatigue (BFI-SF NRS, range 0-10) AUC change from baseline**	5.492	(-4.000, 14.984)	ANCOVA	0.2532	
Mean proportion of days with opioid use over 6 months	Givosiran: 23% Placebo: 38%	NR	NR	NR	
PCS of SF-12 (range	3.939	(0.592, 7.285)	t-test	0.0216	

Reference	Balwani, et al. (2020)[14]				
0–100) in AIP, mean change from baseline* **					
EQ-5D-5L VAS (range 0–100), mean change from baseline* **	Givosiran: 5.2 Placebo: -1.3	NR	NR	NR	Clinically-meaningful change
PGIC at 6 months†	Givosiran: 59.4% Placebo: 18.4%	NR	NR	NR	
PPEQ at 6 months (Givosiran vs Placebo, % patients)‡					
1. Travelling >1 day for work or pleasure	35.1 vs 13.2	NR	NR	NR	
2. Participating in social activities	35.1 vs 7.9	NR	NR	NR	
3. Planning future events	35.1 vs 10.5	NR	NR	NR	
4. Doing household chores	35.1 vs 5.3	NR	NR	NR	
5. Exercising moderately	32.4 vs 5.3	NR	NR	NR	
6. Convenience of current porphyria treatment	72.2 vs 8.1	NR	NR	NR	
7. Overall satisfaction with porphyria treatment	72.2 vs 13.5	NR	NR	NR	
8. Study drug helping more normal life	66.7 vs 10.8	NR	NR	NR	
Days of school/work missed at 6 months (Givosiran vs Placebo, mean)	2.4 vs 6.9	NR	NR	NR	

* Pain data not normally distributed; ANCOVA method not valid. Post-hoc analysis using non-parametric stratified Wilcoxon method. ** A higher score indicates worse manifestation; *** A higher score indicates better physical health and functioning. † Proportion of patients reporting "much improved" or "very much improved". None of the placebo patients reported that their condition was "very much improved". ‡Percentage of patients with response "Much Better" for Q1–7 or with response "Always" or "Most of the time" for Q8 at Month 6. AAR: annualised attack rate; AHP: acute hepatic porphyria; AIP: acute intermittent porphyria; ALA: aminolevulinic acid; ANCOVA: analysis of covariance; AUC: area under the curve; BFI-SF: Brief Fatigue Inventory-Short Form; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; Cr: creatinine; EQ-5D-5L: EuroQol 5-Dimension 5-Level Questionnaire; ITT: intent to treat; LS: least square; mmol: millimole; MMRM: mixed-effects model repeated measures; mol: mole; NR: not reported; NRS: numeric rating scale; PBG: porphobilinogen; PCS: Physical Component Summary; PGIC: Patient Global Impression of Change Questionnaire; PPEQ: Porphyria Patient Experience Questionnaire; RR: rate ratio; SF-12: 12-Item Short Form Health Survey; VAS: visual analogue scale. Source: Balwani et al. (2020)[14]

Primary outcomes

The primary endpoint was the AAR in patients with AIP during the 6-month randomised intervention period, considering acute attacks that required hospitalisation, an urgent healthcare visit, or IV hemin administration at home.[14] Givosiran met the primary endpoint in ENVISION (givosiran AAR: 3.2 [95%CI: 2.25,4.59] versus placebo AAR: 12.5 [95%CI: 9.35,16.76]; rate ratio: 0.26 [95%CI: 0.16, 0.41]; $p=6.04x10^{-9}$).[14] The lower composite AAR among patients taking givosiran represented a 74% mean reduction in attacks compared with patients on placebo. The efficacy of givosiran was also evident when considering each component of the composite endpoint independently, as there was a lower rate of attacks that required hospitalisation, urgent care, or IV hemin use noted in patients with AIP who received givosiran (Figure 8).[14]

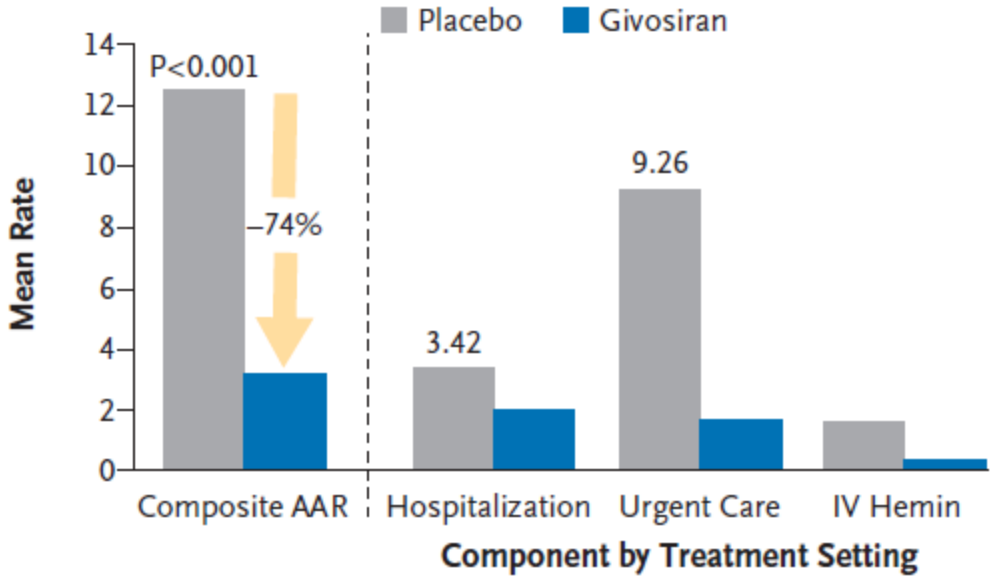


Figure 8. Mean composite AAR in AIP and endpoint components in ENVISION
AIP: acute intermittent porphyria; AAR: annualised attack rate; IV: intravenous. Source: Balwani et al. (2020)[14]

Givosiran treatment resulted in a 90% reduction in median composite AAR over the 6-month study period compared to placebo (1.0 vs 10.7, Figure 9), and the proportion of AIP patients who were attack free was approximately 3-fold higher with givosiran than with placebo (16.3% vs 50.0%).[14] These findings demonstrate the ability of givosiran to substantially reduce the risk and frequency of AHP attacks.

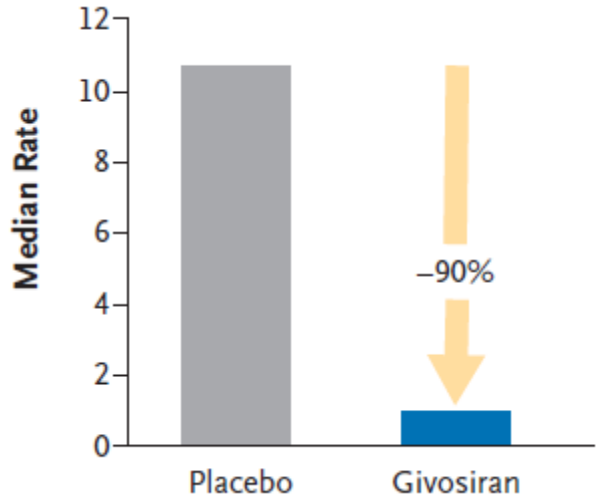


Figure 9. Median AAR in ENVISION
AAR, annualised attack rate. Source: Balwani et al. (2020)[14]

AAR subgroup analysis

In a pre-specified subgroup analysis of AAR in AIP patients, the significant treatment benefit of givosiran compared to placebo was consistent across all subgroups except prior opioid use when not having attacks (Figure 10).[14] Although the 95% CI for this subgroup crossed 1.0, the point estimate lay within the 95% CIs in the other subgroups.

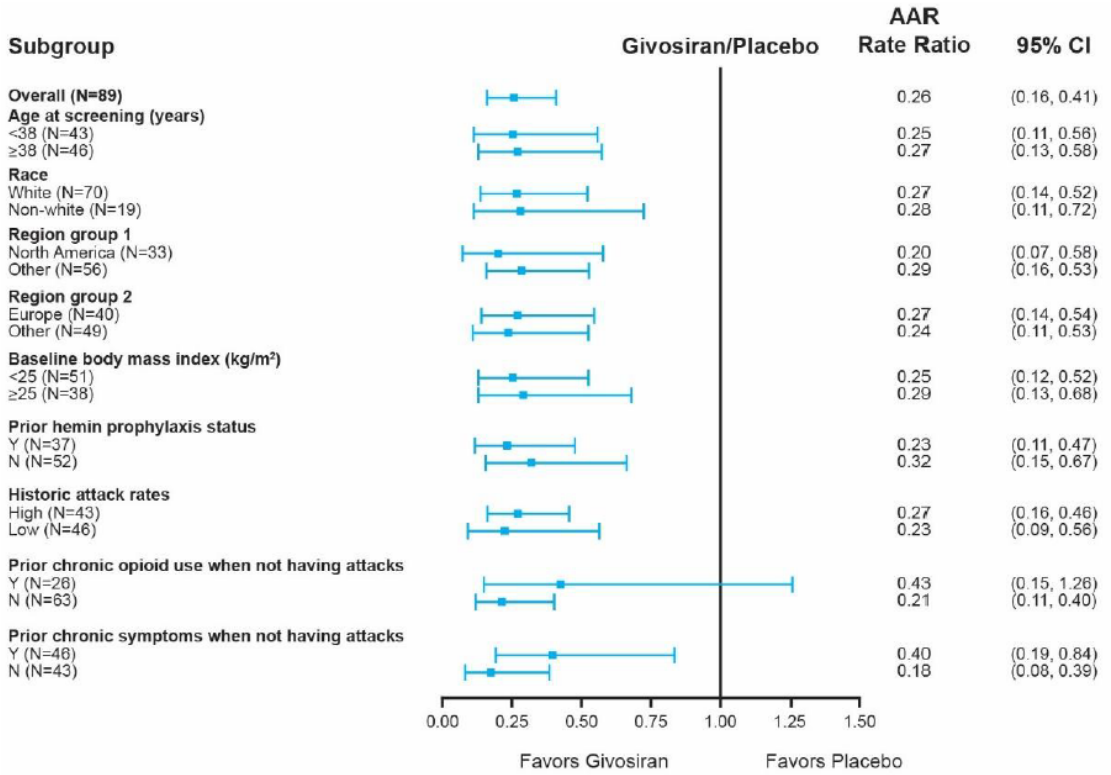


Figure 10. Pre-specified subgroup analysis in ENVISION
AAR: annualised attack rate. Source: Balwani et al. (2020)[14]

Secondary endpoints

Similarly to the results seen in AIP, the key secondary endpoint, composite AAR in all AHP patients, was significantly lower among patients who were randomised to givosiran relative to placebo (rate ratio: 0.27; 95%CI: 0.17,0.43; $p=1.35x10^{-8}$), representing a 73% mean reduction in the AAR.[14] A summary of secondary efficacy endpoint results is provided in Table 19.[14]

Table 19. Secondary efficacy endpoints from ENVISION*

Secondary End Points	Placebo (N = 43)	Givosiran (N = 46)	Difference†	p value
Urinary ALA — mmol/mole of creatinine				
Month 3 LSM (±SE)	20.0±1.5	1.8±1.4	–18.2±2.0	<0.001
Month 6 LSM (±SE)	23.2±2.5	4.0±2.4	–19.1±3.5	<0.001
Urinary porphobilinogen (mmol/mole of creatinine)				
Month 6 LSM (±SE)	49.1±5.0	12.9±4.6	–36.2±6.8	<0.001
Annualised no. of days of hemin use				
Mean (95% CI)	29.7 (18.4 to 47.9)	6.8 (4.2 to 10.9)	0.23 (0.11 to 0.45)§	<0.001
Annualised attack rate in patients with AHP				
Mean (95% CI)	12.3 (9.2 to 16.3)	3.4 (2.4 to 4.7)	0.27 (0.17 to 0.43)§	<0.001
Daily worst score for pain‖				
Median of change in AUC from baseline (IQR)	5.3 (–23.0 to 11.1)	–11.5 (–29.2 to 3.0)	–10.1 (–22.8 to 0.9)‡	0.046
Daily worst score for fatigue‖				
LSM (±SE) of change in AUC from baseline	–4.2±4.7	–11.1±4.5	–6.9±6.5	NS
Daily worst score for nausea‖				
LSM (±SE) of change in AUC from baseline	–4.0±3.5	1.5±3.3	5.5±4.8	NT
SF-12**				
LSM (±SE) of change from baseline at Month 6	1.4±1.2	5.4±1.2	3.9±1.7	NT

* All secondary end points are reported in patients with acute intermittent porphyria for time points during the 6-month intervention period unless otherwise stated. Statistical significance was not tested if the end point did not meet the conditions of the prespecified hierarchical order. † Differences are for the givosiran group, as compared with the placebo group. ‡ Because of a significant deviation from normal distribution, the planned methods of a mixed model for repeated measures or analysis of covariance were

not valid. A nonparametric stratified Wilcoxon signed-rank test was therefore conducted. The median of the between group difference was estimated with the use of the Hodges–Lehmann method. § This value is a rate ratio (95% CI) for the comparison between givosiran and placebo. ‖ Scores for pain, fatigue, and nausea were measured on a numerical rating scale ranging from 0 to 10, with higher scores indicating more severe symptoms. ** Scores on the Physical Component Summary of the 12-Item Short-Form Health Survey, version 2 (SF-12), range from 0 (worst functioning) to 100 (best functioning), with published literature in other chronic diseases suggesting that a change of 2 to 5 points represents a clinically meaningful difference. AHP: acute hepatic porphyria; ALA: delta-aminolevulinic acid: AUC: area under the curve: CI: confidence interval; IQR: interquartile range; LSM: least squares-mean; NT: not tested: NS: not significant; SE: standard error

Givosiran showed robust and sustained reductions in urinary ALA and PBG over the 6-month follow-up period (Figure 11, Table 19).[14]

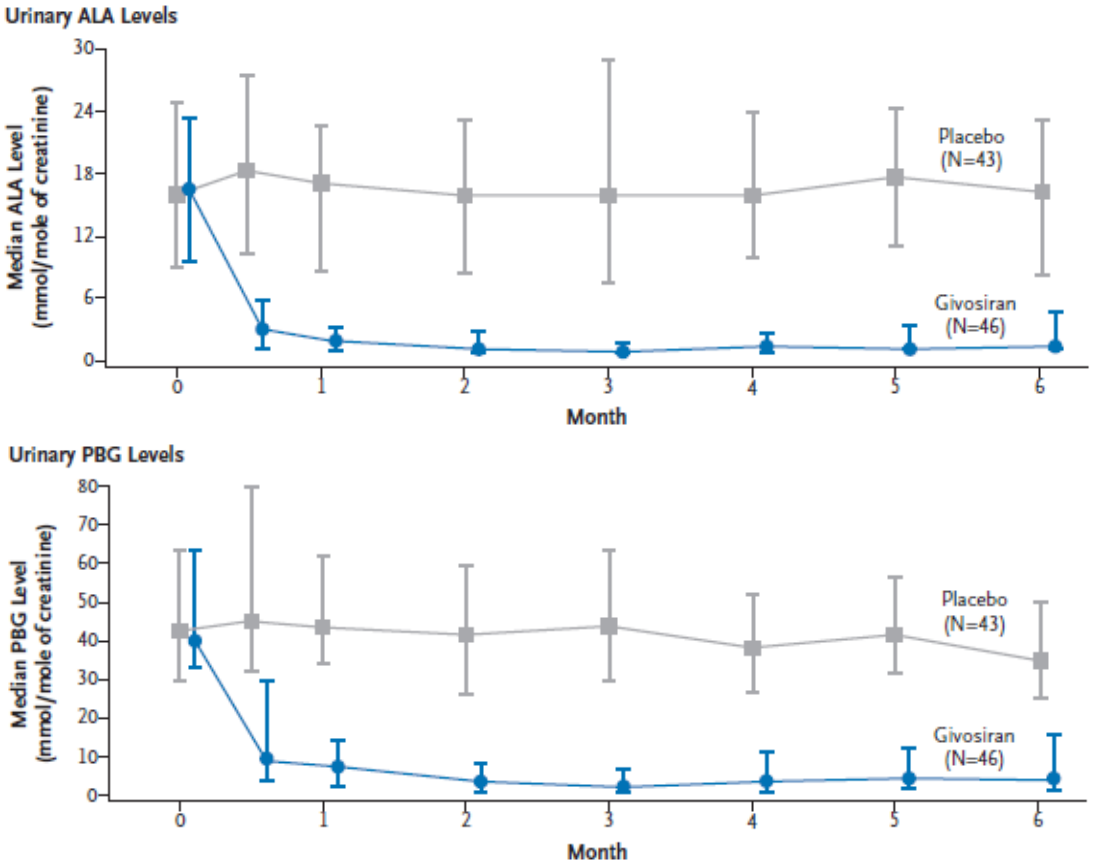


Figure 11. ENVISION: ALA and PBG levels in AIP patients
At 6 months, median ALA and PBG were reduced by 86% and 91%, respectively, compared to baseline.
AIP: acute intermittent porphyria; ALA: aminolevulinic acid; PBG: porphobilinogen. Source: Balwani et al. (2020)[14]

Givosiran treatment resulted in 77% fewer mean annualised days on hemin compared with placebo (Table 19).[14] Givosiran-treated patients also had a greater reduction in daily worst pain throughout the 6-month trial period compared with patients taking placebo (Table 19, Figure 12). This difference could not be attributed to analgesic use, which was lower in the givosiran group over 6 months.[14]

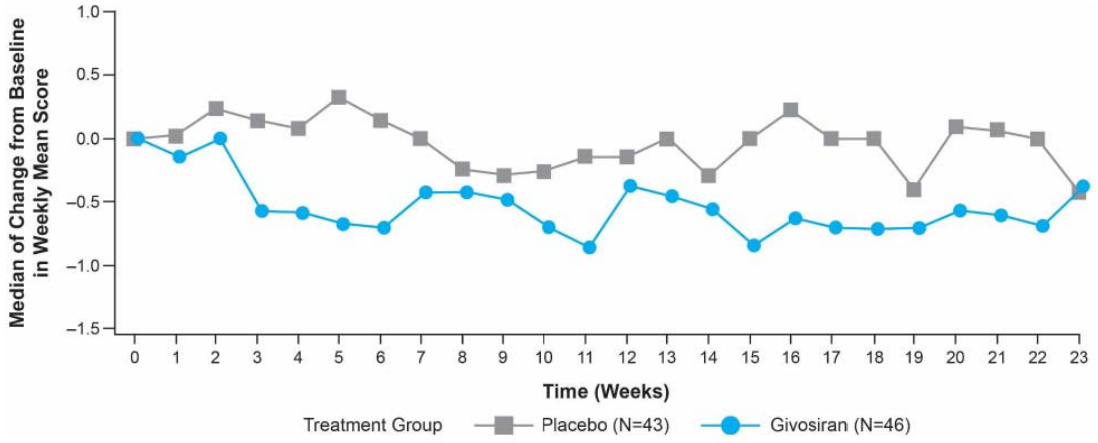


Figure 12. Median change from baseline in worst daily pain score over 6 months in ENVISION
Source: Balwani et al. (2020)[14]

Givosiran had a positive impact on patient QoL, with the greatest increases observed for the domains of bodily pain and social and physical functioning (Figure 13).[14]

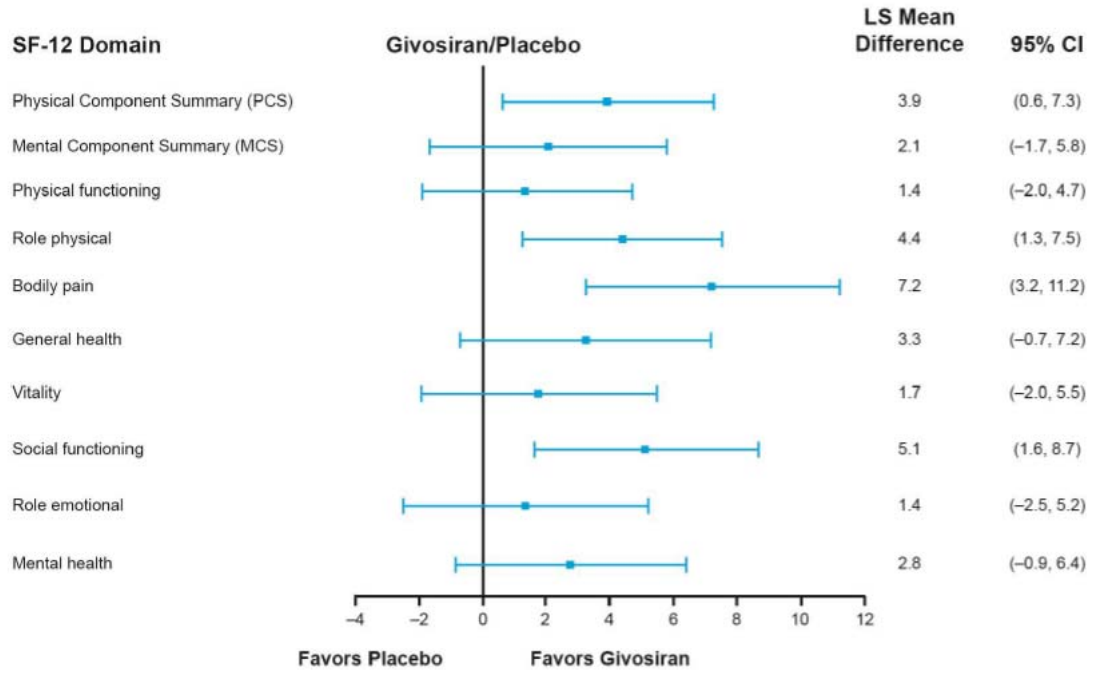


Figure 13. ENVISION: Forest plot diagram showing the change from baseline to Month 6 in SF-12 domain scores

AIP: acute intermittent porphyria; LS: least square; SF-12: 12-Item Short Form Health Survey. Source: Balwani et al. (2020)[14]

Using the PGIC instrument, 59.4% of givosiran-treated AHP patients reported that their condition was 'Very much improved' or 'Much improved' at Month 6, compared to 18.4% of placebo-treated patients reporting that their condition was 'Much improved' (Figure 14).

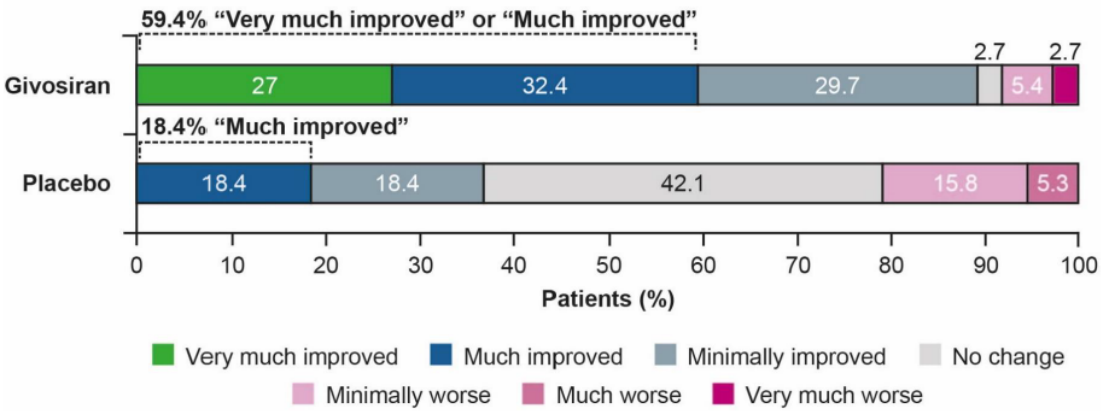


Figure 14. ENVISION: PGIC in AHP at 6 months

AHP: acute hepatic porphyria; PGIC: Patient Global Impression of Change. Source: Balwani et al. (2020)[14]

Similarly, the PPEQ instrument demonstrated a more than 5-fold improvement in the overall satisfaction with porphyria treatment in patients treated with givosiran compared with patients receiving placebo (72.2% vs 13.5%; Figure 15).

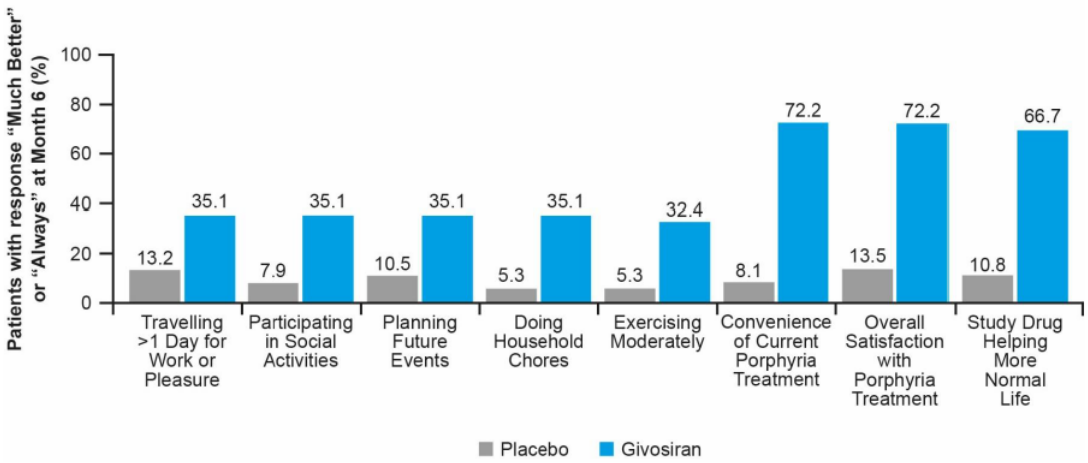


Figure 15. ENVISION: PPEQ in AHP at 6 months

The figure presents the percent of patients with response 'Much Better' (other options were "Minimally Better", "No Change", "Minimally Worse", "Much Worse"). AHP: acute hepatic porphyria; PPEQ: Porphyria Patient Experience Questionnaire. Source: Balwani et al. (2020)[14]

Post hoc analyses of ENVISION

Post hoc analyses were carried out to further describe the effect of givosiran on AHP attack severity and disease modifying efficacy between AHP attacks.

Impact of givosiran on attack severity

Givosiran reduced both the frequency and severity of AHP attacks, as outlined in Table 20. Severe attacks were defined as attacks accompanied by severe pain (median pain score ≥7 on a 0 to 10 NRS). The proportion of severe attacks in AHP patients was lower for those taking givosiran (21.1%) compared with those on placebo (32.0%). Moreover, even among those patients who experienced at least one attack, a lower proportion of givosiran patients (41.7%) compared with placebo patients (63.2%) had a severe attack.[119,120]

Table 20. Composite porphyria attacks with median pain score ≥7, ENVISION trial, AHP patients

	Placebo (N=46)	Givosiran (N=48)
Total number of attacks	297	90
Total number of attacks with median pain scores ≥7*, n (%)	95 (32.0)	19 (21.1)
Number of patients with at least one attack	38	24
Number of patients with at least one attack with median pain score≥7*; n/N (%)	24/38 (63.2)	10/24 (41.7)

*The BPI-SF NRS is an 11-point scale: 0=no pain; 10=pain as bad as you can imagine. Median pain scores of attacks were calculated based on pain scores collected during each composite attack. AHP: acute hepatic porphyria; BPI-SF NRS: Brief Pain Inventory-short form numeric rating scales. Source: ENVISION Clinical Study Report (2020)[119]; Kauppinen (2020)[120]

The decrease in severe attacks in givosiran-treated patients was accompanied by a lower proportion of givosiran patients compared to placebo recipients using analgesics. Givosiran-treated patients had fewer opioid use days during the DB period of ENVISION than placebo-treated patients (givosiran: mean: 23.1 days; median: 3.0 [0.0–36.5] days; placebo (mean: 35.6 days; median 8.5 [1.8–72.3] days).[119] Similarly, the overall analgesic use during attacks was also lower for givosiran/givosiran treated patients compared with placebo/givosiran-treated patients. After 12 months of OLE follow-up, figures for analgesic use were 73.3% vs 85.0% (opioids) and 60.0% vs 75.0% (non-opioids).[120]

In addition, while hospitalisation for attacks may be determined by local healthcare treatment practices, hospitalisation rates may also be reflective of attack severity. Givosiran led to a 43% reduction in AHP attacks requiring hospitalisation compared to placebo.[119]

Efficacy of givosiran between attacks

Treatment with givosiran resulted in a consistent reduction in pain scores both during and between attacks (i.e., 'not during attacks').[119] The 'during attack' time period included all investigator-adjudicated porphyria attacks (i.e., attacks as defined in the porphyria attack composite endpoint plus attacks at home not treated with hemin). The median of change from baseline in daily worst pain between attacks (i.e., 'not during attacks') was lower for givosiran than for placebo, which reflects less pain both during and in between attacks (Figure 16).[119]

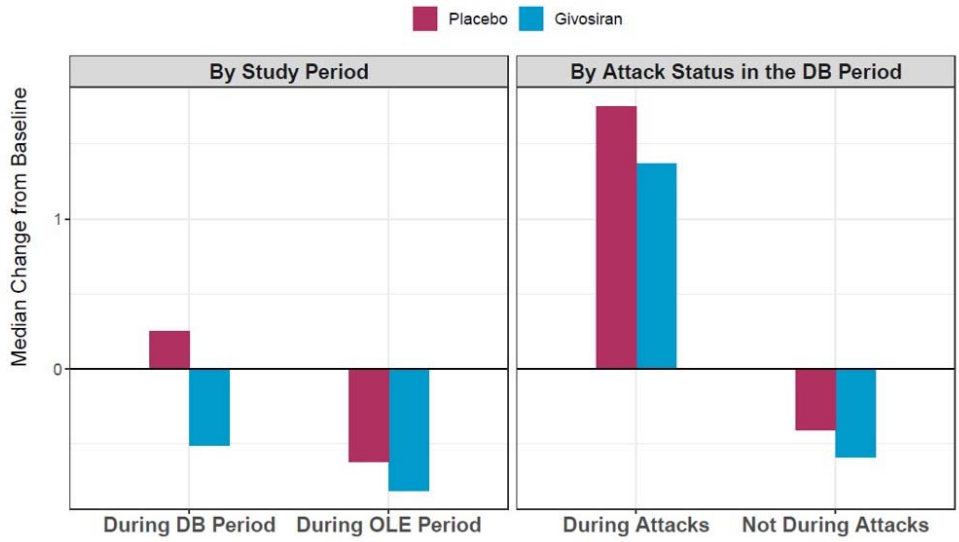


Figure 16. Median change from baseline in pain score by study period and all attack status in AIP patients (AIP patients in full analysis set)

Changes <0 indicate improvement. Placebo patients received placebo during the DB period and crossed over to givosiran during the OLE period. All Investigator-adjudicated attacks are included. AIP: acute intermittent porphyria; DB: double-blind; OLE: open-label extension. Source: ENVISION Clinical Study Report (2020)[119]

In addition, on days between attacks, givosiran consistently demonstrated a lower proportion of days with daily pain scores across a range of ≥2 to ≥7 as well as a lower proportion of days with a daily pain score worse than baseline compared to placebo (Figure 17).[119]

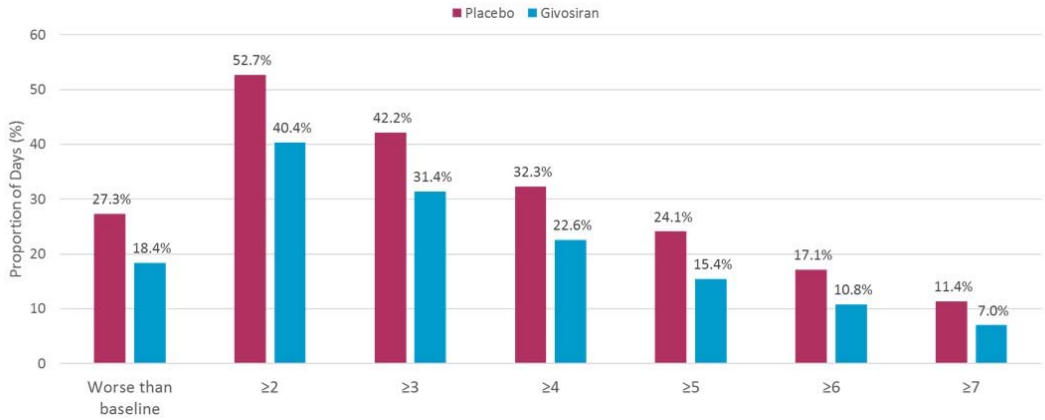


Figure 17. Daily worst pain on days between attacks in AIP patients, ENVISION

All Investigator-adjudicated attacks are included. AIP, acute intermittent porphyria. Source: ENVISION Clinical Study Report (2020)[119]

Importantly, the reduction in pain with givosiran was not attributable to increased analgesic use as it was accompanied by a lower proportion of patients requiring analgesic use during and between all attacks (Figure 18).[119]

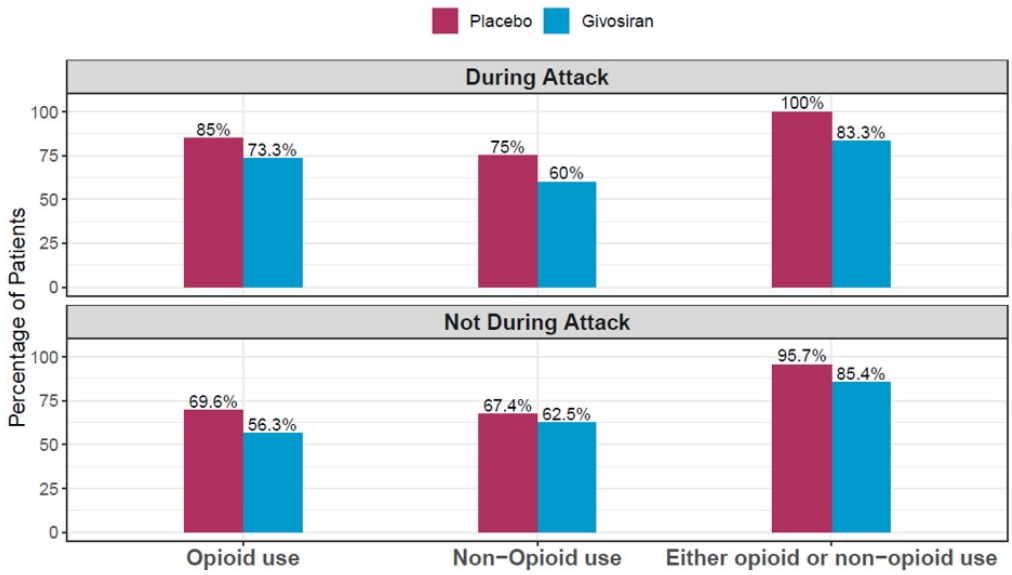


Figure 18. Summary of analgesic usage by all attack status in AHP patients, ENVISION
All Investigator-adjudicated attacks are included. AHP, acute hepatic porphyria. Source: ENVISION Clinical Study Report (2020)[119]

Hemin use by subgroup

A post-hoc analysis evaluated hemin use by subgroups during the 6-month double-blind period of ENVISION. Patients were required to stop prophylactic hemin use prior to screening but were able to receive hemin if experiencing an attack on study.

At baseline, patients had a history of hemin prophylaxis (40%), iron overload (33%), chronic indwelling venous catheters often required for IV hemin administration (71%), as well as infection (18%) and thrombosis (7%), both related to central venous access. AHP patients receiving givosiran experienced a 74% (ratio 0.26; 95% CI: 0.13, 0.52) reduction in annualised days of hemin use compared to placebo. Additionally, 54.2% (26/48) of givosiran-treated patients had zero days of hemin use compared to 26.1% (12/46) on placebo. Givosiran patients had fewer median annualised days of hemin use compared to those on placebo whether or not at baseline they had a history of chronic symptoms, a history of opioid use between attacks, or a high or low historical AAR (Figure 19). The median annualised days of hemin use was zero for givosiran patients in all subgroups except for patients with high historical AAR who had 5 days vs. 41 days for placebo patients.[121]

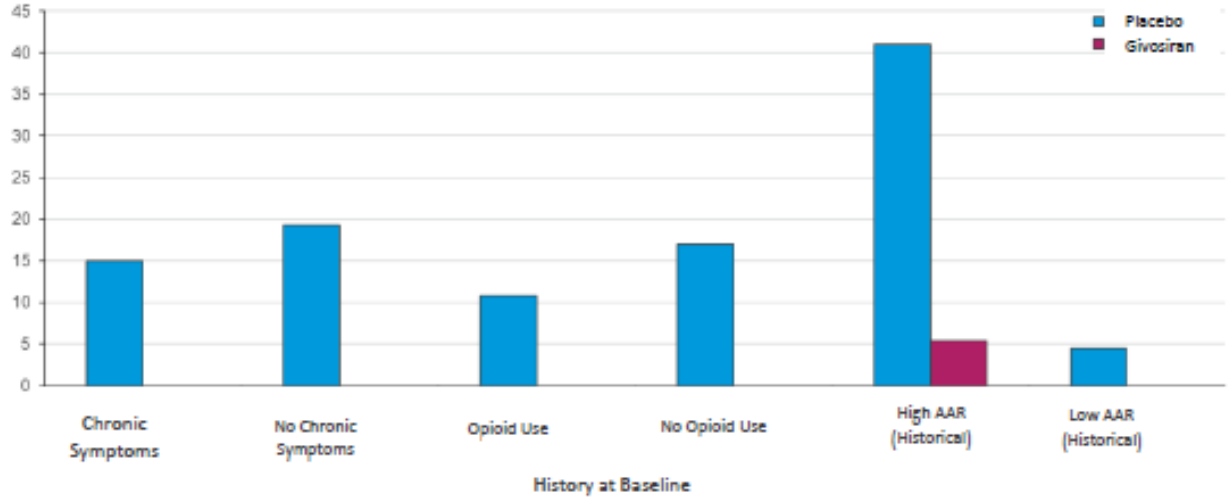


Figure 19. Median days of hemin use during the 6-month double-blind period of ENVISION
For patients on hemin prophylaxis, low<7, high≥7; those not on hemin prophylaxis: low<12, high≥12.
AAR: annualized attack rate; high and low historical AARs were based on numbers of attacks during the 6 months preceding the study period. Source: Bonkovsky et al. (2020)[121]

Outcomes by prior hemin prophylaxis status

IV hemin is approved to treat acute attacks and is sometimes used off-label prophylactically. In ENVISION, patients were required to discontinue prophylactic hemin treatment at study entry but could receive hemin for acute attacks. A post-hoc analysis was conducted to evaluate outcomes in AHP patients with or without prior hemin prophylaxis.[121]

For AHP patients on prior hemin prophylaxis (median historical AAR: 9.0), a 77% reduction in mean AAR was observed with givosiran treatment versus placebo in the DB period (Table 21). A similar reduction (63%) in mean AAR was observed in those without prior hemin prophylaxis (median historical AAR: 7.0). In both groups, further reduction in AAR was observed in patients who continued on givosiran in the OLE period (Table 21). A similar reduction in AAR was also observed in both groups of placebo patients who received givosiran in the OLE (Table 21). The percentage of patients with 0 composite attacks increased in each group following 6-months of givosiran treatment in the OLE with 55% and 67% in the patients who had continued givosiran treatment (Table 21).[121] These results demonstrate that patients who received hemin prophylaxis prior to ENVISION showed substantial clinical benefit when off hemin prophylaxis and being treated with givosiran, similar to those without prior hemin prophylaxis.

Table 21. AAR and % of 0 attacks in AHP patients with and without prior hemin prophylaxis use

``	Prior Hemin Prophylaxis Use	Mean AAR		Median[a] AAR		% of 0 Attacks	
		6mo DB	OLE Thru Month 12	6mo DB	OLE Thru Month 12	6mo DB	OLE Thru Month 12
Givosiran/Givosiran	**Yes**	5.21	3.67	2.1 (0, 7.9)	0 (0, 5.5)	45.0	55.0
	No	3.33	1.85	0 (0, 6.2)	0 (0, 2.2)	51.9	66.7
Placebo/Givosiran	**Yes**	22.40	4.74	23.8 (8.7, 31.3)	1.8 (0, 7.4)	5.6	35.3
	No	8.62	2.57	6.7 (1.0, 13.3)	1.8 (0, 4)	25	46.4
Givosiran vs Placebo: AAR Ratio (95% CI)[b]	**Yes**	0.23 (0.12, 0.46)					
	No	0.37 (0.18, 0.77)					

Note: Per the ENVISION protocol, a patient was considered to have received prior hemin prophylaxis if they had received ≥2 consecutive administrations [days] of hemin, >1 week apart in the absence of porphyria attack signs and symptoms, with the intent to prevent porphyria attacks from occurring. [a]Median (Q1, Q3). [b]AAR ratio and 95% CI were estimated from a negative binomial regression model with treatment group as a fixed effect, and the logarithm of the follow-up time as an offset variable. AAR, annualised attack rate; AHP, acute hepatic porphyria; CI, confidence interval; Mo, month; DB, double-blind; OLE, open-label extension. Source: Bonkovsky et al. (2020)[121]

ENVISION OLE

AHP patients who continued on givosiran during the OLE period showed a maintained reduction of the composite porphyria attack rate (Figure 20) and of urinary ALA (Figure 21) and PBG (Figure 22) levels. Similar results were obtained for AHP patients that were switched from placebo to givosiran at the start of the OLE period.[119]

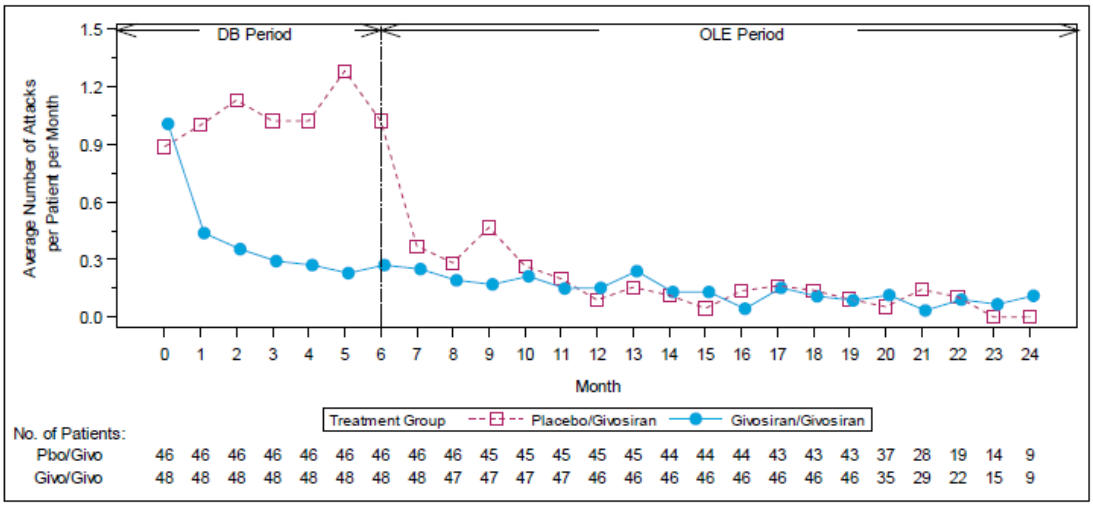


Figure 20. ENVISION OLE: Monthly attack rate in AHP (18-month follow-up)

AHP: acute hepatic porphyria; OLE: open-label extension. Source: Alnylam Pharmaceuticals (data on file, 2020).[119]

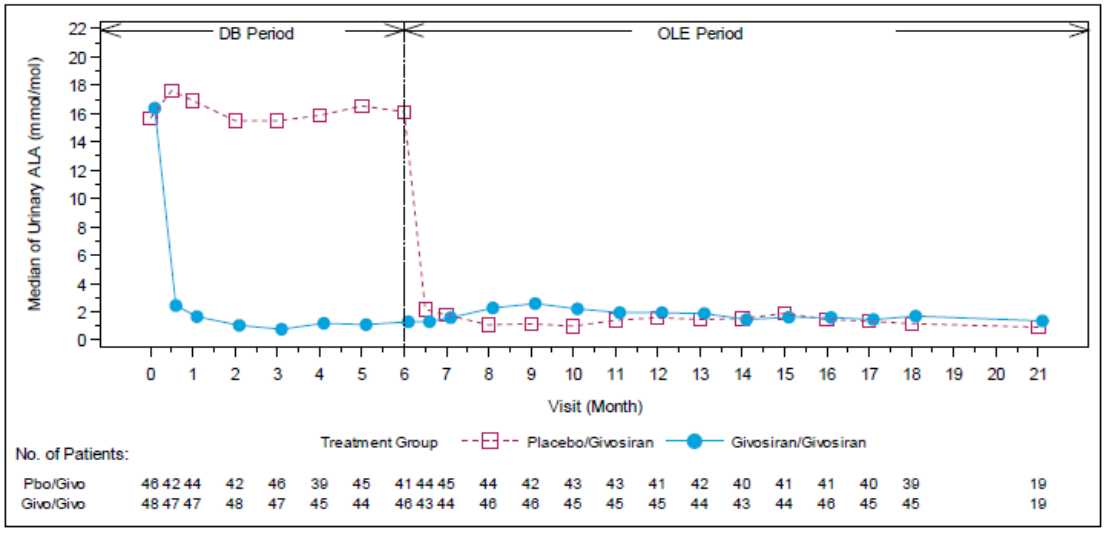


Figure 21. ENVISION OLE: Urinary ALA in AHP (11-month follow-up)
AHP: acute hepatic porphyria; ALA: aminolevulinic acid; OLE: open-label extension. Source: Alnylam Pharmaceuticals (data on file, 2020).[119]

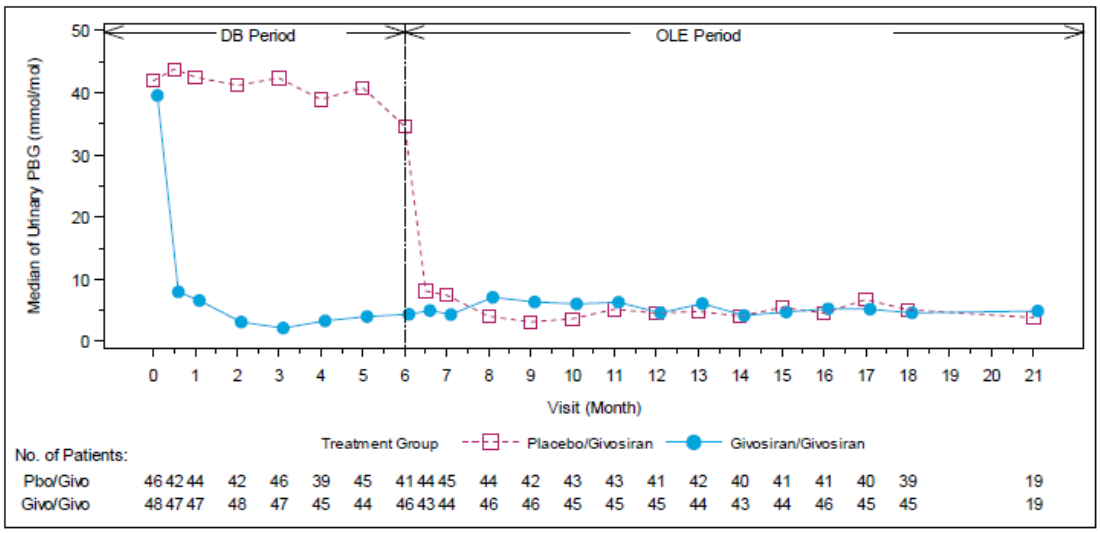


Figure 22. ENVISION OLE: Urinary PBG in AHP (11-month follow-up)
AHP: acute hepatic porphyria; OLE: open-label extension; PBG: porphobilinogen. Source: Alnylam Pharmaceuticals (data on file, 2020).[119]

Additional findings from the ENVISION OLE that further demonstrate the immediate and long-term effectiveness of givosiran in reducing the rate of acute attacks, decreasing the requirement for other medications, and improving QoL in patients with AHP include:

- An increase in the percentage of patients taking givosiran with zero days of hemin use from the RCT to the OLE period (54.3% vs 70.2%).[119]
- Maintenance of reductions in pain in givosiran-treated patients and decreased pain among patients crossing over from placebo.[119]
- Reductions in opioid or non-opioid analgesic use among patients crossing over to givosiran from placebo (28.5% of days reduced to 23.5% of days).[119]
- Sustained levels of physical function (SF-12 PCS scores) among patients randomised to givosiran and improvement among patients crossing over from placebo.[119]
- Further increases to almost maximum PGIC scores (97.8%) among patients maintained on givosiran and similar improvements among patients crossing over from placebo (88.4%).[119]
- Further improvements with continued givosiran treatment in every category of the PPEQ, with patient crossing over from placebo showing improvements similar to those observed among givosiran-treated patients during the ENVISION RCT.[119]

Phase 1 trial

A summary of the results from the phase 1 trial evaluating the safety, tolerability, and pharmacokinetic/pharmacodynamic profile of givosiran is provided in Table 22. The safety data from the givosiran phase 1 trial are presented in Section 9.7.2. The following secondary and exploratory endpoint results were reported:

- In Part A, a single 2.5-mg/kg dose of givosiran resulted in a rapid, dose-dependent, mean maximum reduction in ALAS1 mRNA from baseline of 86% (SE±8) and a reduction of 91% (SE±3) in urinary ALA and of 96% (SE±1) in urinary PBG.[13]
- In Part C, similar results were seen in patients with recurrent attacks, where all patients who received monthly injections of givosiran had sustained reductions in ALAS1 mRNA, urinary ALA, and urinary PBG over 168 days of follow-up (Figure 23).[13]

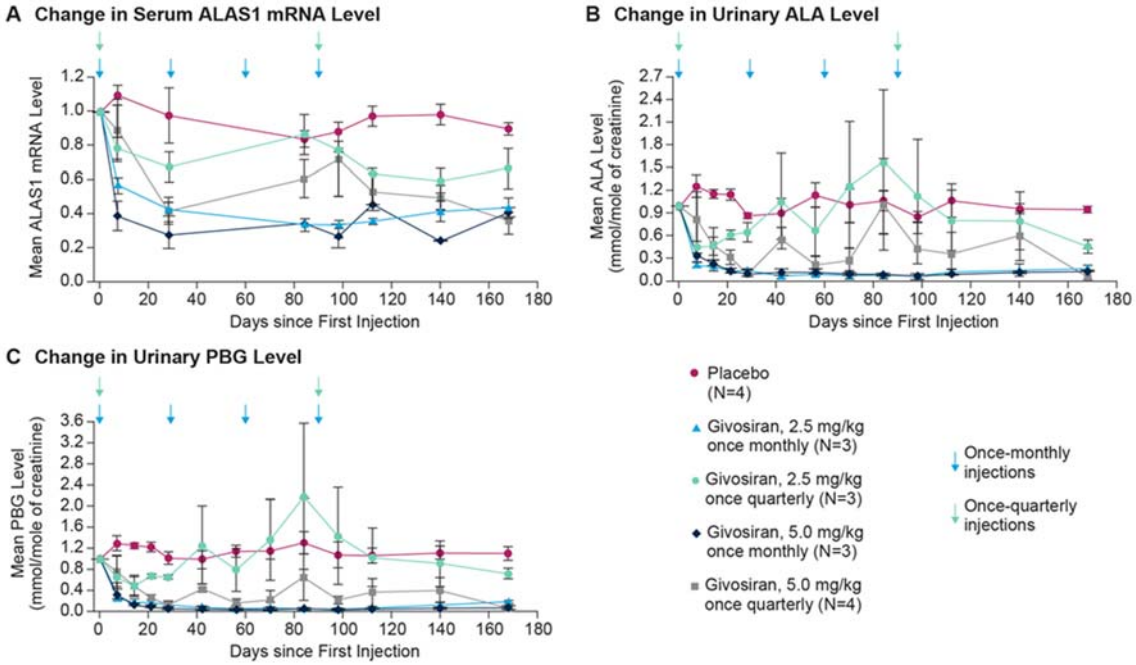


Figure 23. Phase 1 trial of givosiran, Part C: Change from baseline in ALAS1 mRNA (A), and urinary ALA (B) and PBG (C) levels in patients with AIP and recurrent attacks

Bars represent SE. AIP, acute intermittent porphyria; ALA, aminolevulinic acid; ALAS1, ALA synthase 1; mRNA, messenger ribonucleic acid; PBG, porphobilinogen; SE, standard error. Source: Sardh et al. (2019)[13]

Table 22. Summary of outcomes from the givosiran Phase 1 trial

Reference	Givosiran Phase 1[13]				
Study name	NCT02452372				
Size of study groups	Part A: Givosiran=15, Placebo=5; Part B: Givosiran=8; Part C: Givosiran=13, Placebo=4				
Study duration	Part A: 42 days; Part B: 70 days; Part C: 168 days				
Type of analysis	ITT				
Outcome name (unit)	**Effect Size**		**Statistical test**		**Comments**
	Value	**95%CI***	**Type**	**p-value**	
Safety (primary endpoint)	-	-	-	-	To be described in detail in Section 9.7 Adverse events
Urinary ALAS1 mRNA, mean maximum % reduction from baseline (SEM)					
Part A, single 2.5 mg/kg dose	86 (8)	NR	NR	NR	
Part C, 2.5 mg/kg QM	67 (3)	NR	NR	NR	
Part C, 5.0 mg/kg QM	74 (6)	NR	NR	NR	
Urinary ALA, mean maximum % reduction from baseline (SEM)					
Part A, single 2.5 mg/kg dose	91 (3)	NR	NR	NR	
Part C, 2.5 mg/kg QM	>90	NR	NR	NR	
Part C, 5.0 mg/kg QM	>90	NR	NR	NR	

Urinary PBG, mean maximum % reduction from baseline (SEM)					
Part A, single 2.5 mg/kg dose	96 (1)	NR	NR	NR	
Part C, 2.5 mg/kg QM	>90	NR	NR	NR	
Part C, 5.0 mg/kg QM	>90	NR	NR	NR	
Mean AAR / % reduction vs placebo, Part C					
2.5 mg/kg Q3M	10.1 / 39.7	(-38.5, 73.7)	NR	NR	
5.0 mg/kg Q3M	10.1 / 40.1	(-28.2, 71.9)	NR	NR	
2.5 mg/kg QM	2.9 / 82.8	(44.5, 94.7)	NR	NR	
5.0 mg/kg QM	4.1 / 76.2	(28.4, 92.1)	NR	NR	
Placebo	16.7 /-		NR	NR	
Annualised number of hemin doses / % reduction vs placebo, Part C					
2.5 mg/kg Q3M	20.3 / 14.0	(-186.1, 74.1)	NR	NR	
5.0 mg/kg Q3M	17.0 / 27.7	(-121.4, 76.4)	NR	NR	
2.5 mg/kg QM	2.9 / 87.8	(44.8, 97.3)	NR	NR	
5.0 mg/kg QM	5.7 / 77.6	(11.0, 94.4)	NR	NR	
Placebo	34.3 /-		NR	NR	

*95%CI for percent reduction versus placebo. AAR: annualised attack rate; ALA: aminolevulinic acid; ALAS1: aminolevulinic acid synthase 1; CI: confidence interval; kg: kilograms; mg: milligrams; mRNA: messenger ribonucleic acid; n, N: number, sample size; NR: not reported; PBG: porphobilinogen; Q3M: every 3 months; QM: monthly; SEM: standard error of the mean. Source: Sardh et al. (2019)[13]

Phase 1/2 OLE

The ongoing phase 1/2 OLE evaluates the long-term safety and tolerability of givosiran treatment.[51,97] The safety data are presented in Section 9.7.

ALA and PBG lowering (91% and 96%, respectively) reported from the phase 1 study[13] was maintained over 24 months with continued dosing in the phase 1/2 OLE.[51] These results demonstrate a robust and sustained reduction in ALA and PBG with givosiran treatment over the long-term.

The reduction in the AAR following treatment with givosiran that was reported in the phase 1 trial was sustained in the phase 1/2 OLE, with a mean AAR reduction of 95% (mean OLE AAR: 0.8, vs run-in phase mean AAR: 16.2).[13,51] Compared with a mean AAR of 20.2 during the run-in phase of the trial, patients in the placebo group experienced a 97% mean decrease in the AAR when treated with givosiran during the OLE (mean AAR=0.6).[51] This represented a 96% mean reduction in the AAR relative to that observed while they were being treated with placebo (mean AAR during phase 1 in the placebo group was 16.7).[51]

Hemin studies

Hemin RCT

The hemin (haem arginate) RCT (N=12) evaluated patients with AIP admitted to hospital for an acute attack.[103] Over the course of follow-up, the authors found no statistically significant between-group differences in the requirement for pain medication (p=0.10), daily median pain score (8 in both hemin and placebo), or duration of hospital stay (p=0.40).[103] Significantly lower urinary ALA and PBG levels were reported in the hemin group compared with the placebo group by Day 8 (ALA: 18 µmol per 24 h vs 160 µmol per 24 h; p<0.01; PBG: 40 µmol per 24 h vs 235 µmol per 24 h; p<0.01). A significant reduction in platelet count in the hemin group by Day 7 was also reported (p<0.01 compared with baseline).[103] A summary of the outcomes reported in this study is provided in Table 23.

Table 23. Summary of outcomes from the hemin RCT

Reference	**H1A**				
Study name	Controlled Trial of Haem Arginate in Acute Hepatic Porphyria				
Size of study groups	N=12				
Study duration	Duration of hospital stay				
Type of analysis	NC				
Outcome name (unit)	**Effect Size**		**Statistical test**		**Comments**
	Value	**Range***	**Type**	**p-value**	
Pethidine equivalents	HA: 6,425	50–20,650	NR	0.10	

Reference	H1A				
(mg) during study, mean (range)	Placebo: 8,150	0–17,650			
Pain score (range 0-10), median daily	HA: 8 Placebo: 8	NR	NR	NR	
Duration of hospital stay, mean days (range)	HA: 8 Placebo: 11	3–26 2–28	NR	0.40	
Urinary ALA (µmol per 24h), median (range) by Day 8	HA: 18 Placebo: 160	7–44 47–228	NR	<0.01	
Urinary PBG (µmol per 24h), median (range) by Day 8	HA: 40 Placebo: 235	22–105 128–427	NR	<0.01	
Platelet count (x10^9/l), median (range) by Day 7	HA: 211 Placebo: no change	152-399	NR	NR	p<0.01 compared with baseline†

*95% CIs were not reported. †Comparison made within HA group only, change from baseline. ALA: aminolevulinic acid; CI: confidence interval; h: hours; HA: haem arginate (hemin); l: litre; mg: milligrams; n, N: number, sample size; NC: not clear; NR: not reported; PBG: porphobilinogen; µmol: micromole. Source: Herrick et al. (1989)[103]

9.6.2. Justification of the inclusion of outcomes in Table 18 from any analyses other than intention-to-treat

The primary analysis of the ENVISION RCT was conducted using the full analysis set (FAS) in AIP patients, which included all randomised AIP patients who received at least one dose of study drug.[119] The FAS_{AIP} and AIP intent to treat (ITT_{AIP}) populations are identical, as no patients are excluded from the analysis due to study drop out.

All patients who received at least one dose of study medication were included in all the populations analysed in the phase 1 trial of givosiran.[13] The ENVISION OLE and the phase 1/2 OLE of givosiran evaluated the long-term clinical efficacy and safety of givosiran.[51,101] The hemin RCT may have been ITT; however, the outcome of three randomised patients (25% of the study cohort) was not reported.[103]

9.7. Adverse events

9.7.1. Details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results

Details of the study selection, study methodology, and critical appraisal and results of the studies are reviewed in Section 9.2 through Section 9.6 and in Appendix 1. Safety data from the ENVISION RCT,[14] and from the phase 1[13] and phase1/2 long-term OLE[51] givosiran studies, as well as from seven hemin studies[91,103,105-107,114,116] are presented in the following sections.

9.7.2. Details of all important adverse events reported for each study

Givosiran studies

ENVISION

All reported safety analyses were performed on the safety population (i.e., patients who received at least one dose of the study drug; n=94). At least one AE was reported in 89.6% (n=43/48) of patients in the givosiran arm and in 80.4% (n=37/46) of patients in the placebo arm (Table 24).[14,119] SAEs were reported in 20.8% (n=10/48) of patients in the givosiran arm and in 8.7% (n=4/46) of patients in the placebo arm (Table 25).[14,119] Three SAEs reported in givosiran-treated patients were considered to be study drug related: one case where the patient had an abnormal liver function test, one case of transaminases increased, and one case of CKD.[14] One patient in the givosiran arm discontinued treatment due to a protocol-defined stopping rule for elevated ALT levels.[14] None of the SAEs reported in the placebo arm were considered to be study drug related.[14] There were no deaths in either treatment group over the course of the study.[14] Common AEs occurring with a ≥5% difference between treatment groups are presented in Table 26.

Table 24. ENVISION: Summary of AEs in AHP patients

AEs	Givosiran (n=48) n (% of patients)	Placebo (n=46) n (% of patients)
At least 1 AE	43 (89.6)	37 (80.4)
At least 1 SAE	10 (20.8)	4 (8.7)
At least 1 severe AE	8 (16.7)	5 (10.9)
At least 1 AE leading to discontinuation	1 (2.1)	0
Deaths	0	0

AE: adverse event; AHP: acute intermittent porphyria; CI: confidence interval; n, N: number, sample size; SAE: serious adverse event. Source: Balwani et al. (2020)[14]

Two CKD AEs were considered to be serious due to elective hospitalisation for diagnostic evaluation. Renal biopsies in both patients were consistent with underlying disease, and there were no signs of immune complex or primary glomerular renal disorders.[14]

Table 25. ENVISION: SAEs in AHP patients

SAEs	Givosiran (n=48) n (% of patients)	Placebo (n=46) n (% of patients)
Chronic kidney disease	2 (4.2)	0
Asthma	1 (2.1)	0
Device related infection	1 (2.1)	2 (4.3)
Gastroenteritis	1 (2.1)	0
Hypoglycaemia	1 (2.1)	0
Liver function test abnormal	1 (2.1)	0
Major depression	1 (2.1)	0
Pain management	1 (2.1)	0
Pyrexia	1 (2.1)	1 (2.2)
Escherichia urinary tract infection	0	1 (2.2)
Fractured sacrum	0	1 (2.2)
Sepsis	0	1 (2.2)
Septic shock	0	1 (2.2)

AHP: acute intermittent porphyria; CI: confidence interval; GFR: glomerular filtration rate; n: number of patients; AE: serious adverse event. Source: Balwani et al. (2020)[14]

Table 26. ENVISION: Common AEs (≥5% difference in treatment groups)

AEs	Givosiran (n=48)	Placebo (n=46)
AEs with higher frequency in the givosiran group, n (%) / number of events		
Injection-site reaction	8 (16.7)/15	0
Nausea	13 (27.1)/15	5 (10.9)/6
Chronic kidney disease	5 (10.4)/5	0
Decreased GFR	3 (6.3)/3	0
Rash	3 (6.3)/3	0
Alanine aminotransferase increased	4 (8.3)/6	1 (2.2)/1
Fatigue	5 (10.4)/6	2 (4.3)/2
AEs with higher frequency in the placebo group, n (%) / number of events		
Pyrexia	1 (2.1)/3	6 (13.0)/7
Hypoesthesia	0	4 (8.7)/5
Dyspepsia	0	4 (8.7)/4
Vomiting	2 (4.2)/5	5 (10.9)/5
Urinary tract infection	3 (6.3)/4	6 (13.0)/6
Back pain	1 (2.1)/1	4 (8.7)/4

AE: adverse event; CI: confidence interval; GFR: glomerular filtration rate; n: number of patients. Source: Balwani et al. (2020)[14]

Liver disorders

ALT elevation (>3 times the upper limit of normal [ULN]) was reported in seven of the 48 patients taking givosiran (14.6%) and in one of the 46 patients taking placebo (2.2%).[14] While there was considerable variability in ALT levels, most ALT elevations were mild to moderate in severity, occurred approximately 3 to 5 months after givosiran started, and resolved or stabilised by the end of the study (Figure 24).[101] Dosing was continued in all but two patients who met the pre-specified protocol interruption and stopping rules. One patient discontinued givosiran permanently due to a protocol-defined stopping rule of ALT>8xULN. Another patient had their dose interrupted due to a protocol-specified rule (Alanine aminotransferase [ALT] increased 5.4xULN and aspartate transaminase [AST] increased 3.6xULN). This patient had received four

doses of givosiran. After their liver function tests returned to normal, the patient then resumed givosiran at a 1.25 mg/kg dose without recurrence of the event. The remaining five of seven patients with ALT elevations had resolution with ongoing givosiran dosing by Month 6 (Figure 24). It should be noted that an imbalance in liver transaminase elevations was observed at baseline, with abnormally elevated ALT concentrations in 20.8% of patients in the givosiran group and 4.3% in the placebo arm.[119]

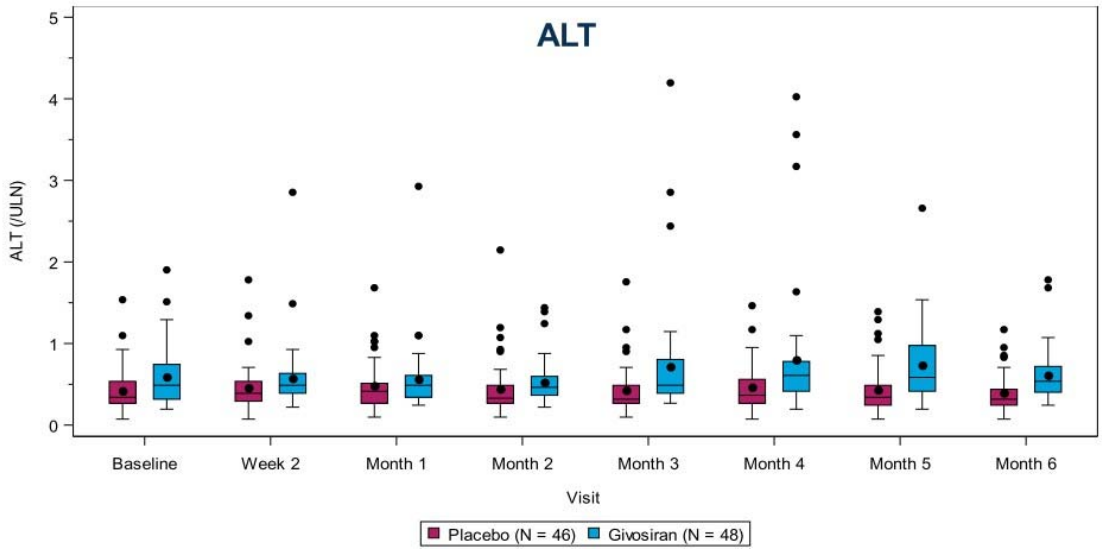


Figure 24. ENVISION: impact on givosiran on ALT
ALT: alanine aminotransferase; ULN: upper limit of normal. Source: Gouya et al. (2019)[101]

Renal disorders

Renal AEs were reported in 7/48 (15%) givosiran patients and in 2/46 (4.3%) of placebo patients.[14] These were generally small increases in serum creatinine (median change 0.07 mg/dL at Month 3) and decreases in estimated glomerular filtration rate (eGFR) (Figure 25) and included five AEs of CKD among givosiran patients.[14] Four of the five patients had a pre-existing medical history of CKD and the AEs were reported as a worsening of chronic renal failure.[119] Most of the renal AEs were mild to moderate in severity and resolved or stabilised by Month 6 without treatment interruption. The two cases of SAEs of CKD associated with elective hospitalisation for diagnostic evaluation have been described previously in this section.

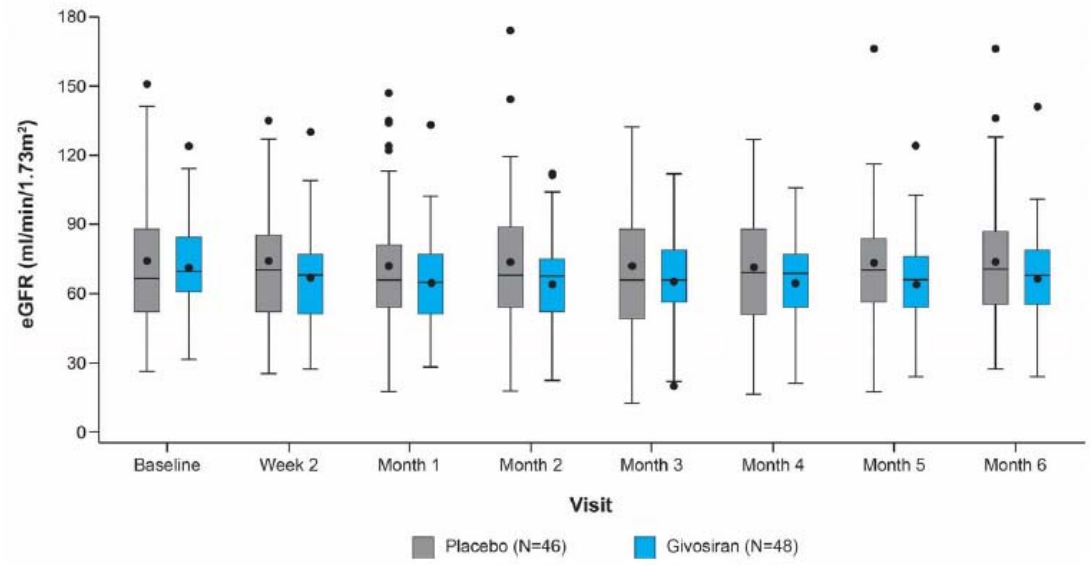


Figure 25. ENVISION: impact of givosiran on eGFR
eGFR: estimated glomerular filtration rate; ULN: upper limit of normal. Source: Balwani et al. (2020)[14]

Injection-site reactions

In the DB period of ENVISION, 20 injection-site reactions (ISRs) were reported in 12 givosiran patients (16.7%). All ISRs were mild or moderate in severity; none were serious or led to treatment interruption or discontinuation.[55]

Gastrointestinal symptoms

Gastrointestinal symptoms are well-described in AHP and are associated with the autonomic dysfunction that occurs with this disease. [55] Nausea was reported in 13 patients taking givosiran (27.1%) and in five patients taking placebo (10.9%).[14,55,119] No nausea SAEs were reported, and most were mild in severity.[55] One severe AE of nausea in a patient that was treated with givosiran was assessed as being unlikely due to the study drug.[55] Vomiting was reported in two (4.2%) patients taking givosiran and in five (10.9%) patients taking placebo.[14,55,119] Most events were mild or moderate in severity. [55] A severe AE of vomiting occurred in the same givosiran patient who had experienced severe nausea. This event was also assessed as being unlikely due to the study drug and resolved within 1 day of onset with no change in dosing. No events of vomiting led to study drug interruption or discontinuation.[55]

Other AEs

All reported AEs of rash (3 patients in the givosiran group; 6.3%) were mild in severity. [55] Two of the AEs were considered to be possibly related to the study drug. [55] All rashes resolved without change in dose to the study drug.[55]

Pyrexia was reported in one givosiran patient (2.1%) and in six patients taking placebo (13.0%).[14,55,119] The givosiran patient experienced three events, all of which were mild or moderate in severity.[14,55,119]

Fatigue was reported in five patients taking givosiran (10.4%) and in two patients taking placebo (4.3%).[14,55,119] Two AEs in two givosiran-treated patients were considered possibly related to study drug. All AEs of fatigue were mild in severity.[55] Acute Pancreatitis was reported in one givosiran-treated patient (2.1%) and in three placebo-treated patients (6.5%).[55] No cases of anaphylactic reaction or severe hypersensitivity that were considered related to givosiran were reported in the placebo-controlled DB period.[55] The safety analysis was consistent across the subgroups of AHP that were tested.[55]

ENVISION OLE

Interim safety data from the ENVISION OLE indicate that the long-term safety profile of givosiran is consistent with that observed during the randomised trial. [14,55,119] The 18-month ENVISION OLE-data encompasses both the 2.5 and 1.25 mg/kg givosiran once monthly doses that were assessed during the

OLE period, and report no new treatment related SAEs (i.e., no CKD, renal or hepatic AEs, pancreatitis, or anaphylaxis) or new AEs leading to discontinuation, and no deaths (Table 27).[119] This data includes AEs reported during the DB-period and the OLE-period.

Table 27. ENVISION OLE: Overall summary of AEs

	Placebo/Givosiran (N=46, PY=49.7)	Givosiran/Givosiran (N=48, PY=75.4)	All Givosiran (N=94, PY=125.2)
At least 1 AE	43 (93.5)	47 (97.9)	90 (95.7)
At least 1 study drug related AE	27 (58.7)	34 (70.8)	61 (64.9)
At least 1 SAE	9 (19.6)	15 (31.3)	24 (25.5)
At least 1 study drug related SAE	1 (2.2)	2 (4.2)	3 (3.2)
At least 1 severe AE	12 (26.1)	12 (25.0)	24 (25.5)
At least 1 study drug related severe AE	4 (8.7)	6 (12.5)	10 (10.6)
At least 1 AE leading to discontinuation	1 (2.2)	1 (2.1)	2 (2.1)
Death	0	0	0

AE: adverse event; N: number of patients; OLE: open-label extension; PY: person-years; SAE: serious adverse event. Source: Alnylam Pharmaceuticals (data on file, 2020)[119]

During the 6-month DB period and the OLE period (10 January 2020 data cut; 18 months of follow-up and 12 months of OLE follow-up), hepatic AEs mapping to the Drug related hepatic disorders standardised MedDRA query (SMQ) were reported in 16 patients (17%); the majority of hepatic AEs were laboratory abnormalities within the investigations system organ class (SOC). All AEs were mild or moderate in severity. One patient with an SAE of liver function test (LFT) abnormal (ALT 9.9×ULN) discontinued treatment due to a prespecified protocol stopping rule and withdrew from the study. Two other patients have had transient dose interruptions due to elevations of LFTs. Overall, 10 patients (10.6%) had ALT elevations >3×ULN; including 7 patients in the givosiran/givosiran group during the DB period and 3 patients in the placebo/givosiran group. The elevations primarily occurred within the first 3–5 months of givosiran treatment and were transient in nature.

Renal AEs mapping to the CKD SMQ were reported in 16 patients (17%) with 10 patients (10.6%) having AEs within the Investigations SOC; the majority of which were characterised by increases in serum creatinine and/or decreases in estimated glomerular filtration rate (eGFR). Most of the AEs were mild or moderate in severity and resolved without treatment or treatment interruption. None led to discontinuation of study treatment. Two patients with medical histories of pre-existing CKD and hypertension had SAEs of CKD and were admitted for diagnostic evaluation that included kidney biopsies during the DB period. The results of the kidney biopsies were consistent with their underlying AHP and comorbidities. On laboratory analysis, changes in creatinine and eGFR have been noted that were mostly transient and often reversible. These changes tended to occur at the onset of treatment and stabilise over time.[119]

Phase 1 trial

The safety and tolerability data for patients treated with any dose of givosiran versus those treated with placebo in the phase 1 trial are presented in Table 28.

Table 28. Phase 1: AEs and SAEs

AE	Givosiran (n=33)*† n (% of patients)	Placebo (n=10)* n (% of patients)
Any AE	30 (91)	10 (100)
Any SAE	6 (18)	0
Any severe AE	4 (12)	2 (20)
Most common AE (occurring in >2 patients)		
Nasopharyngitis	9 (27)	2 (20)
Abdominal pain	8 (24)	1 (10)
Nausea	6 (18)	3 (30)
Diarrhoea	4 (12)	1 (10)
Back pain	3 (9)	2 (20)
Fatigue	3 (9)	0

AE	Givosiran (n=33)*† n (% of patients)	Placebo (n=10)* n (% of patients)
Headache	3 (9)	2 (20)
Injection-site reaction	3 (9)	0
Oropharyngeal pain	3 (9)	0
Rash	3 (9)	0
Vomiting	3 (9)	3 (30)

*Parts A, B, and C combined. †Two patients in Part A received two injections (either one placebo and one givosiran injection or two givosiran injections at different doses). Three patients were treated in both Part A and Part B. AE: adverse event; n, N: number, sample size; SAE: serious adverse event. Source: Sardh et al. (2019)[13]

The SAEs that occurred in 6/33 patients (18%) in the givosiran group were unrelated to the study drug and included: abdominal pain (two patients) and spontaneous abortion, influenza A infection, functional GI disorder (opioid bowel dysfunction), staphylococcal bacteraemia, auditory hallucination, and haemorrhagic pancreatitis (one patient each).[13]

One givosiran-treated patient in the Phase 1 trial experienced a severe AE (elbow bursitis) while in follow-up more than 1 year after completing treatment in Part B.[13] This SAE was considered not related to study treatment. Additional treatment for the bursitis was required and the event was not resolved.[97]

Three givosiran-treated patients in Part C of the Phase 1 trial experienced severe AEs: influenza A infection and pain in an extremity due to a fall; functional GI disorder (opioid bowel dysfunction); staphylococcal bacteraemia; auditory hallucination; and haemorrhagic pancreatitis. Two placebo-treated patients experienced severe AEs in the form of viral gastroenteritis and diarrhoea.[13] The case of haemorrhagic pancreatitis occurred in a patient with a complex medical history and was subsequently fatal.[13] This event was assessed as unlikely to be related to the study drug due to the presence of gallbladder sludge (previously reported) and the lack of a clear temporal relationship of the event to the study drug.[13]

Phase 1/2 OLE

Preliminary data from the phase 1/2 OLE study have reported long-term safety results in patients treated with givosiran (Table 29). All 16 patients (100%) in the OLE reported at least one AE, and ten SAEs were reported in 6/16 patients (37.5%).[51,122] Only one SAE, an anaphylactic reaction, was considered to be study drug related, and occurred in one patient after the third dose of givosiran. This patient had previously received two doses (5 mg/kg Q3M) in the phase 1 study and had a history of asthma and atopy. The event resolved with medical management, and the patient permanently discontinued from the study.[51,122]

Table 29. Phase 1/2 OLE: AEs and SAEs

AE	Givosiran (n=16) n (%)
Any AE	16 (100)
Any SAE	6 (37.5)
Deep vein thrombosis	1 (6.3)
Anaphylaxis	1 (6.3)
Synovitis	1 (6.3)
Abdominal pain	1 (6.3)
Pyrexia	2 (12.6)
Infection	2 (12.6)
Change in mental status	1 (6.3)
Bacterial sinusitis	1 (6.3)

AE: adverse event; OLE: open-label extension; SAE: serious adverse event. Source: Bonkovsky et al. (2019)[51]; Stein et al. (2020)[122]

AEs occurring in more than three patients included abdominal pain, fatigue, nausea, injection-site erythema, nausea, headache, myalgia, nasopharyngitis, diarrhoea, injection-site pruritus, and an increased international normalised ratio.[51] Seven of the 16 patients (44%) had ISRs, most commonly erythema, and all were considered mild to moderate.[51] No clinically significant laboratory changes, including liver function tests, were reported.[51]

Hemin studies

Data on AEs associated with hemin treatment in AHP patients are limited, and it is challenging to differentiate the AE profiles associated with acute versus prophylactic treatment with hemin. As discussed

below, key safety concerns associated with hemin therapy include phlebitis, venous access, raised serum ferritin levels and possible prophylactic hemin dependency.

The assessment of AEs as a primary outcome was reported in one prospective hemin study, in which hemin was made available to 130 patients for up 8 months, both as prophylaxis and for the treatment of acute attacks. Among the patients who received hemin for prophylaxis only (n=19), three AEs were reported in three patients, and one SAE was reported in one patient.[105] Specific AE and SAE data on 21 patients who received hemin for both acute attacks and as prophylaxis were not provided, so the overall rate of AEs and SAEs associated with hemin prophylaxis and frequent hemin administration in this study is unclear. Among those receiving hemin for acute treatment only (n=90), AEs were reported in 40 patients (44%) and SAEs were reported in 18 patients (20%).[105] A summary of reported AEs is provided in Table 30. Due to the reliance on retrospective data for the diagnosis of the participants and the lack of diagnostic laboratory values for almost half the patients in the study, the diagnosis of AHP could not be confirmed in all cases.[105] Additionally, this study was not designed with any specific outcome measures, exclusion criteria, or follow-up requirements, and acute attacks were not confirmed in the majority of patients.[105]

Table 30. AEs reported in prospective hemin study

AE	Total AEs n (%)	Possibly or probably related to treatment n (%)
Headache	18 (9.2)	5 (2.6)
Nausea	15 (7.7)	8 (4.1)
Pyrexia	9 (4.6)	6 (3.1)
Phlebitis	7 (3.6)	6 (3.1)
Vomiting	7 (3.6)	4 (2.1)
Catheter-related complication	7 (3.6)	3 (1.5)
Pain	4 (2.1)	3 (1.5)
Convulsion	4 (2.1)	0
Rash	3 (1.5)	3 (1.5)
Pharyngitis	3 (1.5)	0
Diarrhoea	3 (1.5)	3 (1.5)
Adverse drug reaction	3 (1.5)	3 (1.5)
Cellulitis	3 (1.5)	2 (1.0)
Dizziness	3 (1.5)	1 (0.5)
All others*	106 (54)	24 (12)
TOTAL	195 (100)	71 (36.4)†

*Number of occurrences <3. †The total number (and percentage) of reported AEs attributed to hemin was reported in the paper as 48 (25%). However, the addition of all the reported AEs in Table 3 of this study brings the total to 71 (36.4%). AE: adverse event; n, N: number, sample size. Source: Anderson et al. (2006)[105]

An additional nine hemin studies have reported AEs.[19,20,91,103,106,107,111,114,116] The most consistently reported AE in these studies was phlebitis, occurring in 4%–75% of patients taking hemin (Table 31).

Table 31. Occurrence of phlebitis in hemin studies

Study	Duration of follow-up	Patients with phlebitis n/N (%)
Herrick et al. (1989)[103]	Hospitalisation	5/12 (42)
Anderson et al. (2006)[105]	Treatment of acute attack and prophylaxis up to 8 months	7 events in 130 patients
Mustajoki and Nordmann (1993)[106]	Hospitalisation	1/24 (4)
Bissell (1988)[107]	NR	1/8 (8)
Neeleman et al. (2018)[19]	3–38 years	4/11 (36)
Marsden (2015)[91]	1–150 months	3/22 (14)
Hift et al. (2005)[111]	Hospitalisation	14/17 administrations (17.7%)
Nordmann et al. (1995)[116]	Hospitalisation	“75% of cases”
Mustajoki et al. (1986)[114]	11 days	1/14 (14)

n, N: number, sample size; NR: not reported.

Reports of AEs related to hemin prophylaxis include a study by Marsden et al. (2015), which reports loss of venous access (8/22 patients [36.4%]); infection (5/22 patients [22.7%]), and iron overload confirmed by MRI (1/22 patients [4.5%]).[91] This study also reported the median serum ferritin level in 19/22 patients to be 208 µg/L (reference range: 20–200), but the range of patient values was very wide (21-3165), indicating that a large proportion of patients had significantly elevated levels.[91] A statistically significant correlation between serum ferritin and the number of hemin doses administered was established (correlation coefficient [r]=0.884; p<0.001).[91] The authors also reported that stopping or reducing the frequency of

hemin was difficult and was associated with an exacerbation of symptoms in some patients, indicating a 'dependency' to hemin.[91]

In a study by Neeleman et al. (2018), all 11 patients with recurrent AIP were on hemin prophylaxis for a median of 51 months (range: 14–171 months).[19] Nine of the 11 patients (82%) were assessed as having elevated serum ferritin and possible iron overload.[19] Attempts to wean patients off hemin prophylaxis resulted in acute attacks being triggered in nine of the 11 patients (82%).[19]

Schmitt et al. (2018) reported serum ferritin levels above the reference range in 85% of 27 patients that received frequent hemin administration, and confirmed iron overload in 11 of 12 patients that were assessed by MRI.[20] The remaining five hemin studies, all of which related to the treatment of acute attacks, did not report AEs.[108-110,113,115]

9.7.3. Brief overview of the safety of the technology in relation to the scope

The safety profile of givosiran in patients with AHP has been well characterised in placebo-controlled trials[13,14] and in ongoing long-term extension studies.[51,101,119] The cumulative safety data to date show that givosiran is generally well-tolerated and has a safety profile that is clinically manageable.

In the ENVISION trial, the frequency of AEs and SAEs were comparable between the givosiran and placebo arms.[14] The majority of ALT elevations observed in patients taking givosiran were mild to moderate, occurred approximately 3–5 months after givosiran was started, and resolved or stabilised by the 6th treatment month.[14] Any observed increases in serum creatinine among patients taking givosiran were generally small (median change of 0.07 mg/dL at Month 3) and resolved or stabilised by Month 6. Any observed deceases in eGFR also resolved or stabilised by the final assessment at 6 months. Twelve-month data from the OLE phase of ENVISION indicate that the long-term safety profile of givosiran is consistent with that seen in the randomised trial phase.[101,119]

In the phase 1 trial of givosiran, SAEs were not considered to be related to the study drug.[13] One death in a patient with a complex medical history was reported in the givosiran group, and the cause of death was assessed as being unrelated to treatment. The safety profile of givosiran reported in the OLE to date is consistent with observations made during ENVISION and the phase 1 trials.

Given the clinical benefit of givosiran in terms of attacks averted, symptom improvement, and improvements in physical functioning and QoL (See Section 10.2), the benefit to risk profile of givosiran is favourable.

9.8. Evidence synthesis and meta-analysis

9.8.1. Description of the technique used for evidence synthesis and/or meta-analysis

No meta-analyses or indirect comparisons were feasible due to the lack of comparable RCTs with adequate data for any comparator to givosiran.

9.8.2. Rationale for why evidence synthesis is not considered appropriate

As described in Section 9.3.1, only one phase 3 RCT on givosiran was included in the submission and no relevant RCTs for comparators that could be used in an indirect treatment comparison were identified.

9.9. Interpretation of clinical evidence

9.9.1. Principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology, including the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated

Givosiran is an effective therapy with a favourable safety profile, and has demonstrated the ability to reduce the frequency of AHP attacks and to reduce daily pain and improve patient QoL:

- Givosiran is a disease-modifying therapy that directly addresses the underlying disease process by targeting ALAS1, resulting in rapid, substantial, and sustained reductions in the toxic porphyrin precursors ALA and PBG.[14]
- The immediate and sustained reduction in ALA and PBG levels, and the resulting concurrent and significant reduction in attack rates, validates the observed efficacy of givosiran in relation to disease biomarkers and the underlying pathology of AHP.[14]
- Givosiran specifically targets the accumulation of ALA and PBG, leading to a 74% mean reduction in attacks requiring hospitalisation, urgent care, and IV hemin. In the pivotal ENVISION trial, 50% of patients who were treated with givosiran were attack free with a significant reduction in chronic symptoms after 6 months of givosiran treatment.[14]
- Givosiran significantly reduces chronic and acute pain associated with AHP, and leads to reduced requirement for both opioid and non-opioid analgesics.[14]
- Givosiran therapy improves QoL, particularly the dimensions of physical role, bodily pain, and social functioning, as measured by the SF-12 instrument.[14]
- The majority of givosiran-treated patients report their condition to be improved or very much improved after 6 months of treatment, as measured by the PGIC.[14]
- Almost three-quarters of patients taking givosiran reported overall satisfaction with their treatment, as measured by the PPEQ.[14]
- Patients who are treated with givosiran miss fewer days from work, reflecting an improved ability to maintain normal daily functioning while on treatment.[119]

Givosiran met the primary endpoint in the ENVISION trial and demonstrated a significant reduction in the frequency of acute attacks versus placebo.[14] Reductions in all three components of the composite outcome were observed, with the mean composite AAR among patients taking givosiran being reduced by 74% relative to that of patients taking placebo ($p=6.04x10^{-9}$).[14] The phase 1 results supported the reduction in attack frequency in patients treated with givosiran relative to those in the placebo group. Preliminary data from the ENVISION OLE and the phase 1/2 OLE demonstrate consistent effectiveness in controlling the frequency of AHP attacks over time.[51,101]

Givosiran has a well-characterised safety profile in patients with AHP, and is generally well-tolerated by patients over the long term.[51,101] Most AEs seen in ENVISION were of mild-to-moderate severity and/or resolved or stabilised within 6 months of therapy.[14] The long-term safety of givosiran is being evaluated in the ENVISION OLE and the phase 1/2 OLE. [51,101] Eighteen-month data from the ENVISION OLE indicated that the longer-term safety profile of givosiran is consistent with that observed in the RCT.[101,119] Recent data from the phase 1/2 OLE show that most observed SAEs are not attributable to the study medication, and that there are no clinically important laboratory changes, including liver function tests.[51] While ISRs do occur, they are most commonly erythema and are mild to moderate in severity.[51,101,119]

9.9.2. Summary of the strengths and limitations of the clinical-evidence base of the technology.

The ENVISION trial is the largest global, randomised, DB trial evaluating the safety and efficacy of givosiran in patients with AHP to date, and the only trial to assess the prevention of recurrent AHP attacks. Although longer durations of treatment may be required to capture the impact of givosiran on some symptoms such as chronic pain,[35] a 6-month trial duration was sufficiently long to capture the highly significant treatment effect in the primary outcome (AAR), the positive safety profile, and the substantially relevant impact on the patient's experience of daily worst pain, QoL, and healthcare resource use. The

results of the phase 1/2 OLE study and the ENVISION OLE confirm the consistent and maintained efficacy and safety of givosiran over time.

The studies of givosiran did not include patients with ADP, and so the full spectrum of AHP is not captured in the givosiran studies. As AIP is the most common of the AHPs and is also the most likely to result in acute attacks, it is also most frequently encountered in clinical practice, which is reflected in the ENVISION study population. ADP is the rarest of all AHPs, and inclusion of these patients in the givosiran studies would have been unlikely given that fewer than 10 documented cases of ADP have been reported in the literature, worldwide.[6]

9.9.3. Brief statement on the relevance of the evidence base to the scope, with focus on the claimed patient- and specialised service-benefits described in the scope

The evidence base for givosiran is robust, including well-designed RCTs, whereas the evidence base for BSC is weaker and based on uncontrolled studies. The evidence base comprised patients who participated in the phase 1/2 RCT[13] and its ongoing OLE,[51] and the phase 3 ENVISION RCT[14] and its ongoing OLE.[101,102]

Population

The pivotal ENVISION trial was directly relevant to the patient population in the UK because most patients in the trial were from Western Europe, which is representative of the UK population. [14]

Outcomes

The outcomes listed in the NICE scope are closely aligned with the outcomes of the ENVISION trial.[14,38]

Clinical effectiveness

ENVISION and its OLE demonstrate very strong evidence of clinical efficacy of givosiran in patients with AHP, [14,101,102] and these benefits are likely to also be achieved in real-world clinical practice in the UK as the recommended dosage is based on the dosage used in the ENVISION trial.

Impact of givosiran beyond direct health benefits

As discussed in detail in Section 7, the use of givosiran is anticipated to result in significant societal economic benefits due to increased productivity and independence of patients and correspondingly reduced burden on caregivers.

9.9.4. Factors that may influence the external validity of study results to patients in routine clinical practice

Both trials enrolled patients internationally and ENVISION enrolled patients from diverse geographic regions. The evidence base included:

- Patients with a range of disease duration
- The three most common types of AHP (i.e., AIP, HCP, VP)
- Patients with and without experience with prior therapies (i.e., opiates, hemin)
- Patients with widely differing attack rates, which was a stratification factor in the randomisation of ENVISION patients (with a minimum of 2 attacks in 6 months prior to enrolment)
- Patients with and without chronic symptoms between attacks

Thus, the ENVISION study captured the heterogeneity of the AHP patient population encountered in clinical practice who would be eligible for givosiran, namely adults and young people aged 12 years or older with recurrent severe AHP attacks, as consistent with the definition by NAPS.

9.9.5. Criteria that would be used in clinical practice to select patients for whom the technology would be suitable

Givosiran is suitable for adults and young people aged 12 years or older with recurrent severe AHP attacks.

10. Measurement and valuation of health effects

- AHP is characterised by severely painful attacks and/or debilitating chronic manifestations between attacks that negatively impact daily functioning and QoL.
- QoL is not assumed to be constant over time and may deteriorate without treatment.
- Several QoL measures in the ENVISION trial showed clinically important and statistically significant improvements in patients treated with givosiran relative to placebo, including measures of daily worst pain (NRS), the PCS of the SF-12, and the PGIC and PPEQ. Consistent trends towards relative improvement with givosiran were also seen with the EQ-5D VAS and Index, the SF-12 MCS, and daily worst fatigue (NRS).

10.1. Patient experience

10.1.1. Aspects of the condition that most affect patients' quality of life

A comprehensive discussion of the effects of AHP on patient's QoL can be found in Section 7.1. AHP is characterised by debilitating acute attacks and ongoing chronic symptoms.[32] The cardinal symptom of AHP is pain, which is often described by patients as unbearable and unrelenting,[32] and which presents in both the acute and chronic phases of the disease.[11] The dominating experience of pain in AHP limits the ability of most patients to function normally and contributes to the reported high rates of anxiety and depression,[11,19] in some cases even leading to suicide.[19,28]

GI effects experienced during an attack include nausea, vomiting, diarrhoea, and constipation. Chronic nausea between attacks may also result in suboptimal nutrition in AHP patients.[11,19] Although AHP patients may have decreased appetite because of chronic nausea, they may feel compelled to eat, as fasting is a trigger for acute attacks.[32] Nausea appears to be more than twice as frequent in AHP patients suffering from recurrent attacks compared to other symptomatic AHP patients.[19]

AHP patients may experience disorientation and psychiatric symptoms during attacks.[11,19] Disorientation and trouble concentrating has also been reported as a frequently occurring chronic symptom, affecting patients' ability to perform simple cognitive tasks such as remembering a list of items, following conversations, and reading through a page in a book.[26,32]

Feelings of malaise and fatigue are common acute and chronic symptoms and affect patients' energy levels and their ability to carry out activities of daily living.[11,19]

Patients who experience repeated attacks may develop chronic neurological impairment, (e.g., paraesthesia, motor weakness, paralysis, urine incontinence, advanced neuropathy)[19] which contributes to the experience of pain, and also seriously limits the ability to function normally and to perform basic activities such as getting out of bed and walking to the bathroom.[26,32] As a result, assistance from caregivers is often required.

The majority of patients with recurrent AHP attacks experience most aspects of these major categories of symptoms, which impacts their ability to support themselves and function socially, leading to feelings of isolation, anxiety, depression, helplessness, and strained relationships with friends and family.[26,32]

10.1.2. How a patient's health-related QoL is likely to change over the course of the condition

Study results have shown that if left untreated, the debilitated condition of the majority of patients with recurrent AHP will not improve.[119] Testimonials from AHP patients also highlight their anxiety concerning hemin administration:

'*The only thing is that when I do go in to hospital for treatment for the porphyria, the haem arginate needs to go in through the veins intravenously, and because it's very thick, I ended up, last time I ended up getting a small blood clot in the forearm*.'[32]

'*So, the last dose of haem I had, my line was getting blocked basically, and…I told them that they should flush it after the haem had gone through and "no, no, no, it's fine, it'll be fine". So, I don't think they flushed it after the second dose of haem. So, they tried to give the third dose the day after, and it was getting blocked and I think they dropped the bag and it split. And then I think they gave me the fourth lot the day after that obviously and they didn't flush that properly. And so, I ended up with an enormous swelling on my arm, basically where the haem had gone in to my tissue*.' [32]

Patients are hyper vigilant over the course of their condition, as anything that causes physical and emotional strain, however minimal, could trigger an AHP attack.[26,32] Patients may try and reduce the frequency of their attacks through strict lifestyle changes aimed at reducing stress and removing potential triggers, including taking hormone inhibitors, not staying out too late and ensuring enough rest is taken, minimising travel and driving, restricting protein intake, increasing carbohydrate intake, staying hydrated, taking medication safe lists with them and/or wearing medical alert bracelets, taking pain medication when experiencing prodromal symptoms, and reducing working hours and workload. [26,32] In spite of taking such measures, most patients find that attacks cannot be fully prevented and patients and caregivers feel the impact of AHP every day.[26,32] For patients who have recurrent attacks, the physical and emotional impact is cumulative, as they often do not have enough time to fully recover between attacks.[32]

10.2. Health-related QoL data derived from clinical trials

Table 32 summarises the health-related QoL data derived from the ENVISION RCT, which was described in detail in Section 9.

Table 32. Health-related QoL data derived from the ENVISION clinical trial

Study name NCT number Author	Instrument	Method of valuation	Measurement points	Appropriate for CEA	Results with CI
ENVISION **NCT03338816** **Balwani et al. (2020)[14]**	Daily worst pain	BPI-SF NRS	Daily, up to 6 months	No	AUC change from baseline (AIP): Givosiran: -12.876 Placebo: -0.196 Treatment difference: -12.680 (-25.526, 0.166) P=0.0530 (ANCOVA)†; P=0.0455 (Wilcoxon)
	Daily worst fatigue	BFI-SF NRS	Daily, up to 6 months	No	AUC change from baseline (AIP): Givosiran: -11.148 Placebo: -4.208 Treatment difference: -6.940 (-19.837, 5.957) P=0.2876
	Daily worst nausea	NRS	Daily, up to 6 months	No	AUC change from baseline (AIP): Givosiran: 1.481 Placebo: -4.011 Treatment difference: 5.492 (-4.000, 14.984) P=0.2532
	SF-12 PCS and MCS		Baseline 3 months 6 months	Yes*	LS Mean change in in PCS at 6 months (AIP): Givosiran: 5.369 Placebo: 1.431 Treatment difference: 3.939 (0.592, 7.285) P=0.0216 LS Mean change in MCS at 6 months (AIP): Givosiran: 3.7 Placebo: 1.3
	EQ-5D-5L	VAS	Baseline 6 months	Yes*	LS mean change in VAS at 6 months (AIP): Givosiran: 6.8

Study name NCT number Author	Instrument	Method of valuation	Measurement points	Appropriate for CEA	Results with CI
		MAUI based on 5 HRQoL dimensions			Placebo: 2.8 Treatment difference: 4.0 (-3.3, 11.4) LS mean change in Index at 6 months (AIP): Givosiran: 0.0212 Placebo: -0.0076 Treatment difference: 0.0286 (-0.0303, 0.0876)
	PGIC	Global assessment of perceived overall health status	6 months	No	Patients reporting greater improvement in overall health status at 6 months (%): Givosiran: 89.0 Placebo: 37.0
	PPEQ	Series of questions that assess treatment experience	6 months	No	Patients responding “Much better” or “Always” at 6 months (%); Givosiran/Placebo Travelling>1 day: 35.1/13.2 Participating in social activities: 35.1/7.9 Planning future events: 35.1/10.5 Doing household chores: 35.1/5.3 Exercising moderately: 32.4/5.3 Convenience of current porphyria treatment: 72.2/8.1 Overall satisfaction with porphyria treatment: 72.2/13.5 Study drug helping more normal life: 41.7/5.4

Note: Consistency with the reference case is included in the scope. *While both the SF-12 and the EQ-5D-5L index may be used to derive utility values, their estimates obtained from the ENVISION trial could not be applied to the CEA for givosiran because these instruments were administered at specific time points (Baseline, 3 months, 6 months) and not at times where they could capture the patient experience that was relevant in the model (i.e., during acute attack, during chronic symptoms). †Pain data not normally distributed; ANCOVA method not valid. Post-hoc analysis using non-parametric stratified Wilcoxon method. AIP: acute intermittent porphyria; ANCOVA: analysis of covariance; AUC: area under the curve; BFI-SF: Brief Fatigue Inventory-Short Form; BPI-SF: Brief Pain Inventory-Short Form; CEA: cost-effectiveness analysis; CI: confidence interval; EQ-5D-5L: EuroQol 5-Dimension 5-Level Questionnaire; HRQoL: health-related quality of life; MAUI: multi-attribute utility instrument: MCS: Mental Component Summary; NRS: numeric rating scale; PCS: Physical Component Summary; PGIC: Patient Global Impression of Change Questionnaire; PPEQ: Porphyria Patient Experience Questionnaire; SF-12: 12-Item Short Form Health Survey.

10.3. Mapping

The acute attack disutility and mean attack duration considered in the model were obtained from observations in the EXPLORE study.[11] In EXPLORE, EQ-5D-5L data were collected at scheduled 6-month intervals. The EQ-5D-5L data were mapped to EQ-5D-3L to derive utility values, using UK tariffs, according to the mapping function developed by van Hout et al. 2012.[123,124]

10.4. Health-related QoL studies

As with the search strategies to identify clinical and economic data, the SLR was designed to identify relevant QoL evidence in the published literature. The search strategy is provided in Appendix 1. The inclusion and exclusion criteria are shown in Table 10 of Section 9.2. The QoL results of the SLR are reported in Table 32.

The search results for QoL evidence included one givosiran study,[14] two hemin studies,[91,103] and 18 non-interventional studies. Among the non-interventional studies included in the SLR, 13 studies quantified the frequency of symptoms affecting QoL (e.g., pain, fatigue, nausea)[11,19,29,73,74,111,125-131] and two studies described patient QoL qualitatively.[23,29,132] Five non-interventional studies described the measurement of QoL in AHP.[11,85-87,133,134]

10.4.1. Details of studies in which health-related QoL is measured

The QoL data from the ENVISION trial have been described in detail in Table 32 and in Section 9.6.1.

Among the two hemin studies and five non-interventional studies that measured QoL, only the EXPLORE study reported utility values that were compatible with the economic model. The two hemin studies[91,103] and

the remaining four non-interventional studies[86,87,133,134] were therefore excluded from the submission and their details are provided in Appendix 2. The details of the QoL assessments from the EXPLORE study are provided below in Table 33.

Table 33. Health-related QoL data from the EXPLORE study

Study name NCT number Authors	Instrument	Method of valuation	Measurement points	Consistency with reference case	Appropriate for CEA	Results
EXPLORE NCT02240784 **Gouya et al. (2020)[11]** **Alnylam (data on file)[22,135]**	EQ-5D-5L	MAUI based on 5 HRQoL dimensions	Baseline 6 months 12 months During attack	Yes	Yes	Mean (SD) <u>Baseline:</u> Index: 0.78 (0.1537) VAS: 66.1 (23.2) <u>6 months:</u> Index: 0.80 (0.1389) VAS: 70.0 (19.0) <u>12 months:</u> Index: 0.77 (0.1605) VAS: 70.2 (20.8) Index while not on attack: 0.6259* Index while on attack: 0.4083*
	Pain	11-point NRS	Baseline Peak across all attacks	Yes	No	Mean values Baseline: 3.7 Peak across all attacks: 6.4

*These estimates were obtained from patients who were not on hemin prophylaxis. CEA: cost-effectiveness analysis; EQ-5D-5L: EuroQol 5-Dimension 5-Level Questionnaire; HRQoL: health-related quality of life; MAUI: multi-attribute utility instrument; NRS: numeric rating scale; SD: standard deviation; VAS: visual analogue scale

10.4.2. Key differences between the values derived from the literature search and those reported in or mapped from the clinical trials

Please see Section 10.3.

10.5. Adverse events

10.5.1. How adverse events impact on health-related QoL.

Although it is expected that several AEs may have a negative impact on patients' QoL, the included published studies provided no data specifically on the relationship between AEs and QoL in patients with AHP. No explicit impact of AEs on QoL was modelled in order to avoid double-counting. Therefore, the potential impact of treatment-specific AEs is implicit within the set of utilities derived from each treatment arm.

10.6. Quality-of-life data used in cost-effectiveness analysis

10.6.1. Summary of the values chosen for the cost-effectiveness analysis

The gender- and age-specific utility of the general population is used as a base to subtract the utility decrements of AHP, considering both the temporary disutility associated with acute attacks and the long-term utility decrement associated with presence of chronic symptoms/comorbidities and late complications. This approach allows AHP related disutilities to be considered independently of the decreasing utility of the aging cohort. The utility in the general population, by age and gender, is estimated using the equation reported in the study by Ara and Brazier 2011:[136]

EQ-5D = 0.9508566 + 0.0212126*male - 0.0002587*age - 0.0000332*age^2

Based on a framework proposed by Neeleman et al. (2018)[19] and on data of attack frequency and related QoL from the ENVISION trial, the economic model builds on four distinct alive health states of increasing severity during which patients could either experience chronic symptoms only (i.e., asymptomatic) or acute attacks as well as chronic symptoms (i.e., symptomatic, recurrent, severe).

The acute attack disutility and mean attack duration considered in the model were obtained from observations in the EXPLORE study.[11,85] EXPLORE was determined to be the optimal source for estimating disutility per attack using EQ-5D because [redacted] of the EQ-5D questionnaires completed in EXPLORE were administered during an attack (Alnylam, data on file). In contrast, [redacted] of the EQ-5D assessments in the ENVISION trial were administered during an attack (Alnylam, data on file). Therefore, the data are insufficient to perform the same attack-disutility calculation using ENVISION EQ-5D results as was done for EXPLORE.

In EXPLORE, EQ-5D data were collected at scheduled 6-month intervals, as well as during attacks (along with other questionnaires). An official "during attack" flag was recorded for all questionnaires completed in association with acute attacks, including the EQ-5D. This flag allowed definitive identification of EQ-5D utilities related to attacks, and thus the estimation of the disutility per attack by taking the difference between the utility score during attacks ([redacted]) and when not having an attack ([redacted]). Only utility scores of patients not on hemin prophylaxis were used in these estimates.

The EQ-5D data collected in ENVISION and its OLE were not used to estimate the utility values by health state because the short collection period does not allow observation of changes in QoL due to presence of chronic conditions. For this reason, the long-term QoL decrements associated with each chronic condition separately were obtained from the literature and were then applied to the proportion of the cohort with each condition in every health state based on prevalence data reported by Neeleman et al. (2018)[19] (See

Table 6 in Section 6.1.2).

Targeted literature search

To incorporate the QoL impact of chronic conditions in the model, utility values were needed for chronic pain and neurologic and psychiatric symptoms. The QoL SLR retrieved no studies in patients with AHP quantifying QoL for chronic conditions. Therefore, a targeted literature search was undertaken to identify utility values for these chronic conditions independently of the presence of AHP.

The target literature review was conducted using PubMed and Google. The search strings used were "Health State Utility Values" OR "EQ5D Values" OR "EQ-5D Values" OR "Health-related quality of life" AND "chronic pain" OR "neurologic symptoms" OR "psychiatric symptoms". The term "chronic conditions" was also used in combination with those terms to retrieve studies reporting QoL of multiple chronic conditions.

The studies retrieved via the search were screened against the following inclusion criteria: adult patients (humans), UK population, QoL measured with EQ-5D, aggregate utility values reported for chronic pain or neurologic or psychiatric conditions, English language. Titles and abstracts were screened first and only if these appeared to meet inclusion criteria was the full text reviewed.

Search results and evidence selection

A full list of identified studies with details of condition of reference and utility values described is provided in Table 34.

Table 34. Identified studies meeting inclusion criteria for chronic condition disutilities

Study	Condition	Utility, mean (range or SD)	Population	Comments
Hoxer et al. (2019)[137]	Chronic pain in haemophilia	Moderate no chronic pain: 0.70 (0.21) Moderate + chronic pain: 0.51 (0.24)	Mean age: 35 y Proportion female: 62%	Utility in haemophilia without chronic pain is reported which allows estimation of utility decrement for chronic pain. It is unclear if chronic pain is similar in

Study	Condition	Utility, mean (range or SD)	Population	Comments
				haemophilia and AHP.
Stafford et al. (2012)[138]	Migraine pain	No migraine: 0.87 (0.15) Mild pain: 0.66 (0.23) Moderate pain: 0.53 (0.27) Severe pain: -0.20 (0.29)	Mean age: 47 y Proportion female: 76.4%	Utility decrement potentially relevant to chronic pain in AHP could be estimated by subtracting the average of mild and moderate pain from the no-migraine utility (severe migraine pain is not considered relevant to chronic AHP pain since the most severe pain in AHP is expected to occur during acute attacks).
McDermott et al. (2006)[139]	Neuropathic pain	Mild: 0.67 Moderate: 0.46 Severe: 0.16	Mean age: 63 y Proportion female: 50%	Utility without the condition is not reported; utility decrement potentially relevant to chronic pain in AHP was estimated by subtracting the average of mild, moderate, and severe pain from the general population utility (= 0.813).
Hawton and Green (2016)[140]	MS (relapsing-remitting)	EDSS 0: 0.897 (0.132) EDSS 1: 0.763 (0.186) EDSS 2: 0.719 (0.229) EDSS 3: 0.523 (0.317) EDSS 4: 0.596 (0.274) EDSS 5: 0.438 (0.359) EDSS 6: 0.502 (0.275) All: 0.623 (0.294)	Mean age: 50.7 y Proportion female: 73.9%	The study also reports progressive disease, but relapsing-remitting was deemed more similar to AHP. Because neurologic symptoms in AHP vary it is unclear which EDSS levels should be averaged to yield a utility proxy for neurologic symptoms in AHP.
Sullivan et al. (2011)[141]	MS	With the condition: 0.495 (0.037) Utility decrement vs no condition: -0.2271 (0.034)	Mean age: 52.2 y Proportion female: NR	Utility decrement of the condition is reported directly. Disutility is averaged across all MS stages making it unclear if this is an appropriate utility proxy for neurologic symptoms in AHP.
	Paralysis	With the condition: 0.350 (0.058) Utility decrement vs no condition: -0.2466 (0.0994)	Mean age: 45.3 y Proportion female: NR	Utility decrement of the condition is reported directly but likely overestimates the utility decrement due to neurologic symptoms in AHP since paralysis is among the most severe of the different neurologic symptoms associated with AHP.
	Other hereditary and degenerative neuropathy	With the condition: 0.584 (0.030) Utility decrement vs no condition: -0.097 (0.0966)	Mean age: 56.0 y Proportion female: NR	Utility decrement of the condition is reported directly.
Kolovos et al. (2017)[142]	Depression	Remission: 0.70 (0.67–0.73) Minor depression: 0.62 (0.58–0.65) Mild depression: 0.57 (0.54–0.61) Moderate depression: 0.52 (0.49–0.56) Severe depression: 0.39 (0.35–0.43)	Mean age: 56 y Proportion female: 67%	EQ-5D is reported by stage of depression; it is unclear which stage represents the average utility due to psychiatric symptoms in AHP. Psychiatric symptoms in AHP include conditions other than depression, such as anxiety, psychosis and insomnia.
Ara and Brazier (2011)[136]	Mental illness/ anxiety/ depression/ nerves	Without the condition: 0.878 (0.861, 0.894) With the condition: 0.606 (0.585, 0.626)	Mean age: 45.5 y Proportion female: NR	Average utility for different types of psychiatric symptoms is reported, thus avoiding having to pick a single condition as a proxy for psychological symptoms in AHP. Utility without these conditions is reported which allows estimation of utility decrement.

AHP, acute hepatic porphyria; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NR, not reported; SD, standard deviation

Three studies in chronic pain in different indications met the inclusion criteria: Stafford et al. (2012) for migraine,[138] Hoxer et al. (2019) for haemophilia,[137] and McDermott et al. (2006) for neuropathic pain.[139]

McDermott et al. was considered the most relevant because neuropathic pain was deemed to be a better proxy for chronic pain in AHP than chronic pain in haemophilia, given the high prevalence of neurologic conditions in AHP, and given that the pain scores reported by Stafford et al. were specific to pain during migraine attacks, which are likely unrepresentative (i.e., more severe) than chronic pain between attacks. The average between the utility values reported by McDermott et al. for mild, moderate and severe neuropathic pain was subtracted from the utility of the general population with the same average age and proportion of females as in the study to obtain the utility decrement of chronic pain (-0.383). This utility decrement is similar to the values from the other two studies (-0.19 and -0.275 per Hoxer et al. and Stafford et al., respectively).

The targeted search on neurologic symptoms retrieved studies in multiple sclerosis,[140] as well as a catalogue by Sullivan et al of EQ-5D scores for the UK in paralysis and other conditions.[141] For neurologic symptoms, the utility decrement that appeared most relevant was reported by Sullivan et al. for "Other hereditary and degenerative neuropathy". Neurologic symptoms in AHP as reported by Neeleman et al. vary in severity from mild (e.g., paraesthesia) to moderate (e.g., motor weakness) and very severe (e.g., paralysis and advanced neuropathy).[19] Sullivan et al. provided utility decrements that can be applied in the model directly, and using the value for the broad category "Other hereditary and degenerative neuropathy" avoids restricting the disutility measure in the model to a specific neurological condition such as multiple sclerosis or paralysis that may not be fully representative of the entire range of neurologic symptoms in AHP. Moreover, this utility decrement (-0.097) is much lower than the values derived from the other identified studies for neurologic symptoms and is therefore a conservative choice.

As for neurologic symptoms, psychiatric symptoms in AHP include a range of different conditions such as depression, anxiety, insomnia and psychosis.[19,44] For this reason, the study which appears most relevant was by Ara and Brazier 2011, who reported the utility with and without aggregate psychiatric conditions defined as "Mental illness/anxiety/depression/nerves".[136] The utility of the population with the condition was subtracted to the utility of the population without the condition to obtain the utility decrement of psychiatric symptoms in the model (0.27).

Calculation of health-state disutilities due to chronic conditions

To assign health-state utility decrements due to chronic pain, neurologic symptoms, and psychiatric symptoms, we estimated the proportion of the cohort with one, two, or three of these chronic conditions. Because the prevalence data reported by Neeleman et al. did not report the distribution of multiple concurrent chronic conditions,[19] we applied the multiplicative approach developed by Ara and Brazier (2017),[143] which is recommended by the International Society for Pharmacoeconomics and Outcomes Research Good Practices for Outcome Research Task Force.[144] We applied this method by multiplying the utility in the absence of a given condition by the product of the ratios of the utilities for individuals with the conditions to the utility of individuals in the general population.

A utility decrement on the general population utility was obtained from the literature for each higher order category among chronic symptoms/comorbidities (i.e., pain, neurological and psychiatric; Section 6.1.2). Two main studies were used as a source to obtain utility decrements, since they report QoL data of multiple conditions in the UK,[136,141] and the data used in the model for each condition reflect the QoL impact independently from the presence of AHP, since the aim was to obtain the utility decrement of each specific condition.

Estimation of the proportion of the cohort in a given health state with one but not the other two chronic conditions was calculated from the values reported by Neeleman et al.[19] as in the following example, in which P signifies prevalence: $P_{Pain\_only} = P_{Pain} \times (1 - P_{Neurological}) \times (1 - P_{Psychiatric})$. Similarly, the proportion of the cohort in a given health state with two conditions was calculated as, for example, $P_{Pain+Neurological} = P_{Pain} \times P_{Neurological} \times (1 - P_{Psychiatric})$. The proportion of the cohort in a given health state with all three conditions was calculated as $P_{Pain} \times P_{Neurological} \times P_{Psychiatric}$.

The proportion of the cohort without any of the conditions was given by 1 x (1 - $P_{Pain)\ x}$ (1 - $P_{Neurological}$) x (1 - $P_{Psychiatric}$). These were assigned a utility decrement of 0.

We then multiplied the utility values for each condition (or combination of conditions) by the proportion of the cohort with the different combinations of conditions in each AHP health state. This method yielded the weighted utility decrements by health state, which were then summed to calculate the total utility decrement associated with chronic conditions, which was then applied to the proportion of the cohort in each health state over the time horizon of the model.

Using the selected utility values for chronic pain, neurologic and psychiatric conditions and the method described above for assigning utility decrements for multiple conditions based on the proportion of the cohort with these conditions in each health state, the utility values by health state are as shown in Table 35.

Table 35. Utility decrements due to chronic conditions, by health state

Health state	Utility decrement
Asymptomatic AHP	[redacted]
Symptomatic AHP	[redacted]
Recurrent AHP	[redacted]
Severe AHP	[redacted]

AHP, acute hepatic porphyria

In addition to patients' utility decrements associated with acute and chronic consequences of AHP, the model considers caregiver disutility by health states. No studies were identified reporting caregiver disutility in AHP. A search was conducted to identify caregiver disutilities in conditions characterised by progressive disability (disease worsening), with stages of severity that could be comparable in terms of caregiver burden to the AHP severity scale used in the current analysis. Like AHP, multiple sclerosis (MS) is chronic disease often associated with an increasing dependence on others for support with activities of daily living, and with a growing need for care at home.[133] Caregiver disutility at different severity stages of MS was therefore used as a proxy for caregiver disutility in the different AHP health states, based on caregiver QoL data reported in the MS study by Acaster et al. 2013.[145] A summary of the QoL values for the CEA is provided in Table 36.

Table 36. Summary of health-related QoL values for the CEA

State	Utility decrement	SE	Reference in submission	Assumptions
Acute attack	[redacted]	[redacted]	EXPLORE[11,22]	Calculated from mean EQ-5D utility (UK tariff) during attack of [redacted] minus utility not on attack of [redacted]
Chronic symptoms/comorbidities				
Pain	-0.383	—	McDermott et al. (2006)[139]	Utility with the condition/disutility: the average between the utility values for mild, moderate, and severe pain. Utility without the condition: utility value for the general population with similar characteristic as in the study, i.e., 63 years of age and 50% females.
Neurological	-0.097	—	Sullivan et al. (2011)[141]	Utility with the condition/disutility: "Other hereditary and degenerative neuropathy". Utility without the condition: the general population utility with the same age as the cohort with the condition in the study, i.e., 56 years of age.
Psychiatric	-0.272	—	Ara and Brazier (2011)[146]	Utility with the condition/disutility: mental illness/anxiety/depression/nerves. Utility without the condition: QoL in patients without mental illness/anxiety/depression/nerves.
Asymptomatic	[redacted]	[redacted]	—	—
Symptomatic	[redacted]	[redacted]	—	—
Recurrent	[redacted]	[redacted]	—	—
Severe	[redacted]	[redacted]	—	—

State	Utility decrement	SE	Reference in submission	Assumptions
Caregiver disutility by health state				
Asymptomatic	-0.002	0.053	Acaster et al. (2013)[145]	Equal to stage 1 MS: mild disability
Symptomatic	-0.045	0.057	Acaster et al. (2013)[145]	Equal to stage 2 MS: moderate disability
Recurrent	-0.142	0.062	Acaster et al. (2013)[145]	Equal to stage 4 MS: initial walking difficulty
Severe	-0.160	0.055	Acaster et al. (2013)[145]	Equal to stage 5 MS: important walking difficulty

CEA: cost-effectiveness analysis; CKD: chronic kidney disease; EQ-5D: EuroQol Five-Dimension Questionnaire; HCC: hepatocellular carcinoma; MS: multiple sclerosis; QoL: health-related quality-of-life; SE: standard error; UK: United Kingdom.

10.6.2. Assessment of the applicability of values available or estimates of any values by clinical experts

The general approach to utility estimation used in the economic model was reviewed with clinical experts.

10.6.3. Definition of what a patient experiences in the health states in terms of HRQL

The health states used in the CEA model aligned with proposed AHP disease stages that differentiated between recurrent cases (>4 attacks per year), Symptomatic cases (at least one attack per year but not meeting the definition of recurrent cases) and Asymptomatic cases (mutation carriers with no attacks).[19] In the CEA model, the "recurrent" category was further subdivided into: Recurrent (>4 and ≤24 attacks per year) and Severe (>24 attacks per year), as clinical experts agree that higher rates of attack are generally associated with greater disease severity for most patients.[56] Exploratory data from ENVISION, namely the change from baseline to Month 6 on the PGIC and the EuroQol VAS (EQVAS), confirmed that there is a clinically-meaningful separation in how patients experience the disease by categories based on the AAR (Figure 26).

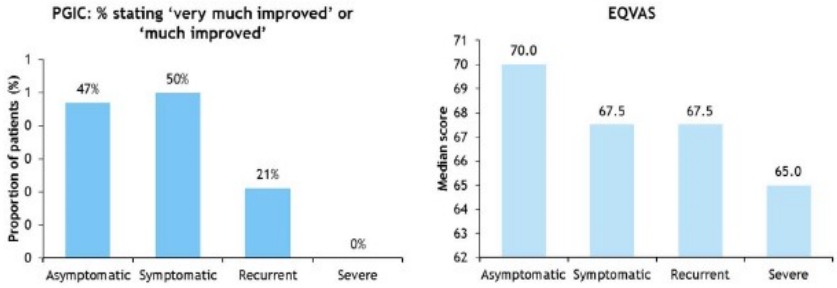


Figure 26. Health-related QoL by health state from ENVISION

EQVAS: EuroQol visual analogue scale; PCS: Physical Component Summary; PGIC: Patient Global Impression of Change Questionnaire; QoL: health-related quality of life. Source: Alnylam data on file (2020)

Expert clinicians in several European countries and the UK validated that these QoL results from ENVISION were consistent with the experience of AHP patients that they see in clinical practice, and that the definitions of model health states were clinically sound.[56]

10.6.4. Health effects identified in the literature or clinical trials that were excluded from the analysis

No relevant health effects identified in the literature or clinical trials were excluded from analysis.

10.6.5. Baseline quality of life assumed in the analysis

Quality of life in patients entering the model at baseline was based on the distribution of patients from ENVISION according to the defined model health states (i.e., Symptomatic, Recurrent, Severe), and the utilities assigned to the acute attacks and chronic symptoms associated with those health states.

10.6.6. Clarification of whether health-related QoL is assumed to be constant over time

QoL in AHP is not assumed to be constant over time, as continuous and relentless accumulation of the metabolites ALA and PBG, which are central to AHP pathophysiology, drive both acute porphyria attacks and chronic porphyria-related symptoms.[18,133] Attacks significantly impact QoL, and the frequency of attacks may change over time; data from the ENVISION RCT showed that the AAR and QoL improved in patients taking givosiran, compared with those taking placebo.[11,14] Accordingly, transition probabilities for the CEA model (See Section 12.1.3) were based on data from ENVISION and the ENVISION OLE and showed the majority of patients who took givosiran transitioning to more favourable health states, compared with patients taking placebo, most of whom experienced no change or a worsening of their condition.[11,14]

10.6.7. Amendment of values

No values have been amended.

10.7. Treatment continuation rules

The givosiran Summary of Product Characteristics (SmPC) suggests discontinuation if anaphylaxis occurs, and to consider discontinuation for clinically relevant transaminase elevations and in breast feeding,[2] Given the very small UK patient population, these scenarios are only expected to affect a very small fraction of the patient population and is therefore not included in the CEA.

Section D – Value for Money and cost to the NHS and personal social services

11. Existing economic studies

11.1. Identification of studies

11.1.1. Strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data

The SLR was designed to identify relevant economic evidence for AHP in the published literature and in unpublished sources. The SLR search strategy has been previously described in Section 9.1 and in Appendix 1.

11.1.2. Inclusion and exclusion criteria used to select studies from the published and unpublished literature

The selection criteria for economic studies are outlined in Table 10 in Section 9.2. The systematic literature search was designed to not only identify economic evaluations and cost studies relating to the treatment of AHP, but to also identify healthcare resource use and productivity losses in AHP, independently of economic evaluations.

11.1.3. Numbers of published studies included and excluded at each stage in an appropriate format

Figure 5 shows the PRISMA diagram for the SLR in AHP and indicates the number of articles that were identified as containing economic evidence (n=19).

11.2. Description of identified studies

11.2.1. Brief review of each study, stating the methods, results and relevance to the scope

Appendix 1 lists the studies identified by the economic SLR. No relevant treatment-related economic evaluations, budget impact analyses, or costing studies were identified. As a result, no studies were considered relevant to the submission. As per the NICE guidance, productivity losses and caregiver time costs are not included in the NHS/PSS perspective for the economic model. Studies that have reported health-related QoL/utility data and their relevance to the scope and applicability to the economic model have been previously described in Sections 10.1.6 and 10.1.7, and in Appendix 2.

11.2.2. Complete quality assessment for each health economic study identified

As no economic evaluations (i.e., cost-effectiveness or cost-utility studies) were identified by the SLR, the Drummond checklist was not used for quality assessment.

12. Economic analysis

- A de novo Markov model was developed that incorporated four different AHP health states.
- The model used data from the pivotal RCT ENVISION or published natural history data highly relevant to the UK, and inputs and assumptions were validated by clinical experts.
- Givosiran compared with BSC yields a discounted incremental cost-effectiveness ratio (ICER) of [redacted], and these results are relatively robust to a range of sensitivity and scenario analyses.
- After 5 years, the model predicts that 95% of givosiran-treated patients will be asymptomatic compared with only 13% of BSC-treated AHP patients.
- The CEA results for givosiran should be considered in context of the high unmet need in this patient population as no efficacious disease-modifying therapy was previously available to treat AHP in the UK.

12.1. Description of the de novo cost-effectiveness analysis

12.1.1. Patients

Patient groups included in the cost-effectiveness analysis

The CEA considers adults and young people aged 12 years or older with recurrent severe attacks of AHP, per the final NICE scope.[38] This target population is consistent with the patient population in ENVISION, which exclusively enrolled patients with a history of repeated acute attacks. Demographic data inputs to the CEA were obtained from the baseline characteristics of the population in the ENVISION trial.[14]

12.1.2. Technology and comparator

Justification for why the comparator used in the cost-effectiveness analysis is different from the scope

The CEA considers givosiran vs established clinical management without givosiran as summarised in Section 8.2.2 and in accordance with the NICE scope. For the purposes of the model, established clinical management without givosiran is defined as best supportive care, consistent with the control arm of the ENVISION trial. In the CEA and in line with the NICE scope, BSC may include the use of gonadotrophin analogues to decrease the frequency of attacks and supportive treatments, such as analgesics and anti-

emetics. Hemin may also be used, in line with its approved indication, as a treatment to speed the resolution of AHP attacks once they have occurred. Due to its extreme rarity in the UK (see Section 8.2.2), liver transplantation is not considered as an established clinical management procedure for AHP in the CEA.

12.1.3. Model structure

Diagram of the model structure

No economic models for givosiran or for other technologies used in UK clinical practice in the indicated population had been published at the time of the model development. We therefore developed a *de novo* CE model in conformity with requirements of NICE as expressed in the Guide to the Methods of Technology Appraisal.[147]

This standard Markov model was developed using Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) to assess costs and effects, life-years (LYs) and quality-adjusted life-years (QALYs) of givosiran and BSC in a simulated cohort of AHP patients. The cohort transitioned across five health states corresponding to the four mutually exclusive categories of AHP disease severity based on the frequency of acute attack (see Sections 6.1.2 and 10.1.11), plus death. Figure 27 shows the design of the *de novo* Markov model for the CEA for givosiran (See Appendix 6 for full model).

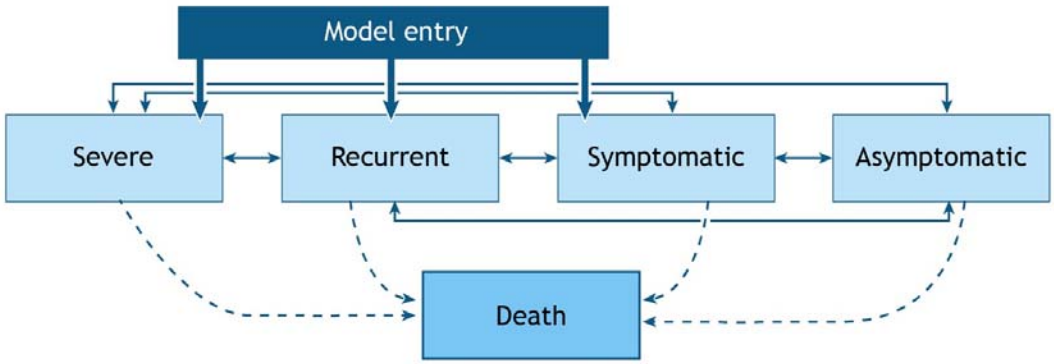


Figure 27. AHP Markov model structure
AHP, Acute hepatic porphyria

Findings from the SLR review yielded no widely accepted, standardised system for classifying patients' disease severity of AHP.[148] The search did yield one relevant framework for staging this condition using mutually exclusive categories, which was proposed by Neeleman et al. (2018)[19] Furthermore, the relevance of this framework in staging the condition for the use of the present economic model was affirmed by expert clinicians with experience in treating patients with AHP.[56] The definitions of the model health states are summarised in Table 37.

Table 37. Definitions of model health states

Disease severity	Patient subgroup definition, number of attacks[19]	Model health state definition, number of attacks per year
Asymptomatic	0 ever	0
Symptomatic	≥1 ever, ≤4 in any year	>0 to ≤4
Recurrent	>4 in any year	>4 to ≤24
Severe*	Not defined	>24

*The existence of a clinically distinct severe health state was supported by the QoL data from the ENVISION trial and validated by expert clinicians who indicated that the definitions of model health states were clinically sound and were consistent with the experience of AHP patients that they see in clinical practice (see Section 10.1.11 and 12.1.4). Sources: Balwani et al. (2020);[14] Neeleman et al. (2018)[19]

According to the ENVISION inclusion criteria, all patients were required to have experienced repeated acute attacks, corresponding to ≥2 attacks in the 6 months prior to study entry. To align with this study population, all patients in the cohort enter the model sorted into the Symptomatic, Recurrent or Severe health states as defined in Table 37, based on the distribution of baseline severity of patients enrolled in ENVISION. The proportion of the cohort entering the model in each health state was obtained by pooling data on the baseline distribution of givosiran and placebo patients in ENVISION.[55]

The efficacy of givosiran and BSC was based on the transition probabilities obtained from the ENVISION trial as well as an additional 12 months of the ENVISION OLE. In each Markov cycle, a patient can transition between any of the following four health states (i.e., Asymptomatic, Symptomatic, Recurrent or Severe) based on the transition probabilities obtained from the ENVISION data. The cohort may transition to death from any alive health states based on population-adjusted norms. In line with current treatment practice and the best evidence available to model mortality in AHP, the model does not incorporate death due to acute attacks, as fatalities due to AHP attacks have become exceedingly rare among diagnosed and treated patients (see Sections 6.1.4 and 12.1.6). The model structure and the definition of the health states were validated by the global AHP expert clinicians Dr. Eliane Sardh (lead position at Porphyria Center Sweden, and member of the steering committee for the European Porphyria Network), Dr. Janneke Langendonk (Director of the Porphyria Centre in Rotterdam and Dutch AHP expert), and Prof. Laurent Gouya (head of the French Referral Centre on Porphyria) (see Sections 12.2.5 and 12.3.3).

12.1.4. Justification of the chosen structure in line with the clinical pathway of care

Basing the model on levels of attack frequency (defined by the AAR) is relevant in the context of a disease that is characterised by recurrent acute attacks, each of which have a debilitating impact on patient wellbeing and QoL (Section 6.1.2). An increase in the frequency of acute attacks is also associated with higher rates of chronic conditions (Section 6.1.2).[19]

The staging system (Table 37) in the present CEA reflects the number of attacks a patient experiences per year, rather than considering the number of attacks that patients experience in any year of their life (i.e., distinguishing between >4 attacks per year vs >4 attacks in any one year over a lifetime). An additional disease category (Severe disease; defined as >24 attacks per year) was also added to the staging system in the economic model to refine the 'recurrent disease' definition proposed by Neeleman et al. (2018).[19] Based on findings from the ENVISION study, it was considered that categorising all patients with more than four attacks per year to be part of one singular health state was an overly broad and crude consideration of patients' disease severity. ENVISION demonstrated a high variation in AAR, ranging from 0 to 53. The addition of the 'Severe disease' health state allows for a more granular estimation of the severity of AHP disease and aligns with the understanding of AHP by global clinical AHP experts (see Section 12.1.3).

Furthermore, QoL data from ENVISION affirms that there is a clinically meaningful separation in how patients experience 'Recurrent' vs 'Severe' disease. Patients with a high AAR (i.e., >24 attacks per year) experience clinically meaningfully worse disease than patients who have >4 to ≤24 attacks per year (Section 10.1.1),[55] thus demonstrating that the 'Severe' health state is distinct from the 'Recurrent' disease state. Structured interviews with expert clinicians confirmed that the definitions of the model health states were clinically sound.[56]

12.1.5. List of all assumptions in the model and a justification for each assumption

Table 38 summarises the assumptions in the CE model for givosiran.

Table 38. Givosiran CE model assumptions

Assumptions	Justification	References

Assumptions	Justification	References
Disease severity is based on the frequency of acute attacks and presence of chronic symptoms.	A framework proposed by Neeleman et al. (2018) stages AHP according to frequency of acute attacks.[19] The frequency of symptoms, comorbidities and late complications were shown to be correlated with three levels of attack frequency.	Section 6.1.2
	QoL data from ENVISION demonstrate the existence of a fourth level of disease severity (>24 attacks per year), which has been validated independently by the expert clinicians Dr. Eliane Sardh, Dr. Janneke Langendonk and Prof. Laurent Gouya.	Section 10.1.1
	The relevance of this framework in staging the condition for the use in the economic model was affirmed by expert clinicians with experience treating patients with AHP.[56]	Section 12.1.3 and 12.1.4
Mortality rate due to an AHP attack is assumed to be 0%.	Due to improved AHP diagnosis and management and broader use of hemin to treat acute attacks (per its indication), attack-related mortality has decreased to low levels over the past decades.[8,17,80]	Section 6.1.4
	No deaths due to attacks were observed in the phase 1 study of givosiran,[13,97] the phase 3 study (ENVISION double-blind period + OLE),[14,119] or the EXPLORE natural history study.[11]	Section 6.1.4
Disutility associated with acute attacks is distinct from the ongoing disutilities associated with chronic health states.	Definitive identification of EQ-5D utilities related to attacks directly observed in the EXPLORE study.[11]	Section 10.6.1
	EQ-5D data from EXPLORE analysed to derive mean 'on attack' and 'off attack' utilities of [redacted] and [redacted], respectively.	Section 10.6.1
The average duration of an acute attack is 7.3 days.	Directly observed in the EXPLORE study and validated by UK expert clinicians.[11,56]	Section 6.1.2
80% of acute attacks are treated in hospital, 5% are treated in an outpatient setting, and 15% are treated in a home setting.	The proportion of patients treated in each setting (i.e., hospital, outpatient, and home) are in line with UK clinical practice and are validated by UK expert clinicians.[56]	Section 12.2.1
The transition probabilities relating to the effectiveness of givosiran that were observed in the ENVISION OLE continue over time beyond the duration of the OLE period. • **A 5-year time point selected for extrapolation limit** • **After 5 years, the cohort is assumed to remain stable**	Directly observed in the ENVISION OLE (18 months of follow-up) and in the OLE period of the phase 1 Part C study (up to 3 years at the latest data-cut (16 October 2019).[97,119]	Section 9.6.1
	The cumulative evidence from these separate studies supports the assumption of continuing benefits of givosiran treatment.	Section 9.6.1
	No indication that there is any diminishing effect of givosiran treatment with ongoing use even over increasingly long periods of follow-up.	Section 9.6.1
After 6 months double-blinded data, patients in the BSC arm are assumed to be stable unless they die.	All patients in the placebo arm of the ENVISION trial transitioned to givosiran in the OLE period and as such, no data were available for these patients beyond six months. A conservative assumption was implemented for transitions in the BSC arm.	Section 12.2.1
Following treatment interruption, the BSC transitions are applied	This assumption was adopted in the absence of data. Data on rates of treatment discontinuation due to any reason in patients receiving givosiran were obtained from the ENVISION double-blind (6 months) and OLE periods (12 months).	Section 12.2.1
AHP cohort mortality HRs for all health states versus the general population were set to 1.3.	These assumptions are based on AHP cohort mortality versus the general population by Baravelli (2020).[69] A scenario analysis will explore a mortality HR of 1.0 for the Asymptomatic health state.	Section 12.2.1
Caregiver disutility for the different AHP states were based on caregiver HRQoL reported for MS.	No studies were identified reporting caregiver disutility in AHP.	Section 10. 4
	Like AHP, MS is a chronic disease often associated with an increasing dependence on others for support with activities of daily living, and with a growing need for care at home.[149] Caregiver disutility at different severity stages of MS were therefore used as a proxy. Consideration of caregiver disutility is well-established in NICE appraisals of MS therapies.[145,150-153]	Section 10.6.1
BSC is assumed to have no price associated with pharmacologic	Patients receiving BSC would not receive a comparable pharmacologic treatment and therefore, no related (treatment or administration) costs	Section 12.1.2

Assumptions	Justification	References
therapy or treatment administration.	would be incurred.	

AAR: annualised attack rate; AHP: acute hepatic porphyria; BSC: best supportive care; EQ-5D: EuroQol 5-Dimension Questionnaire; HR: hazard ratio; HRQoL: health-related quality of life; MS: multiple sclerosis; N/A: not applicable; OLE: open-label extension.

12.1.6. Definition of what the model's health states are intended to capture

Within each of the alive health states, the model estimates the impact of both acute and chronic AHP consequences, considering the following:

- The risk of attacks and related acute symptoms (including AEs of acute hemin treatment). Acute porphyria attacks are included in the model as events that may occur at every cycle in any of the health states, over the entire time horizon of the model. One-off utility decrements and costs associated with acute attacks are considered in the model.
- The presence of chronic conditions found to be correlated with the frequency of attacks, as described in Section 6.1.2 (

- Table 6).[19] The model includes the ongoing impact of chronic conditions on QoL, mortality and costs.

In line with current treatment practice and the best evidence available to model mortality in AHP, the CEA does not incorporate death due to acute attacks. If untreated, AHP attacks are known to be potentially life-threatening,[33] but due to improved AHP diagnosis and management and broader use of hemin to treat acute attacks (per its indication), attack-related mortality has decreased to low levels over the past decades.[17] No deaths due to attacks were observed in the phase 1 study of givosiran (double-blind period + OLE),[13,97] the phase 3 study (ENVISION double-blind period + OLE)[14,119] or the EXPLORE natural history study.[11] On the basis of this evidence, the model assumes a 0% mortality rate due to acute attacks.

12.1.7. Key features of the model not previously reported

Table 39 summarises the additional key features of the model.

Table 39. Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime horizon	The lifetime horizon is the appropriate time scale for the CEA, given that AHP is a chronic and incurable hereditary disease requiring long-term specialist management across a patient's lifetime. In model simulation the time limit is set to approximately 60 years, corresponding to 122 model cycles.	NICE Guide to the Methods of Technology Appraisal (2013)[147]
Discount rate	Both costs and outcomes (LYs and QALYs) were discounted at 3.5% annually.	The chosen discount rate for costs and outcomes is in line with the NICE Guide to the Methods of Technology Appraisal.	NICE Guide to the Methods of Technology Appraisal (2013)[147]
Perspective (NHS/PSS)	Third party payer perspective (NHS and PSS) in England.	In the base-case setting the perspective of the UK NHS/PSS is considered, including only direct medical costs.	NICE Guide to the Methods of Technology Appraisal (2013)[147]
Cycle length	The simulation is conducted in cycles of 6 months.	The cycle duration was selected to match the duration of the double-blind period of the ENVISION study, which is the key source of data for the model.	ENVISION Trial[14]

CEA: cost-effectiveness analysis; LY: life-years; NHS, National Health Service; PSS, Personal Social Services; QALY: quality-adjusted life-years, UK: United Kingdom.

Impact of menopause on disease natural history

Evidence on the natural history of AHP demonstrates that at menopause many women experience a reduction in attacks due to changes in hormonal levels.[10,58,74] This reflects the fact that sex hormones have the capacity to influence the rate of haem biosynthesis by inducing the first enzyme in the haem pathway, ALAS1, thereby precipitating clinical expression of the underlying AHP mutation (Figure 1).[45]

Multiple expert clinicians (see Section 12.1.3) were consulted regarding our health-economic analysis. These experts have noted that, in their experience, the frequency of attacks will attenuate or cease in many, but not all women, at menopause. Although a small minority of patients still experience frequent AHP-related attacks by menopause onset, well-controlled patients have a high likelihood of remaining asymptomatic after menopause. The expert clinicians confirmed that it would therefore be appropriate for the model to assume that patients who are well-controlled and attack-free (i.e., in the Asymptomatic health state) by menopause onset would no longer require therapy to prevent attacks. This aligns with the natural history of AHP; namely, women are more likely to have AHP attacks, with the majority aged between 20 and 40 years,[44] and this has been linked to changes in ovarian physiology.[7,45] Notably, this assumption is applied consistently to patients in the givosiran and BSC arms of the cost-effectiveness model, as it reflects the disease natural history, not a treatment-specific effect. Consistent with expert-clinician opinion that women with poorly controlled AHP (i.e., those still having attacks) are unlikely to experience resolution of attacks and symptoms after menopause, the model considers that women in the Symptomatic, Recurrent, and Severe health states remain at risk after menopause and therefore need to stay on treatment.

The base-case CEA contains a probability distribution function developed by Greer et al[154] for the timing of menopause to reflect the variability in age at menopause onset. This distribution was very close to a distribution obtained by fitting average age of onset and standard deviation from the UK Women's Cohort Study[155] to normal distribution, which was tested in a scenario analysis. The resulting probability distribution by age at menopause onset is shown in Figure 28. The probability of menopause is applied to the female cohort only, taking into consideration that as a greater proportion of females reach menopause, the proportion of the female cohort that remains menopause free diminishes over time.

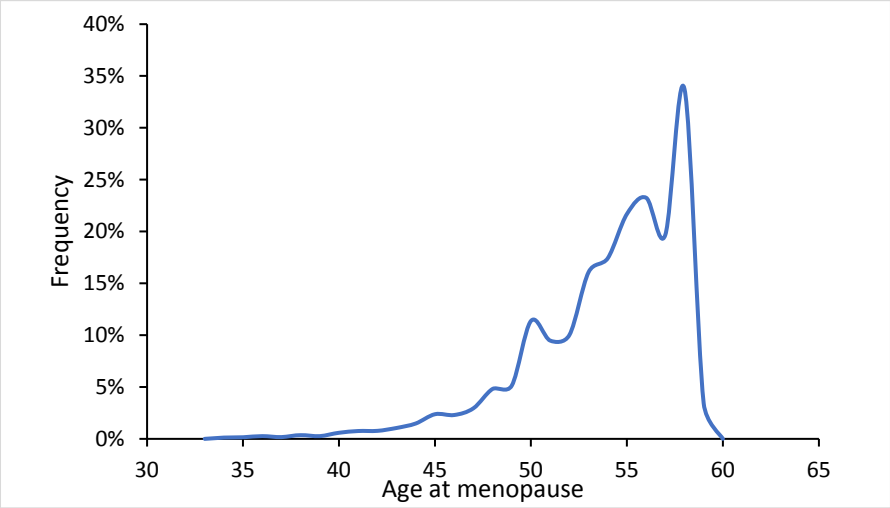


Figure 28. Adjusted cycle probability of menopause onset

12.2. Clinical parameters and variables

12.2.1. Description of how the data from the clinical evidence were used in the cost-effectiveness analysis

Data sources

Data on porphyria-related clinical variables needed to populate the model were identified in the systematic literature review described in this submission (Section 9.1–9.3). Where required, values for clinical variables were also obtained from Alnylam data on file for relevant studies. In addition, three targeted literature searches were conducted in May 2019 to identify studies reporting mortality, QoL, and cost data for each of the chronic symptoms/comorbidities and long term complications identified by Neeleman et al. (2018)[19] and included in the CEA. The targeted searches were not restricted to porphyria-related studies.

Health states

As described in Sections 10.1.11 and 12.1.3, the health states for the model were based on a framework for staging AHP reported by Neeleman et al. (2018),[19] as well as on analyses of QoL data from ENVISION, which affirmed the presence of a clinically 'Severe' health state (>24 attacks per year). The definitions of the model health states are summarised in Table 37 and in Section 10.1.11.

Patients were categorised into each of the model health states by pooling across the givosiran and placebo treatment arms in the ENVISION trial, and calculating patients' respective AAR in the double-blind (0–6 months) and OLE periods (Table 40). The mean AAR for each health state was calculated as the average of these two AAR values (i.e., the average of the AAR in the double-blind period and the AAR in the OLE).

Table 40. Mean AAR by health state from ENVISION

Health state	Mean AAR (95% CI)*
Asymptomatic	0.00
Symptomatic	2.32 (2.12–2.53)
Recurrent	10.20 (8.90–11.50)
Severe	33.10 (28.26–37.93)

AAR: annualised attack rate. *Pooled AAR data at months 6, 12, and 18 for placebo and givosiran.

In the current analysis, AAR estimates are consistent with the definition of attacks used in the primary endpoint of the ENVISION study, which considers AHP attacks as those that require hospitalisation, an urgent healthcare visit, or IV hemin at home.[14] For the purposes of assigning healthcare resource use and associated costs to these attacks, and in line with clinical practice in the UK, the model considers that 80% of acute attack treatment occurs in hospital, 5% of acute attacks are treated in an outpatient setting, and 15% are treated at home (Section 12.3.3).[56]

Each attack is assigned a one-off disutility weighted by the average attack duration, as well as a one-off cost. The description of the disutility associated with an acute attack and its estimation is described in Section 10.6.1.

In addition to the one-off impact of acute attacks, each health state is attributed an ongoing utility value, mortality probability, and cost per cycle. These are estimated based on the presence of chronic symptoms/comorbidities and late complications for Recurrent, Symptomatic and Asymptomatic subgroups of patients (Section 6.1.2).[19] Thus, in the model, the disutility associated with acute attacks (applied only over the duration of attacks) is distinct from the ongoing utility decrements associated with the chronic conditions and applied by health states, as shown in Figure 29. A description of the utility decrements assigned to the chronic conditions included in the health states is provided in Section 10.1.9.

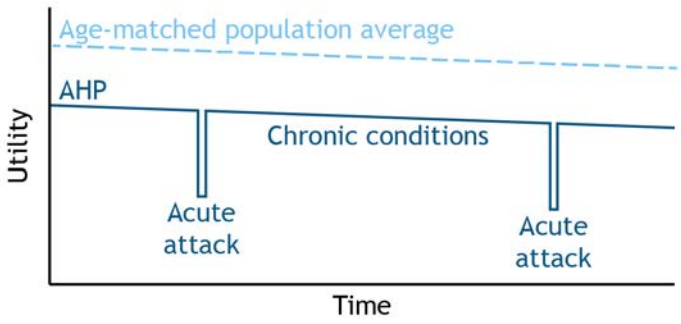


Figure 29. Conceptual schematic of utilities in the model

Note: This schematic depicts utility for a patient who remains in a given model health state (i.e., does not transition to a different health state). The decline in utility over time reflects the decreasing QoL of the general population with increasing age. AHP: acute hepatic porphyria; QoL: health-related quality of life.

Uncontrolled ALA and PBG levels impact both the acute and chronic aspects of AHP (Figure 30). Decreasing levels of these toxic precursors would be predicted to reduce not only the frequency of acute attacks and the impact of the irreversible and cumulative damage they may cause, but also the burden of chronic conditions. In the CEA, long-term complications such as CKD and HCC are not considered as

incidence data are poor or not available. These conditions can also not be included as prevalence conditions by health state, since they are not known to be reversible (i.e., there is no evidence that the conditions will improve with improvements in AHP health states). On the other hand, the CEA does consider chronic conditions which can be reverted with lower AHP attack frequency, such as pain, neurologic symptoms, and psychiatric conditions.

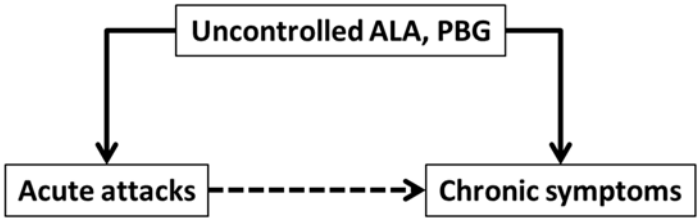


Figure 30. Role of toxic haem precursors in acute and chronic conditions of AHP
AHP: acute hepatic porphyria; ALA: aminolevulinic acid; PBG: porphobilinogen. Sources: Anderson et al. 2005,[43] Pischik and Kauppinen 2015,[17] Peoc'h et al. 2018,[46] and Wang 2019.[8]

Baseline characteristics

The characteristics of the simulated patient cohort at model entry, based on the baseline characteristics of the population in ENVISION are shown in Table 41.

Table 41. Baseline model cohort characteristics (ENVISION population)

	Model Input
Initial age (years)	41.64
Weight (kg)	[redacted]
Percentage of females	85.7%

Source: Alnylam, data on file

Treatment effectiveness

The effectiveness of treatment is measured in terms of changes in AAR from baseline over time, which are used to inform the transition probabilities in the CEA. Changes in AAR are modelled in terms of transitions over time between AHP disease severity stages (i.e., Severe, Recurrent, Symptomatic, and Asymptomatic).

The effectiveness of treatment was obtained from the ENVISION study, considering both the 6-month double-blind and the OLE periods at the latest data cut-off, at which time all patients who had not discontinued had complete 18-month efficacy data. All patients randomised to double-blind treatment enrolled in the OLE except one patient in the placebo arm.[14,119]

The duration of the double-blind period in ENVISION was sufficient to show a significant treatment effect in AAR and most secondary endpoints. However, an additional 18 months of data from the OLE period has provided additional evidence on efficacy, safety, and discontinuation (See Section 12.2.2). In addition, given the inclusion criteria, which required all patients enrolled in ENVISION to have ≥2 attacks in the prior 6 months, all patients were classifiable as either Symptomatic, Recurrent, or Severe at study start, and therefore in the double-blind period there were no transition probabilities available from the Asymptomatic category. Including data from the OLE allowed estimation of transition probabilities from the Asymptomatic health state. For BSC, only data from the placebo arm in the double-blind period of ENVISION were used since all patients switched to givosiran during the OLE period.

Distribution of the cohort at baseline

The proportion of the cohort entering the model in each health state was obtained by pooling data on the baseline distribution of givosiran and placebo patients in ENVISION (Table 42). The distribution of the cohort at baseline in ENVISION was derived based on the historical AAR of patients in each study arm. Overall, 27.2% of the cohort entered the model in the Symptomatic health state, 63.0% in the Recurrent health state, and the remaining 9.8% in the Severe health state.

Table 42. Distribution of the cohort at baseline in ENVISION

Health state	Givosiran (n)	Placebo (n)	Pooled (n)
Asymptomatic	0	0	0
Symptomatic	13	12	25
Recurrent	29	29	58
Severe	6	3	9
Total	**48**	**44**	**92**

Source: Alnylam, data on file.

Transition probabilities – Givosiran

Transition probabilities in the givosiran arm of the model are estimated from observations at 6 months during the double-blind period of ENVISION and at 12 months during the OLE period. By 6 months, the majority of patients had improved to the Asymptomatic or Symptomatic categories (Table 43). Of the Severe patients at study start, all showed AAR reductions. Similar trends in AAR were observed in the OLE period (6–12 months [Table 44]; 12-18 months [Table 45]).

Table 43. Number of givosiran patients transitioning between health states from baseline to month 6, ENVISION double-blind period

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic					0
Symptomatic					13
Recurrent					29
Severe					6
Total					48

Source: Alnylam, data on file.

Table 44. Number of givosiran patients transitioning between health states from month 6 to month 12, ENVISION OLE period.

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic					23
Symptomatic					7
Recurrent					17
Severe					0
Total					47

Source: Alnylam, data on file.

Table 45. Number of givosiran patients transitioning between health states from month 12 to month 18, ENVISION OLE period.

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic					29
Symptomatic					9
Recurrent					8
Severe					0
Total					46

Source: Alnylam, data on file.

Data from the ENVISION double-blind period (Table 43) and OLE (Table 44 and Table 45) were used to estimate givosiran transition probabilities in the first and second cycles, respectively (Table 46 and Table 47) and in cycles 3–10 (Table 48). Patients in the ENVISION OLE period maintained or further improved the health state amelioration achieved in the double-blind period (Figure 32, Figure 33). This finding was consistent with the observation from the OLE period of the phase 1/2 Part C study that patients on givosiran showed maintenance of attack reduction for up to 30 months in the most recently presented results (Section 9.6.1),[51] and for up to 3 years at the latest data-cut of 16 October 2019 (Data on file). The concordance of evidence from these separate studies supports the assumption of continuing benefits of givosiran treatment, with no indication from increasingly long periods of follow-up that there is any

diminishing effect of givosiran treatment with ongoing use. Therefore, the model assumes that the transition probabilities observed in the ENVISION OLE period continue over time beyond the duration of the OLE period. A 5-year time point was selected as a reasonable extrapolation limit for this trend. After that point, the cohort is assumed to remain stable (i.e., no further transitions between alive AHP severity health states, though transitions to death occur).

Table 46. Givosiran health-state transition probabilities in cycle 1, based on ENVISION double-blind month 6 data

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]

Source: Alnylam, data on file.

Table 47. Givosiran health-state transition probabilities in cycle 2, based on ENVISION OLE month 6 to month 12 data

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]

Source: Alnylam, data on file.

Table 48. Givosiran health-state transition probabilities in cycles 3 to 10, based on ENVISION OLE month 12 to month 18 data

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]

Source: Alnylam, data on file.

Transition probabilities - BSC

Transition probabilities in the BSC arm of the model are estimated from observations at 6 months in the double-blind period of ENVISION. No data for BSC are available beyond Month 6 because at this point patients transitioned to givosiran in the OLE. Among the Recurrent patients, nine patients showed worsening and four showed improvement in frequency of attacks (Table 49).

Table 49. Number of placebo patients transitioning between health states from baseline to month 6, ENVISION double-blind period

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]	0
Symptomatic	[redacted]	[redacted]	[redacted]	[redacted]	12
Recurrent	[redacted]	[redacted]	[redacted]	[redacted]	29
Severe	[redacted]	[redacted]	[redacted]	[redacted]	3
Total	[redacted]	[redacted]	[redacted]	[redacted]	44

Source: Alnylam, data on file.

Observations in the ENVISION double-blind period (Table 49) were used to estimate BSC transition probabilities in the first cycle (Table 50). Because no data are available beyond 6 months, a simplifying assumption was implemented where we assumed that in the BSC arm patients remain stable (i.e., no improvement or worsening) after the end of the 6-month DB period.

Table 50. BSC health-state transition probabilities, based on ENVISION double-blind month 6 data

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe
Asymptomatic	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]

Source: Alnylam, data on file

This is believed to be a highly conservative extrapolation assumption, given that worsening health status is expected in AHP patients in the absence of disease-modifying therapy, so the freezing of health states in BSC patients after 6 months does not reflect the reality that AHP is a chronic disease. On the contrary, data from the placebo arm of ENVISION reveal a strong positive relationship between time from diagnosis and AAR at 6 months (Figure 31; regression coefficient 0.62; P=0.007), demonstrating disease worsening over time in the absence of effective treatment.

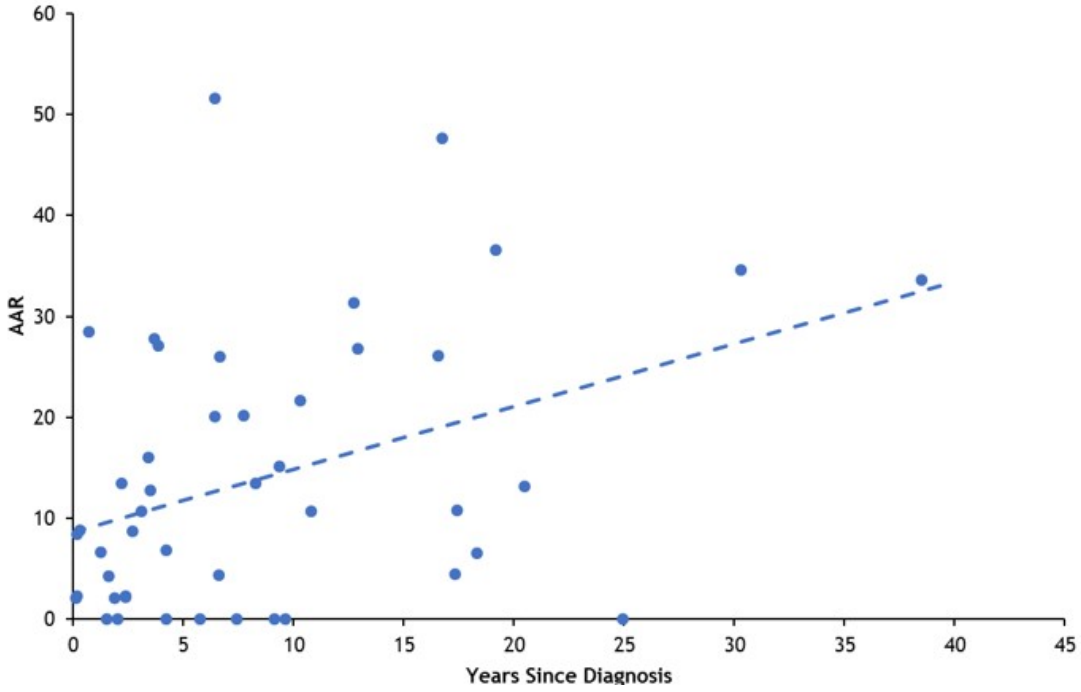


Figure 31. Association between AAR and years since AHP diagnosis in ENVISION
Regression coefficient 0.62, P=0.007, 95% CI 0.18, 1.06. AAR: annualised attack rate; AHP: acute hepatic porphyria. Source: Alnylam, data on file.

Givosiran treatment discontinuation

Treatment discontinuation represents unplanned interruption of treatment due to any reason. A time-on-treatment (ToT) curve was used in the analysis to simulate the proportion of the cohort discontinuing treatment with givosiran at each cycle of the model. Following treatment interruption, the cohort was assumed to remain in their existing health state and experience no additional benefit of givosiran treatment (i.e., probabilities of transitioning are set to 0, and adopt the effect over time of BSC). This assumption was made because there are no data on what might happen post-discontinuation.

Data on treatment discontinuation due to any reason in patients receiving givosiran were obtained from the ENVISION double-blind (6 months) and OLE periods (12 months). Beyond the trial period, ToT was extrapolated by fitting parametric models to observed time-to-event data. Akaike information criterion (AIC) and Bayesian information criterion (BIC) estimators were used to evaluate the relative quality (i.e., fit) of the parametric models considered, namely: Exponential, Weibull, Gompertz, Log-Normal, and Log-Logistic (Table 51).

Table 51. Fit statistics of parametric models to givosiran time-on-treatment data

	AIC	BIC
Exponential	64.84667	67.38996
Weibull	66.78662	71.87321
Gompertz	66.64297	71.72956
Log-Normal	66.13278	71.21937
Log-Logistic	66.70088	71.78747

AIC: Akaike information criterion; BIC: Bayesian information criterion.

Table 52 presents the parameters used to extrapolate ToT data over time with each of the tested parametric models. The CEA uses the Log-Logistic model.

Table 52. Model parameters for parametric functions to extrapolate givosiran time on treatment curves

	Exponential	Weibull	Gompertz	Log-Normal	Log-Logistic
_cons	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ln parameter		[redacted]		[redacted]	[redacted]
Parameter		[redacted]	[redacted]	[redacted]	[redacted]

General population mortality

General population mortality is defined as age- and gender-specific all-cause mortality and has been included in the model based on country-specific mortality tables for England.[156] The general mortality rate used in the model corresponds to the age of the cohort at each given cycle and has been adjusted based on the proportion of females in the analysis (Table 41).

AHP mortality

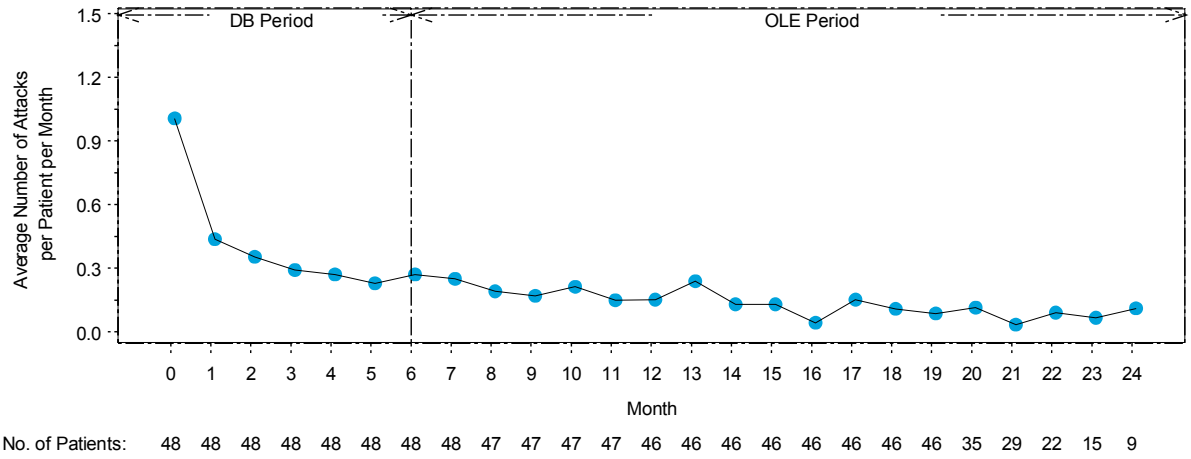
A recently published retrospective, population-based, cohort study by Baravelli et al., based on data from 333 patients with AHP in the Norwegian Porphyria Registry collected from 1992–2017, found an overall mortality hazard ratio (HR) for AHP patients of 1.3 (95% CI 1.0, 1.8) compared with the general population.[81] The study found no statistically significant difference in mortality risk between hospitalised AHP patients, non-hospitalised AHP patients, or asymptomatic AHP patients. A survival benefit could be expected for a disease-modifying treatment with demonstrated clinical efficacy; however, since currently available data do not enable us to address the question of whether givosiran conveys a survival benefit, a conservative assumption was made that the mortality rate would be the same in all health states, yielding the same survival between givosiran and BSC treatment arms. Thus, the base-case analysis considers a mortality HR of 1.3 vs the general population in all model health states.

12.2.2. Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Data on treatment discontinuation due to any reason in patients receiving givosiran were obtained from the ENVISION double-blind (6 months) and OLE periods (12 months). Beyond the trial period, ToT was extrapolated by fitting parametric models to observed time-to-event data as described in Section 12.2.1.

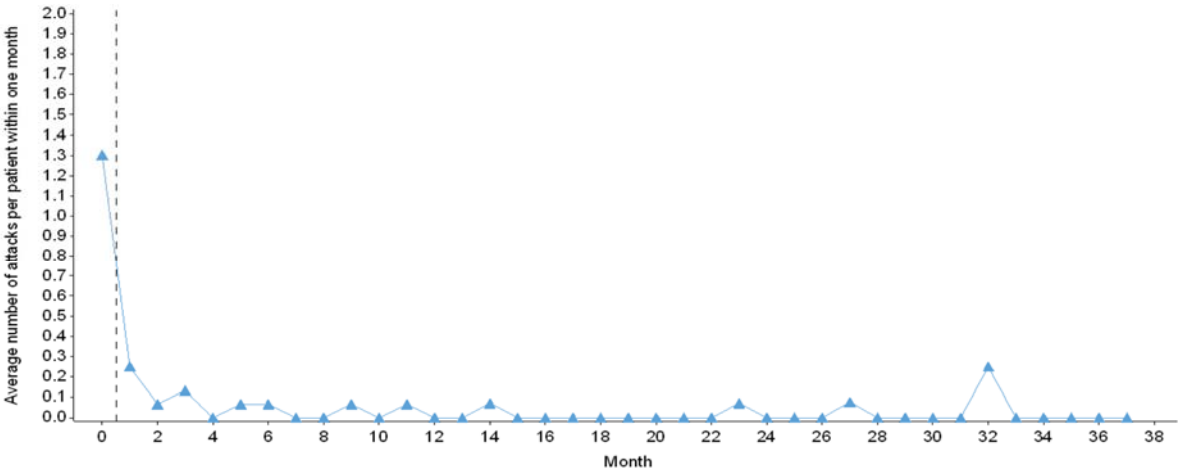
Patients in the ENVISION OLE period not only maintained the improvement achieved in the double-blind period but showed continual improvement beyond the initial beneficial effect of givosiran in the double-blind period for 2 years in the latest analysis (Figure 32A).[119] Furthermore, of 21 patients who were asymptomatic in the givosiran arm at 6 months, 89.5% remained continuously free of attacks by month 18 (2 developed attacks and 2 discontinued; Alnylam, data on file). These findings are consistent with the observation from the OLE period of the phase 1/2 Part C study that patients on givosiran showed maintenance of attack reduction for 3 years at the latest data-cut of 16 October 2019 (Figure 32B).[97]

A) ENVISION double-blind period and OLE



No. of Patients: 48 48 48 48 48 48 48 48 47 47 47 47 46 46 46 46 46 46 46 46 35 29 22 15 9

B) Phase 1 study and phase 1/2 OLE



N= 16 16 15 15 15 15 15 15 15 15 15 15 15 15 14 14 14 14 14 14 14 14 14 14 14 14 13 12 8 5 5 4 4 4 3 3 2

Figure 32. Consistent trends in attack rate in (A) the ENVISION trial and OLE, and (B) phase 1 study and phase 1/2 open-label extension

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; OLE: open-label extension. Sources: ENVISION Clinical Study Report[119]; Phase 1/2 Study Clinical Study Report[97]

The concordance of evidence from these separate studies supports the assumption of continuing benefits of givosiran treatment and increasing the length of follow-up with givosiran shows that there is no indication of diminishing efficacy of givosiran treatment with prolonged use. The proportion of patients on givosiran in ENVISION achieving Asymptomatic health status increased from 50% at Month 6 to 62% at Month 12 and 85% at Month 18 (Figure 33). Therefore, the model assumes that the transition probabilities observed in the ENVISION OLE period continue over time beyond the duration of the OLE period. A 5-year time point was selected as a reasonable extrapolation limit for this trend. After that point, the cohort is assumed to remain stable (i.e., no further transitions between alive AHP severity health states, though transitions to death occur).

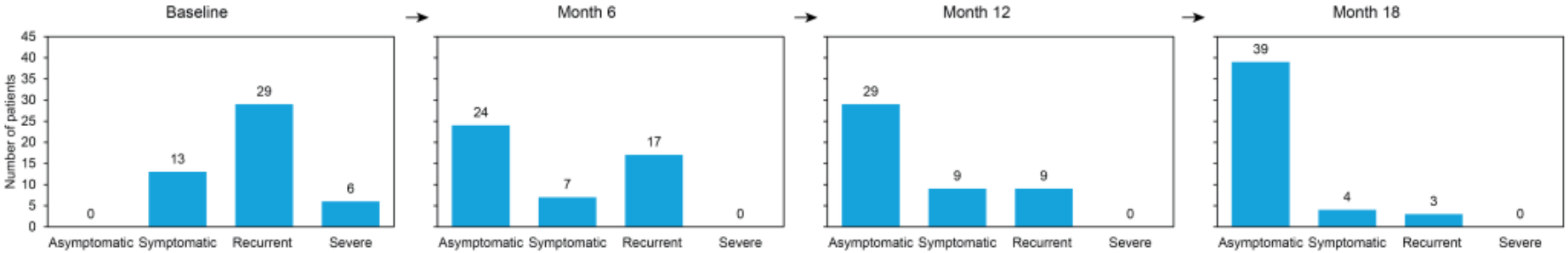


Figure 33. Health-state distribution of patients who received givosiran in the double-blind and OLE periods of ENVISION at baseline and Months 6, 12, and 18
Source: Alnylam, data on file

As described in detail in Section 12.2.1, observations in the ENVISION double-blind period (Table 49) were used to estimate BSC transition probabilities in the first cycle (Table 50). No data for BSC are available from ENVISION beyond month 6 because at this point patients transitioned to givosiran in the OLE. Data from the EXPLORE natural history study also cannot be used to inform transition probabilities for BSC because the attack rate in the pre-study period may have issues with reliability, as it incorporates patient recall of past attacks, and the burdensome set of assessments required for each and every attack in EXPLORE led to patients under-reporting attacks during the study to avoid completing the assessments.

12.2.3. Linking of intermediate outcome measures to final outcomes

In ENVISION, patients who received givosiran had a significantly lower rate of porphyria attacks and better results for multiple other disease manifestations than those who received placebo. There was no need to use surrogate endpoints in ENVISION, as clinical endpoints could be measured directly. No intermediate measures were therefore linked to the final clinical outcome in the model.

12.2.4. Inclusion of adverse events in the cost- effectiveness analysis

The incidences of AEs associated with givosiran and BSC in the model were based on data from ENVISION. The analysis included only severe treatment-related AEs during the 6-month double-blind period (Safety Analysis Set), with adjustments to incidence made to account for the 6-month cycle length (Table 53).

Table 53. Cycle probabilities of treatment related AEs

	Givosiran (cycle incidence)	BSC/placebo (cycle incidence)
Asthenia	0.021	0.000
Lipase increased	0.000	0.022
Iron overload	0.021	0.000
Headache	0.021	0.000

AE: adverse event; BSC: best supportive care.
Source: ENVISION CSR[55]

12.2.5. Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

In 2019, Alnylam Pharmaceuticals in collaboration with BresMed conducted a series of structured face-to-face or telephone interviews with three UK expert clinicians. The objective of the interviews was to discuss specific UK resource use for patients with AHP, and to validate the structure and some of the key parameters of the economic model.[56] The three clinicians (Dr. Stein, a consultant at King's College Hospital; Professor Rees, a consultant haematologist at King's College London; and Dr. Badminton, a Chemical Pathologist consultant within the Cardiff Porphyria Service based at Cardiff University Medical School) have a combined 48 years of experience in treating 215 patients with AHP.[56] Givosiran will be initiated within the NAPS Highly Specialised Service. The three interviewed clinicians are the lead consultants of the NAPS and have previously been investigators on Alnylam-sponsored studies, speakers at congresses, or advisors to Alnylam. No iteration was used in the collation of the expert clinician opinions. The clinical advisers assessed the applicability of the model parameters and inputs used in the analysis that are summarised in Table 54.[56]

Table 54. Model parameters assessed by UK expert clinicians

Parameters/inputs	Details
Health state definitions in CEA model versus Neeleman et al. (2018)[19]	All clinicians believed Alnylam's definitions of these health states could be considered appropriate and clinically sound.[19,56] The clinicians all agreed with Neeleman et al. (2018)[19] that a lower number of attacks is associated with lower severity in the majority of the patients with AHP that they treat and manage.
Acceptability of Neeleman et al. (2018)[19] estimates of prevalence of chronic conditions for Asymptomatic, Symptomatic and Recurrent patients	The consulted clinical experts (Section 12.5.5) agreed the prevalence of the health states shown in Neeleman et al.'s publication is similar for their patients with AHP in the UK. The health states capture patients with an AAR >4, which is similar to the NAPS and NHS England definition of patients covered by the Highly Specialised Services policy.[44] Only patients in the Recurrent model health state would initiate givosiran treatment in clinical practice. However, they all noted the prevalence of chronic conditions in the Asymptomatic group is higher than the clinicians would expect for the majority of their asymptomatic patients in the UK.
Prevalence of chronic conditions for Severe patients	All clinicians believed the prevalence of chronic symptoms was similar between Severe and Recurrent groups of patients with AHP.
The average duration of an acute attack is 7.3 days.	The consulted clinical experts validated the average duration of an attack observed in the EXPLORE study.[11] (see Section 12.1.5)

Source: Alnylam Pharmaceuticals (2020)[56]

12.2.6. Summary of all variables included in the cost-effectiveness analysis

The patient characteristics and clinical variables used in the CE model are summarised in Table 55. The QoL inputs to the CE model are summarised in Section 10.2.

Table 55. Summary of clinical variables applied in the cost-effectiveness model

Variable	Value	OWSA Lower value	OWSA Upper value	PSA distribution	Source
Initial age (y)	41.64	37.90	45.39	Gamma	**ENVISION[55]**
Weight (kg)	[redacted]	[redacted]	[redacted]	Gamma	**ENVISION[55]**
Proportion of females	85.7%	65.9%	97.5%	Beta	**ENVISION[55]**
Age at menopause	Probability distribution				**Greer et al. (2003)[154]**
Initial cohort distribution					**ENVISION[55]**
Asymptomatic	0.00	–	–	–	
Symptomatic	0.27	0.22	0.33	Dirichlet	
Recurrent	0.63	0.51	0.75	Dirichlet	
Severe	0.10	0.08	0.12	Dirichlet	
Extrapolation of givosiran from cycle 4 - number of cycles	7	6	8	Gamma	**ENVISION[55]**
AAR by health state					**ENVISION[55]**
Asymptomatic	0.00	–	–	–	
Symptomatic	2.32	2.12	2.53	Gamma	
Recurrent	10.20	8.90	11.50	Gamma	
Severe	33.10	28.26	37.93	Gamma	
Severe treatment-related AE per-cycle incidence					**ENVISION[55]**
Givosiran					
Asthaenia	0.021	0.017	0.025	Gamma	
Lipase increased	0.000	0.000	0.000	Gamma	
Iron overload	0.021	0.017	0.025	Gamma	
Headache	0.021	0.017	0.025	Gamma	
Placebo					
Asthaenia	0.000	0.000	0.000	Gamma	
Lipase increased	0.022	0.017	0.026	Gamma	
Iron overload	0.000	0.000	0.000	Gamma	
Headache	0.000	0.000	0.000	Gamma	

AAR: annualised attack rate; AE: adverse event; OWSA: one-way sensitivity analysis; PSA: probabilistic sensitivity analysis.

12.3. Resource identification, measurement and valuation

12.3.1. NHS costs

Description of how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff

NHS reference costs and Prescribed Specialised Services Research Unit (PSSRU) costs for the clinical management of this condition are listed in Table 87 in Appendix 5.

Resource identification, measurement and valuation studies

The SLR summarised in Table 11 and Appendix 1 was designed with broad search terms to capture any relevant resource data for the NHS in England.

Details of the process used when clinical advisers assessed the applicability of the resources used in the model

The process used to assess the applicability of resources used in the model has been described in Section 12.2.5. The full report describing this process is in Appendix 3.

12.3.2. Technology and comparators' costs

List price for the technology

The list price for givosiran is £41,884.43 per 189 mg/vial.[157]

Justification if the list price is not used in the de novo cost- effectiveness model

The list price of the technology was used in the base-case CE model.

Annual costs associated with the technology and the comparator technology applied in the cost effectiveness model.

The cost of the pharmacologic therapy includes both the drug and the administration costs. The dose considered in the model is 2.5 mg per kg of body weight per administration. For the dose calculation, the model considers the average weight of the European patients in ENVISION, corresponding to [redacted] kg, as the weight of European patients in ENVISION is expected to be more representative of the weight of patients in the UK than the weight of US ENVISION patients. Thus, the total dose per administration is [redacted] mg. BSC is assumed to have no incremental price associated with its use, as patients in the givosiran arm can also receive established clinical management and thus the cost of BSC should cancel out across treatment arms in the model (Table 56).

Table 56. Drug price

	Mg per vial	Unit	Price (£)	Price per mg (£)	Price per vial (£)
Givosiran	189	1	41,884.43	221.61	41,884.43
BSC	NA	NA	0	0	0

BSC: best supportive care; NA: not applicable.

As givosiran is administered once per month, 6 administrations are considered per cycle of the analysis. No vial sharing is included, meaning that any opened vial may not be reused and therefore the entire cost is accounted for even if the dose administered in less than the entire vial. The relative dose intensity (RDI) for givosiran was assumed to be [redacted] based on ENVISION. Table 57 presents a summary of givosiran drug cost per administration and per cycle.

Table 57. Givosiran drug cost per cycle

	Dose per admin (mg/kg)	Admin cycle	RDI	Drug cost per admin (£)	Drug cost per cycle (£)
Givosiran	2.5	6	[redacted]	41,884.43	[redacted]

RDI: relative dose intensity.

Givosiran is administered subcutaneously. The cost of SC administration (£37) was obtained from the latest published NHS reference costs based on 'PSSRU 2020, Unit Costs of Health and Social Care 2019, nurse visit'.[158] Based on 6 administrations per cycle and the respective cost, the resulting administration cost per cycle is £222. The cost of administration for BSC was assumed to be £0.

The total cost of givosiran treatment per cycle, including both drug acquisition and administration costs, is [redacted]. For patients who interrupt treatment, a £0 pharmacological treatment cost is applied.

12.3.3. Cost of AHP attacks

The cost of AHP attacks is applied as a per-event cost to the proportion of the cohort having an attack. Costs are inflated to 2020 using the Hospital & Community Health Service Pay and Prices Index from the PSSRU Unit Costs of Health and Social Care 2017 (for cost sources up to 2015), and the NHS Cost Inflation Index Pay and Prices Index from the PSSRU Unit Costs of Health and Social Care 2019 (for cost sources from 2016 to 2019).

The approach to estimate the cost of AHP attacks depends on the location of treatment. A micro-costing approach is applied to the proportion of patients treating attacks with hemin at home and in urgent healthcare visits, including costs for drugs (including for hemin and management of hemin side effects, pain medications, antiemetics, antihistamines, and antipsychotics) and healthcare professional visits.

Costing of attacks treated in hospital uses a HRG approach, incorporating the NHS cost for non-elective long stay code WH08A: Unspecified Pain with CC Score 1+. The duration of inpatient hospitalisation per attack is 7.3 days, based on the mean duration of attacks requiring treatment at a healthcare facility and/or hemin administration from the EXPLORE study,[11] and validated in interviews with expert UK clinicians.[56] Costing of attacks treated in hospital also includes transportation costs and additional healthcare cost components that would not be included in the HRG cost (dietician and physiotherapist visits, albumin, PBG urine test, liver function text, liver imaging, and ultrasound).

Incorporating these components according to NHS costs and rates yields total costs per AHP attack of [redacted], [redacted], and [redacted] for attacks treated with hemin at home, in an urgent healthcare visit, and by inpatient hospitalisation, respectively.

12.3.4. Cost of AHP chronic conditions

In addition to the per-event cost of acute attacks, the model considers the per-cycle cost associated with chronic conditions, which is applied to the proportion of the cohort with each condition in each health state based on prevalence data reported by Neeleman et al. (2018) (Table 58).[19] As a conservative assumption in the absence of data in this study for the Severe health state, the prevalence of these conditions is set to be the same as for the Recurrent health state.

Table 58. Prevalence of AHP chronic conditions by health state

	Severe	Recurrent	Symptomatic	Asymptomatic
Pain	**100%**	**100%**	**92%**	**30%**
Headaches	36%	36%	29%	13%
Chest pain	9%	9%	4%	2%
Back pain	46%	46%	33%	8%
Abdomen pain	91%	91%	79%	28%
Upper Extremities pain	36%	36%	25%	4%
Lower Extremities pain	46%	46%	25%	6%
Genitalia pain	0%	0%	8%	0%
Neurological	**82%**	**82%**	**46%**	**17%**
Paraesthesias	36%	36%	8%	8%
Motor weakness	46%	46%	21%	8%
Paralysis	9%	9%	21%	2%
Urinary incontinence	0%	0%	4%	0%
Advanced Neuropathy	27%	27%	21%	0%
Psychiatric	**82%**	**82%**	**33%**	**19%**
Anxiety	46%	46%	21%	6%
Depression	36%	36%	13%	9%
Psychosis/Hallucinations	36%	36%	4%	9%
Insomnia	27%	27%	21%	11%
Suicidality	18%	18%	0%	2%

AHP: acute hepatic porphyria. Source: Neeleman et al. (2018)19

The ongoing annual cost of managing each chronic condition in England was obtained from country-specific studies, independently from the presence of AHP. Costs are inflation-adjusted to year 2020. Table 59 presents a summary of the annual cost of all AHP chronic conditions considered in the model, with respective sources.

Table 59 – Annual costs of AHP chronic conditions (updated to 2020 price level)

	Annual cost, £		
	Source	Inflated to 2020	Reference
Pain			
Headaches	468	526	McCrone et al. (2011)[159]
Chest pain	3,326	3,663	Ghosh et al. (2012)[160]
Back pain	870	915	The Guardian (2016)[161]
Abdomen pain		915	Assumed equal to back pain
Upper Extremities pain		915	Assumed equal to back pain
Lower Extremities pain		915	Assumed equal to back pain
Genitalia pain		915	Assumed equal to back pain
Neurological			
Paraesthesias	190	200	The Guardian (2016)[161]
Motor weakness	1,920	2,020	The Guardian (2016)[161]
Paralysis	10,028	10,645	Rose et al. (2015)[162]
Urinary incontinence	720	757	The Guardian (2016)[161]
Advanced Neuropathy	3,340	3,514	The Guardian (2016)[161]
Psychiatric			
Anxiety	547	681	McCrone et al. (2008)[163]
Depression	1,400	1,744	McCrone et al. (2008)[163]
Psychosis/Hallucinations	10,328	12,862	McCrone et al. (2008)[163]
Insomnia	547	681	McCrone et al. (2008)[163]
Suicidality	1,582	1,843	Knapp et al. (2011)[164]

AHP: acute hepatic porphyria

The annual cost of each chronic condition is applied to the prevalent cohort (i.e., multiplied by proportion of cohort affected) in each health state as defined in Table 58. The sum of the weighted cycle costs of all chronic conditions considered represents the total economic impact associated with AHP chronic consequences by health state (Table 60).

Table 60 – Summary of overall annual cost impact of chronic conditions by health state

Health state	Annual cost (£)
Asymptomatic	[redacted]
Symptomatic	[redacted]
Recurrent	[redacted]
Severe	[redacted]

The costs of AHP chronic conditions are applied at each cycle of the model and therefore require adjustment to fit model cycle length (6 months). All identified annual costs were therefore divided by two assuming that the 6-month cost is exactly half of the total annual cost.

12.3.5. Health-state costs

The per-cycle costs by health state, as well as the one-off costs associated with the treatment of acute attacks, are presented in Table 61.

Table 61. List of health states and associated costs in the CE model

Health-states	Base-case	OWSA Range		PSA distribution
		Lower value	Upper value	
Per-cycle costs by health state (£)				
Asymptomatic	[redacted]	[redacted]	[redacted]	Gamma
Symptomatic	[redacted]	[redacted]	[redacted]	Gamma
Recurrent	[redacted]	[redacted]	[redacted]	Gamma
Severe	[redacted]	[redacted]	[redacted]	Gamma
One-off costs of acute attack (£)				
Weighted average cost of attack treatment	[redacted]	[redacted]	[redacted]	Gamma

12.3.4. Adverse-event costs

The costs of severe treatment-related AEs (described in Section 12.2.4) that are included in the CE model are summarised in Table 62.

Table 62. List of AEs and summary of costs included in the CE model

AE	Base-case	OWSA Range		PSA distribution
		Lower value	Upper value	
Asthenia	109.00	87.64	130.36	Gamma
Lipase increased	109.00	87.64	130.36	Gamma
Iron overload	109.00	87.64	130.36	Gamma
Headache	109.00	87.64	130.36	Gamma

12.3.5. Miscellaneous costs

An end-of-life care cost is included in the current analysis and is estimated based on data and calculations reported in the NICE technology appraisal document for ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [TA451] (Table 63).[165] The total end-of-life cost of £5,248 is included in the model as a one-off cost and is applied to the proportion of new deaths at each cycle of the model.

Table 63. Data to estimate end-of-life care cost

	Model input
Proportion being treated in hospital	51.5%
EOL hospital days	21.50
Cost of palliative care in hospital (£ per day)	437.00
Proportion being treated in hospice	23.1%
EOL hospice days	17.40
Cost of community palliative care per day (£)	103.00
End-of-life care cost (£)	**5,247.80**

EOL: end of life. Source: NICE (2017)[165]

In patients with AHP, frequent use of opiates (especially at the high doses often needed to manage AHP-related pain) can increase the risk of addiction.[17,166] Therefore, the cost of opioid addiction is incorporated in the model for Recurrent and Severe patients. The per-cycle cost of opioid addiction for a patient with opioid addiction is estimated at £1,381, based on Shei et al. (2015).[167] The prevalence of opioid addiction is set at 82% in the Recurrent health state based on Neeleman et al.[19]; the same prevalence is assumed for the Severe health state.

Other opportunities for resource savings or redirection of resources that it has not been possible to quantify

In the clinician survey described in Section 12.2.5, it was noted that in the context of healthcare use related to acute AHP attacks, costs could be reduced by emergency self-administration at home or homecare administration of hemin, vascular access assessments, gabapentin use, and the use of telephone calls instead of face-to-face visits.[32]

12.4. Approach to sensitivity analysis

12.4.1. Investigation of the uncertainty around structural assumptions

Deterministic (one-way) and probabilistic sensitivity analyses were conducted on the model base-case parameters. Scenario analyses were conducted to further test the uncertainty around specific model inputs and assumptions.

12.4.2. Justification for and details of deterministic and probabilistic sensitivity analyses undertaken

Deterministic (one-way) sensitivity analysis

To evaluate the sensitivity of model results to variation in input parameters, a series of one-way sensitivity analyses were performed in which key model parameters were varied one at a time around their base-case values. The 95% confidence limits were used as the high and low values when reported in the data

reference. If not reported, the 95% CI was approximated by setting high and low values at the base-case value ± 1.96xSE. When the SE was not reported, 10% of the base-case value was used as a proxy. High and low values used in the one-way sensitivity analyses are presented in Table 65.

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to assess the robustness of the model to parameter uncertainty. In the PSA, 1000 simulations were performed in which model parameters were varied simultaneously by sampling at random from hypothetical distributions. The distributions used for each variable in the PSA are also reported in Table 65. Population characteristics were not included in the PSA since they represent first order uncertainty.

Scenario analyses

Outcomes of various scenario analyses relative to the base case are summarised in Table 64 and discussed in detail below.

Table 64. Outcomes of scenario analyses relative to the base case

#	Scenario	Incremental Costs (£)	Incremental QALYs	ICER	% change
0	Base case	[redacted]	[redacted]	[redacted]	[redacted]
1	Givosiran efficacy: recycling up to year 3	[redacted]	[redacted]	[redacted]	[redacted]
2	Probability of menopause onset based on a normal distribution fitting mean age of menopause and SD of UK women's cohort study	[redacted]	[redacted]	[redacted]	[redacted]
3	BSC efficacy: DB ENVISION for cycle 1, then probability of disease worsening up to year 5	[redacted]	[redacted]	[redacted]	[redacted]
4	Mortality Scenario Analysis	[redacted]	[redacted]	[redacted]	[redacted]
5	Alternative assumption for prevalence of chronic conditions	[redacted]	[redacted]	[redacted]	[redacted]
6	Alternative caregiver disutility assumption 1	[redacted]	[redacted]	[redacted]	[redacted]
7	Alternative caregiver disutility assumption 2	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care; DB: double blind; HR: hazard ratio; HS: health state; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life-year; SD: standard deviation; UK: United Kingdom.

Alternative extrapolation of Givosiran efficacy: recycling up to year 3

In the base case, the model assumes that the transition probabilities observed in the ENVISION OLE period continue over time beyond the duration of the OLE period. A 5-year time point was selected as a reasonable extrapolation limit for this trend. After that point, the cohort is assumed to remain stable (i.e., no further transitions between AHP severity health states, though transitions to death occur). To address the uncertainty regarding extrapolation of treatment effects beyond observed data for givosiran, a scenario analysis was performed in which health-state transitions were applied up to cycle 6, matching the 3 years of observed data from the ENVISION double-blind period and OLE, with no further health-state transitions thereafter.

Alternative menopause onset estimation: probability based on the UK Women's Cohort Study

As an alternative to the probabilistic setting of menopause onset based on Greer et al. (2003),[154] 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).[155]

Alternative extrapolation of BSC efficacy: ENVISION double-blind period for cycle 1, then probability of disease worsening up to year 5

In contrast to the base-case analysis, which adopts the highly conservative assumption that health-state transitions in the BSC arm occur only in the first model cycle, a scenario analysis was performed in which BSC efficacy was based on the placebo group in ENVISION for the first cycle, and thereafter a per-cycle

probability of disease worsening was applied to define transition to a health state one level worse (i.e., from Asymptomatic to Symptomatic, from Symptomatic to Recurrent, and from Recurrent to Severe). The probability of disease worsening was estimated based on data on time from diagnosis and AAR at 6 months in the placebo arm of the ENVISION double-blind trial. The estimated 8.4% per-cycle probability of disease worsening was applied in the placebo arm from the second cycle up to cycle 10 (year 5). This probability was also applied post-treatment discontinuation in the givosiran arm.

Mortality Scenario Analysis

In the base-case analysis, all AHP health states are assigned the same mortality HR of 1.3 compared with the general population, based on the increased risk of premature death for the overall AHP cohort in the real-world study reported by Baravelli et al. (HR 1.3, 95% CI 1.0, 1.8).[81] This approach was adopted because the classified subgroups of AHP in this cohort did not have a significant mortality difference compared with the general population (i.e., their HR 95% CIs encompassed 1.0, likely reflecting lower sample sizes in the subgroups), and it was therefore deemed most rigorous to apply the overall HR to all patients. Applying the same HR in the Asymptomatic health state, which more patients in the givosiran arm achieve, as in the other health states should be considered a conservative approach for the base case, since an increased burden of chronic conditions and thus mortality is expected in patients with greater disease severity.

In fact, despite overlapping 95% CIs, the mortality HR point estimate for AHP gene mutation carriers without porphyria symptoms in the Baravelli et al. study did differ from those in other patient subgroups: 0.7 (95% CI 0.3, 1.4) versus 1.0 (95% CI 0.5, 2.5) in AHP patients who had been hospitalised for an acute attack and 1.0 (95% CI 0.6, 1.6) in patients with porphyria symptoms who had never been hospitalised for acute attacks. To reflect the lower point estimate for patients without symptoms compared with those hospitalised for acute attacks, a scenario analysis was performed in which the overall AHP mortality HR of 1.3 was applied only to patients in the Symptomatic, Recurrent, and Severe health states, while patients in the Asymptomatic health state were assumed to have a mortality HR of 1.0 (i.e., no increased mortality relative to the general population).

Alternative assumption for prevalence of chronic conditions

In the absence of robust natural history data on the prevalence of chronic conditions in the Severe health state, the base-case analysis takes the conservative assumption that the prevalence of these conditions is the same as in the Recurrent health state. A scenario analysis was performed in which the prevalence of each chronic symptom, comorbidity and late complication was set at 20% higher than the prevalence in the Recurrent health state.

Alternative caregiver disutility assumption 1

In this scenario analysis, caregiver disutility was considered, but was set such that caregiver disutility when the patient for whom they provided care was in the Severe health state was equal to when the patient was in the Recurrent health state. This scenario analysis was performed given the absence of natural history data for the Severe health state, but should be considered as highly conservative since patients experiencing >24 attacks per year can be expected to place a substantially greater burden on caregivers than those experiencing >4 to ≤24.

Alternative caregiver disutility assumption 2

In this scenario analysis, caregiver disutility for patients in the Asymptomatic and Symptomatic health states was set at 0.

12.4.3. Summary of variables used in the sensitivity analyses

Table 65 summarises the variables used in the one-way, probabilistic, and scenario analyses.

Table 65. Model parameters in the base-case and scenario analyses

Variable	Base case	OSWA Range		PSA distribution
		Lower value	Upper value	
Discount rate outcomes	3.5%	0%	6%	–
Discount rate costs	3.5%	0%	6%	–
Initial age (years)	41.64	37.9	45.39	Gamma
Weight (kg)	[redacted]	[redacted]	[redacted]	Gamma
Proportion of females	85.7%	65.9%	97.5%	Beta
Age at menopause	Probability distribution			
Initial cohort distribution				
Asymptomatic	0.00	–	–	–
Symptomatic	0.27	0.22	0.33	Dirichlet
Recurrent	0.63	0.51	0.75	Dirichlet
Severe	0.10	0.08	0.12	Dirichlet
Extrapolation of givosiran from cycle 4 - number of cycles	7	6	8	Gamma
AAR by health state				
Asymptomatic	0.00	–	–	–
Symptomatic	2.32	2.12	2.53	Gamma
Recurrent	10.20	8.90	11.50	Gamma
Severe	33.10	28.26	37.93	Gamma
Attacks treated with hemin at home	15.0%	0.12	0.18	Dirichlet
Attacks treated in healthcare facility (outpatient)	5.0%	0.04	0.06	Dirichlet
Attacks treated in the hospital (inpatient)	80.0%	0.64	0.96	Dirichlet
Attack-related acute mortality	0	0	0	
HR death vs general population				
Asymptomatic AHP	1.3	1.045	1.555	Gamma
Symptomatic AHP	1.3	1.045	1.555	Gamma
Recurrent AHP	1.3	1.045	1.555	Gamma
Severe AHP	1.3	1.045	1.555	Gamma
Severe treatment-related AE per-cycle incidence				
Givosiran				
Asthenia	0.021	0.017	0.025	Gamma
Lipase increased	0.000	0.000	0.000	Gamma
Iron overload	0.021	0.017	0.025	Gamma
Headache	0.021	0.017	0.025	Gamma
Placebo				
Asthenia	0.000	0.000	0.000	Gamma
Lipase increased	0.022	0.017	0.026	Gamma
Iron overload	0.000	0.000	0.000	Gamma
Headache	0.000	0.000	0.000	Gamma
Acute AHP attack disutility (one-off)	-0.218	-0.515	0.000	Normal
Duration of attack (days)	7.291	5.978	8.604	Gamma
Utility decrements by health state				
Asymptomatic	[redacted]	[redacted]	[redacted]	Normal
Symptomatic	[redacted]	[redacted]	[redacted]	Normal
Recurrent	[redacted]	[redacted]	[redacted]	Normal
Severe	[redacted]	[redacted]	[redacted]	Normal
Caregiver utility decrement by health state				
Asymptomatic	-0.002	-0.106	0.000	Normal
Symptomatic	-0.045	-0.157	0.000	Normal
Recurrent	-0.142	-0.264	-0.020	Normal
Severe	-0.160	-0.268	-0.052	Normal
General population utility parameters				
Fixed	0.95086	0.76449	1.13722	Normal
Sex	0.02121	0.01705	0.02537	Normal
Age	0.00026	0.00021	0.00031	Normal
Age^2	0.00003	0.00003	0.00004	Normal
SC administration costs (per cycle, £)				
Givosiran	37.00	29.75	44.25	Gamma
Placebo	–	–	–	–
Chronic conditions costs (per cycle, £)				
Asymptomatic	[redacted]	[redacted]	[redacted]	Gamma
Symptomatic	[redacted]	[redacted]	[redacted]	Gamma
Recurrent	[redacted]	[redacted]	[redacted]	Gamma
Severe	[redacted]	[redacted]	[redacted]	Gamma
Acute attack costs (one-off, per attack, £)	[redacted]	[redacted]	[redacted]	Gamma
Cost of opioid addiction (per cycle, £)	1,381.08	1,110.39	1,651.77	Gamma
Frequency of opioid addiction (%)				

Variable	Base case	OSWA Range		PSA distribution
		Lower value	Upper value	
Recurrent	82%	0.64	0.95	Gamma
Severe	82%	0.64	0.95	Gamma
Cost of severe AEs (per event, £)				
Asthenia	109.00	87.64	130.36	Gamma
Lipase increased	109.00	87.64	130.36	Gamma
Iron overload	109.00	87.64	130.36	Gamma
Headache	109.00	87.64	130.36	Gamma
End-of-life care cost (£)	5,247.80	4,219	6,276	Gamma
ToT log-logistic parameters				
Intercept	[redacted]	[redacted]	[redacted]	Cholesky
Shape	[redacted]	[redacted]	[redacted]	Cholesky
Scale	[redacted]	[redacted]	[redacted]	Cholesky

AAR: annualised attack rate; AE: adverse event; AHP: acute hepatic porphyria

12.4.4. Rationale for omitting any parameters or variables listed above

No parameters or variables described in Section 12.4.3 were omitted from the sensitivity analyses.

12.5. Results of economic analysis

12.5.1. Base-case analysis

The ICER results for givosiran compared with BSC in terms of LYG and QALYs from the NHS/PSS direct medical perspective, are presented in Table 66. Givosiran compared with BSC yields discounted ICER of [redacted].

Table 66. Base-case results

Technologies	LY	Disc LY	QALY	Disc QALY	Costs (£)	Disc Costs (£)	ICER (£) (Cost/QALY)
Givosiran	39.63	21.33	24.36	13.37	[redacted]	[redacted]	[redacted]
BSC	39.63	21.33	7.07	4.05	[redacted]	[redacted]	[redacted]

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

Proportion of the cohorts in each health state over time

Figure **34** and

Figure **35** present the health-state distribution of the model cohort over time in the givosiran 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 contrast, 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 34. Proportion of the patient cohort across all health states over time (Markov trace) for the givosiran arm

Figure 35. Proportion of the patient cohort across all health states over time (Markov trace) for the BSC arm

BSC: best supportive care

Table 67 and Table 68 summarise the proportion of the patient cohort across all health states over time for the givosiran and the BSC arms, respectively.

Table 67. Proportion of the patient cohort across all health states over time, givosiran arm

Years	Asymptomatic	Symptomatic	Recurrent	Severe	Death
0	0.25337	0.20334	0.49402	0.04891	0.00035
0.5	0.56423	0.15918	0.27417	0.00134	0.00109
1	0.72380	0.13649	0.13344	0.00442	0.00185
1.5	0.86429	0.07095	0.05428	0.00783	0.00265
2	0.91689	0.04503	0.02375	0.01084	0.00349
2.5	0.93645	0.03455	0.01146	0.01317	0.00437
3	0.94385	0.02976	0.00621	0.01489	0.00529
3.5	0.94678	0.02705	0.00378	0.01613	0.00626
4	0.94802	0.02511	0.00256	0.01705	0.00727
4.5	0.94849	0.02358	0.00188	0.01773	0.00832
5	0.94831	0.02253	0.00149	0.01827	0.00941
6	0.94696	0.02119	0.00109	0.01904	0.01173
7	0.94530	0.02000	0.00088	0.01960	0.01423
8	0.94338	0.01892	0.00076	0.02004	0.01691
9	0.94116	0.01793	0.00068	0.02040	0.01983
10	0.93865	0.01702	0.00061	0.02072	0.02300
15	0.92172	0.01338	0.00040	0.02174	0.04276

Years	Asymptomatic	Symptomatic	Recurrent	Severe	Death
20	0.89427	0.01074	0.00028	0.02202	0.07270
25	0.85121	0.00867	0.00020	0.02159	0.11833
30	0.78793	0.00698	0.00012	0.02042	0.18454
35	0.69009	0.00609	0.00002	0.01797	0.28583
40	0.54392	0.00480	0.00001	0.01416	0.43711
45	0.34918	0.00308	0.00001	0.00909	0.63864
50	0.15058	0.00133	0.00000	0.00392	0.84417
54.5	0.04048	0.00036	0.00000	0.00105	0.95811

Table 68. Proportion of the patient cohort across all health states over time, BSC arm

Years	Asymptomatic	Symptomatic	Recurrent	Severe	Death
0	0.00000	0.27174	0.63043	0.09783	0.00000
0.5	0.13487	0.11043	0.46073	0.29327	0.00070
1	0.13477	0.11034	0.46037	0.29305	0.00147
1.5	0.13466	0.11026	0.46002	0.29282	0.00224
2	0.13455	0.11017	0.45963	0.29258	0.00307
2.5	0.13444	0.11008	0.45925	0.29233	0.00391
3	0.13431	0.10997	0.45882	0.29206	0.00483
3.5	0.13419	0.10987	0.45840	0.29179	0.00576
4	0.13405	0.10976	0.45793	0.29149	0.00676
4.5	0.13392	0.10965	0.45747	0.29120	0.00777
5	0.13377	0.10953	0.45696	0.29088	0.00886
6	0.13346	0.10928	0.45592	0.29021	0.01114
7	0.13313	0.10900	0.45478	0.28949	0.01360
8	0.13277	0.10871	0.45357	0.28872	0.01623
9	0.13239	0.10840	0.45225	0.28788	0.01908
10	0.13197	0.10806	0.45082	0.28697	0.02219
15	0.12935	0.10591	0.44188	0.28128	0.04157
20	0.12539	0.10267	0.42836	0.27267	0.07092
25	0.11935	0.09773	0.40772	0.25953	0.11566
30	0.11057	0.09054	0.37773	0.24044	0.18071
35	0.09720	0.07959	0.33206	0.21137	0.27977
40	0.07713	0.06316	0.26349	0.16772	0.42850
45	0.05020	0.04111	0.17150	0.10917	0.62802
50	0.02218	0.01816	0.07577	0.04823	0.83566
54.5	0.00619	0.00507	0.02116	0.01347	0.95410

BSC: best supportive care.

Disaggregated discounted QALYs by health state for givosiran and BSC

The discounted QALYs accrued over time by the different health states are summarised in Figure 36 and Figure 37.

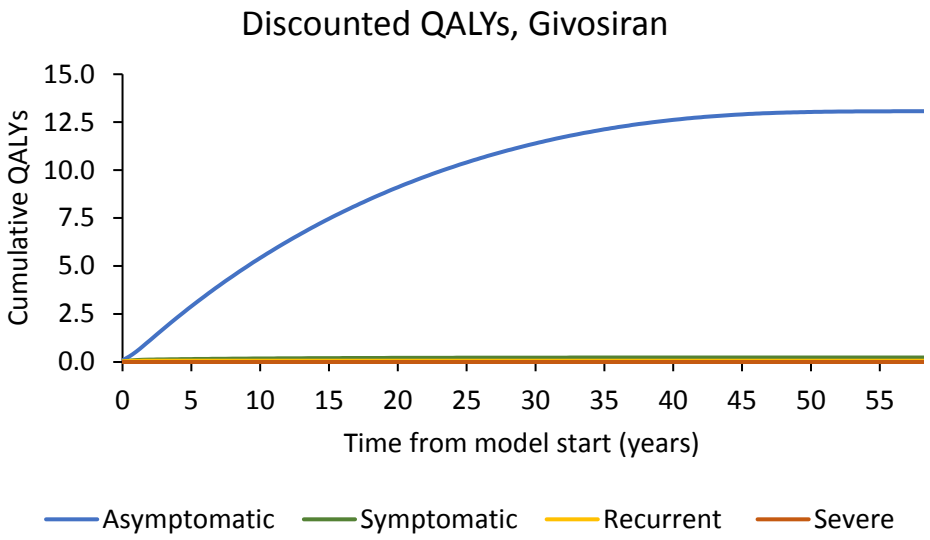


Figure 36. Discounted QALYs over time in the givosiran arm
QALYs: quality-adjusted life years

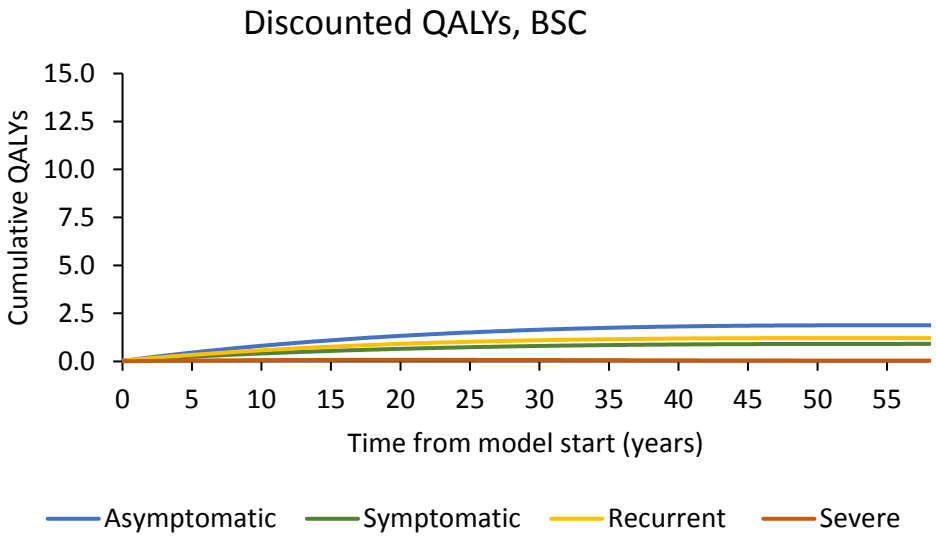


Figure 37. Discounted QALYs over time in the BSC arm
BSC: best supportive care; QALYs: quality-adjusted life years

Disaggregated undiscounted QALYs by health state for givosiran and BSC

The undiscounted QALYs accrued over time by the different health states are summarised in Figure 38 and Figure 39.

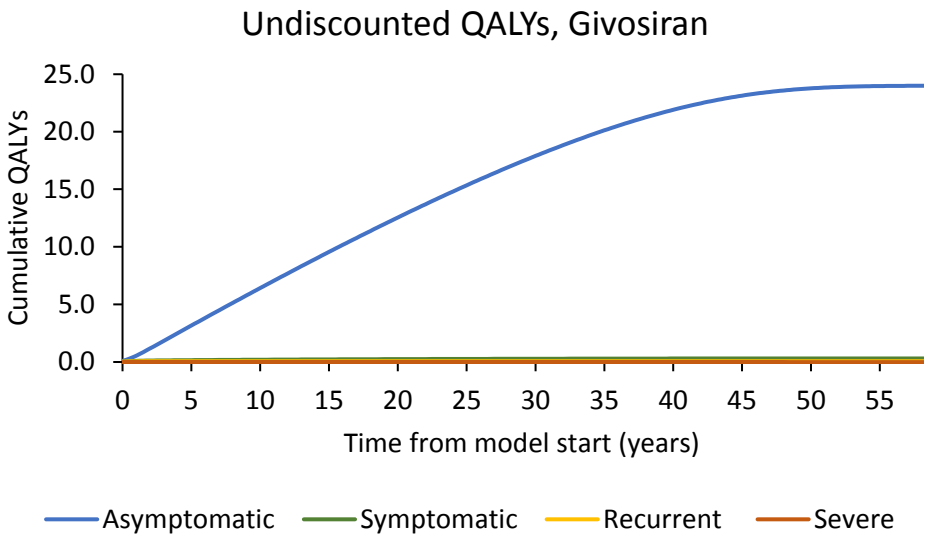


Figure 38. Undiscounted QALYs over time in the givosiran arm
QALYs: quality-adjusted life years

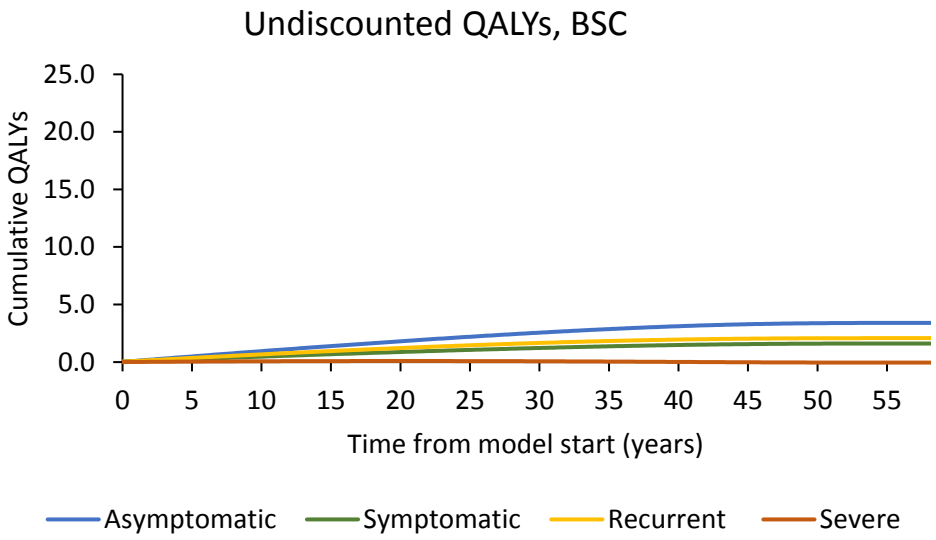


Figure 39. Undiscounted QALYs over time in the BSC arm
BSC: best supportive care; QALYs: quality-adjusted life years

Costs for givosiran and BSC by category of cost

Costs by category of cost per patient are shown in Table 69 and Table 70.

Table 69. Summary of undiscounted costs by category of cost per patient

Item	Givosiran Cost (£)	BSC Cost (£)	Increment	Absolute increment	% absolute increment
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	3,979	0	3,979	3,979	0
Chronic symptoms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attacks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	148	171	-23	23	0
Opioid addiction	3,182	67,720	-64,538	64,538	1
EOL	5,198	5,198	0	0	0
Total	[redacted]	[redacted]	[redacted]	[redacted]	***100%***

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee. AE: adverse event; BSC: best supportive care; EOL: end of life care.

Table 70. Summary of discounted costs by category of cost per patient

Item	Givosiran Cost (£)	BSC Cost (£)	Increment	Absolute increment	% absolute increment
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	3,155	0	3,155	3,155	0
Chronic symptoms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attacks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	111	94	18	18	0
Opioid addiction	2,167	36,431	-34,264	34,264	1
EOL	1,493	1,493	0	0	0
Total	[redacted]	[redacted]	[redacted]	[redacted]	***100%***

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee. AE: adverse event; BSC: best supportive care; EOL: end of life care.

Details of the costs for givosiran and BSC by health state

Cost-breakdowns by health states for givosiran and BSC are presented in Table 71.

Table 71. Cost breakdown by health-state

Undiscounted costs (£)	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Givosiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference					
Givosiran vs. BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discounted costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Givosiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference					
Givosiran vs. BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC: best supportive care

12.5.2. Sensitivity analysis results

Deterministic one-way sensitivity analysis of the 15 most influential model parameters

The percentage change in base case results following lower and upper variation in the 15 most influential model parameters are presented in Table 72 and in Figure 40.

Table 72. Percentage change in base case results following lower and upper variation in the 15 most influential model parameters

Parameters	Lower value (%)	Upper value (%)
1. **ToT log-logistic parameters- Intercept**	[redacted]	[redacted]
2. **Discount rate costs**	[redacted]	[redacted]
3. **Discount rate outcomes**	[redacted]	[redacted]

4. **Proportion of females**	[redacted]	[redacted]
5. **Initial age (years)**	[redacted]	[redacted]
6. **One-off cost (£) - Attack treatment**	[redacted]	[redacted]
7. **Attacks treated in the hospital (inpatient)**	[redacted]	[redacted]
8. **Norm of the general population, Parameters: Fixed**	[redacted]	[redacted]
9. **AAR by health-state - Severe**	[redacted]	[redacted]
10. **Duration of attack (days)**	[redacted]	[redacted]
11. **Acute AHP attack disutility**	[redacted]	[redacted]
12. **Caregivers utility decrements by health state - Recurrent AHP**	[redacted]	[redacted]
13. **Distribution of the cohort at model start - Symptomatic**	[redacted]	[redacted]
14. **Caregivers utility decrements by health state - Asymptomatic AHP**	[redacted]	[redacted]
15. **Utility decrements by health-state - Recurrent AHP**	[redacted]	[redacted]

AAR: annualised attack rate; AHP: acute hepatic porphyria; ToT: time on treatment

Figure 40. TORNADO diagram of the percentage change in base case results following lower and upper variation in the 15 most influential model parameters

AAR: annualised attack rate; AHP: acute hepatic porphyria; BSC: best supportive care; ICUR: incremental cost-utility ratio; ToT: time on treatment

Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis are described in Table 73,

Figure 41 and

Figure 42.

Table 73. Probabilistic sensitivity analysis results

	Costs (£)			QALY			ICUR
	Givosiran	BSC	Incremental	Givosiran	BSC	Incremental	(£/QALY)
Base case				13.37	4.05	9.32	
PSA mean				12.90	4.09	8.81	
PSA 95%CI lower				9.63	1.26	5.63	
PSA 95%CI upper				16.27	7.01	12.32	

BSC: best supportive care; ICUR: incremental cost-utility ratio QALY: quality-adjusted life-year

Figure 41. Results of the 1000 simulations in the PSA for the ICER of givosiran vs BSC
ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life-year.

Figure 42. CE acceptability curve
CE: cost-effectiveness; WTP: willingness-to-pay; QALY: quality-adjusted life-year.

Main findings of each of the sensitivity analyses

The main finding of the deterministic one-way sensitivity analysis was that the base-case ICUR is primarily influenced by the intercept of the log-logistic function to extrapolate ToT, the discount rates on costs and outcomes, the proportion of females in the cohort, and age at initiation of treatment with givosiran.

In the PSA, 98.3% of iterations are located in the North-East quadrant of the cost-effectiveness plane (i.e., positive incremental benefit and higher incremental cost;

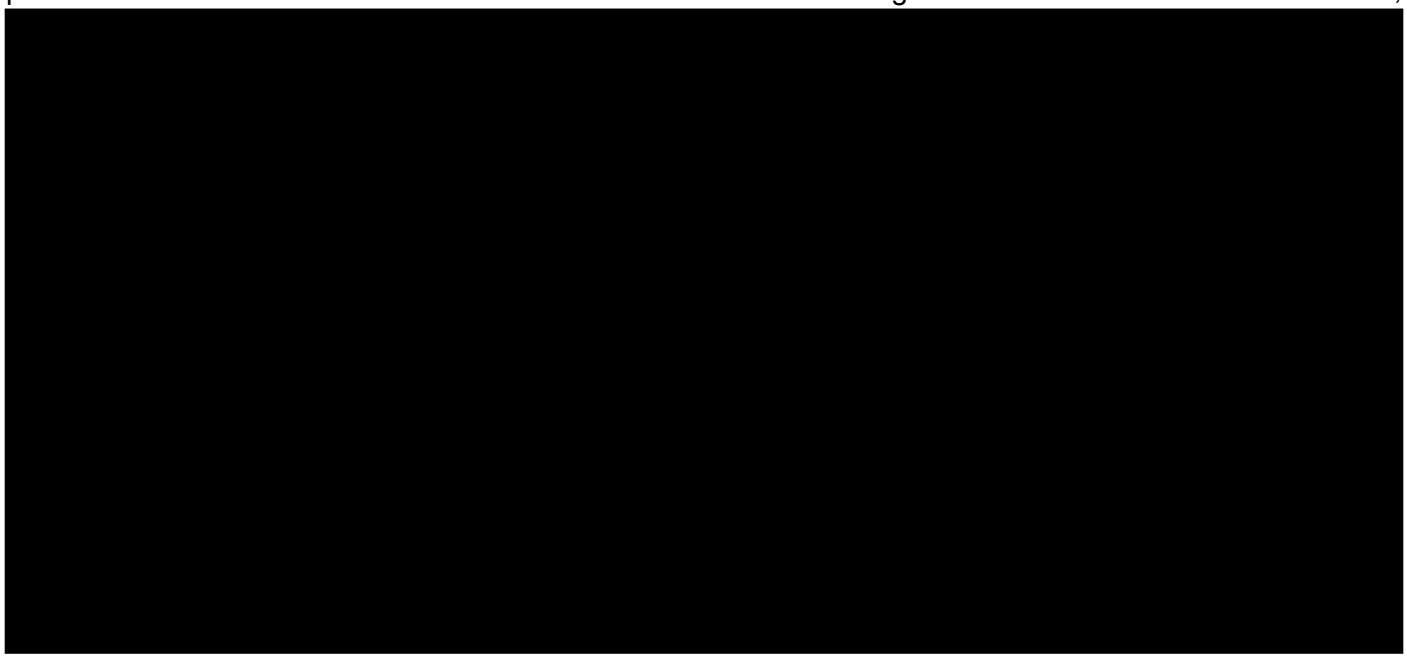


Figure 41), and 1.7% are located in the South-East quadrant (i.e., dominant vs. BSC). Overall, [redacted] of simulations fall below the cost-effectiveness threshold of £100,000/QALY (

Figure 42). The base-case ICER and the PSA mean ICER were similar (Table 73), confirming the overall robustness of the model results.

Key drivers of the cost results

As outlined in Table 72 and in Figure 40, the key drivers of the cost results are [redacted].

12.5.3. Miscellaneous results

Additional results that have not been specifically requested in this template

All relevant results have been presented in the previous sections as part of the template.

12.6. Subgroup analysis

12.6.1. Subgroup analyses

No subgroup analyses were performed for the different AHP subtypes because numbers of patients in ENVISION with subtypes other than AIP were too low for such analyses to be meaningful (n=1, 2, and 2 for HCP, VP, and unidentified mutations, respectively).[14] Because givosiran acts upstream of the steps that differentiate the AHP subtypes (see Figure 1), no difference in effect is to be expected.

12.7. Validation

12.7.1. Methods used to validate and cross-validate the model

Design of the model and its inputs

AHP is a rare disease and published UK-specific health care resource use (HCRU) data were not available. The structured interviews that were used to elicit clinical and HCRU estimates from UK clinical experts and to test assumptions relating to model structure and parameters have been described in Sections 10.1.11, 12.2.5, and 12.3.3.[32]

Model quality-check

The quality checklist used to assess the cost-effectiveness model of givosiran in AHP is based on the transparency and validation check list by Caro et al. (2012)[168] and is summarised in Table 74.

Table 74. Quality checklist for givosiran CE model

Test to be performed	Outcome
Scenario testing	
Make treatment costs equal - sense check results.	BSC drug cost set equal to givosiran drug cost and givosiran discontinuation due to any reason was set = 0. As expected, the total drug cost in BSC was higher than in givosiran arm because in BSC the proportion of female cohort with no attacks at menopause is lower and therefore fewer patients would stop treatment.
Make treatment costs for each arm very high - sense check results.	Yes, only drug costs increase
Treatment Costs: Turn off all health state costs and set AE rates to 0. Total costs should now only include treatment costs; ensure that intervention treatment costs reflect expectations given inputs.	Drug administration, health-state, attack, opioid addiction, end of life costs were put to 0. AE incidence was set = 0 in both arms. Total cost was equal to drug cost. In BSC total cost = 0.
Make AE rates equal; check that associated costs are equal (assuming AE-specific costs), and that LY or QALY results change in the right direction.	Treatment AEs in BSC was set equal to rates in givosiran arm. Only costs were impacted since we do not consider impact of AEs on survival or QoL.
If a survival treatment effect exists, examine relative time in states and make sure times make sense given transition probabilities. Use judgment on LY per state, make sure nothing looks unrealistic.	No survival treatment effect in the model.
If a treatment effect exists, set baseline event rates equal across arms, RR/HR to 1 and AE/other event rates to zero/equivalence, total LY and QALYs should be equal between arms.	Health-state transition probability matrix of givosiran was applied in BSC arm. AEs rates of givosiran were applied in BSC arm. We obtained the same QALYs. Impact of LYs is irrelevant since Incremental LYs is 0 even at base case.
Make both arms entirely equal (all costs, AE rates, OS, PFS). 1) Total LY and QALYs should be equal between arms. 2) Total costs should be equal between arms 3) Total costs per health state should be equal between arms.	Health-state transition probability matrix of givosiran was applied in BSC arm. AEs rates of givosiran were applied in BSC arm. Treatment discontinuation due to any reason in givosiran arm was set =0. BSC drug and administration cost set equal to givosiran drug cost. As a result, both arms were equal in terms of total LYs, costs and QALYs.
If a survival treatment effect exists, turn off transition probability to specific health states, one at a time (assuming multiple health states). Make sure time in state = 0 for each given health state.	No survival treatment effect in the model.

If QoL effect exists, make all utilities and disutilities = 0. Make sure total QALYs = 0	Health-state utility decrements =0, attack disutility =0, general population utility = 0. Then total QALYs in both arms = 0.
If QoL effect exists, make all utilities = 1 and disutilities = 0. Make sure total QALYs = total LYs.	Health-state utility decrements =0, attack disutility =0, general population utility = 1. Then total QALYs in both arms = total LYs.
General check	
Using Formulas | Formula Auditing | Show Formulas, check to ensure consist formulas are used, where necessary.	No issues found.
Check that discount rates are being applied correctly.	Checked in both Markov engine sheets in setting part and LYs, QALYs and costs. No issues found.
Ensure all linked cells refer back to the original source (no spider webs)	No issues found.
Check that cells have appropriate formatting (currency, same number of decimals where appropriate, etc)?	No issues found.
Markov/Survival analysis	
Are the discount rates for costs and outcomes correctly calculated?	Yes
Does the time spent in the health states add up to 1?	Yes. In the givosiran engine, the sum was done for cohort on and off treatment together.
Does the number of subjects remain constant over model cycles?	Yes = 1
Check that time horizon/ cycles/ age are linked in correctly.	Checked in look-up and the Markov engines sheet and no issues were found.
Confirm that the first row of the Markov Trace refers to the correct input.	No issues found, to make it easier to check the rows where formulas are different and cannot be dragged down were highlighted in yellow.
Confirm that cost formulas in Markov Trace refer to the right cells.	No issues found.
Confirm that QALY, LY and PFLY formulas in Markov Trace refer to the right cells.	No issues found.
Is the model type (Weibull, Exponential, Gompertz, etc) calculated correctly?	Checked with respect to ToT curve and no issues were found.
Check that PFS is never greater than OS (check that they never cross).	N/A
Check that the choice of survival functions (e.g. for Weibull) has been justified (see log-likelihood, AIC, BIC, visual inspection, etc).	The log-logistic function was selected based on visual inspection since the probability of discontinuation is expected to be high initially and then decrease over time. Exponential was the best fitting function based on BIC and AIC, however was not selected because a constant probability of discontinuation due to any reason over time does not appear realistic.
If hazard ratios have been used, check they have been applied correctly	No issues found related to mortality HRs versus general population.
Check that the hazard of death in the model doesn't fall below that of the general population.	No issues found.
OWSA	
Check results for OWSA - do they make sense?	Yes, variations around base case ICUR in all parameters move in expected direction.
Are there any problems with the OWSA macro?	No
Check the graphs (example: tornado) - does the scale make sense? Are all axes labeled properly? Is there a legend for the graph? Is the base case result clearly labeled on the graph? Is the diagram sorted?	The axis title in the Tornado diagram was missing and was added, everything else is appropriate.
Do the high and low values make sense?	All high and low values were checked and no issues were found. Confidence intervals were used when available and if not upper and lower values were estimated based on standard deviation.
For custom high/low values, is there data validation to ensure the range makes sense (ensure that the high range can't be lower than the low range; bounded appropriately)	Yes, all proportions were fixed to max 1 as upper value.
PSA	

Do the results of the PSA make sense?	Yes
Are there any problems with the PSA macro?	No
Check the scatterplot and CEAC graphs - do these make sense based on the base case results?	Yes, the CEA cloud is centered around base case results and the CEAC shows is in line with finding of approx. 45% of simulations being falling under WTP.
Check that the average cost and outcomes calculated from PSA array are close to their point estimate values.	No issues found. Mean PSA ICUR is lower by approx. 5,000 GBP compared with base case results.
Check distributions (appropriateness of types of distributions - normal, beta, gamma) and low and high estimates (95% CI and SE).	No issues found.
In the event of negative ICERs, was a net monetary benefit analysis included? Do the graph and results make sense?	N/A

AE: adverse event; AIC: Akaike information criterion; BIC: Bayesian information criterion; BSC: best supportive care; CEA: cost-effectiveness analysis; CEAC: cost-effectiveness acceptability curve; GBP: British pound sterling; HR: hazard ratio; ICUR: incremental cost utility ratio; LY: life-year; N/A: not applicable; OS: overall survival; OWSA: one-way sensitivity analysis; PFLY: progression-free life-years; PFS: progression-free survival; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life-year; QoL: quality of life; RR: risk ratio; ToT: time on treatment.

12.8. Interpretation of economic evidence

12.8.1. Consistency of the results from this cost-effectiveness analysis with the published economic literature

There is a scarcity of published data on the cost-effectiveness of treatments for AHP worldwide. The SLR described in Section 11 did not identify any economic literature for comparison.

12.8.2. Relevance of the cost- effectiveness analysis to all groups of patients and specialised services in England

The CEA results were based on clinical inputs from the pivotal RCT ENVISION which included patients from several European countries, including the UK. ENVISION is the largest randomised trial in AHP patients to date and included patients with the three most common types of AHP found in the UK. The population included a range of disease duration, differing attack rates, and patients with or without prior experience of other therapies (i.e., opiates, hemin). Since the applied settings and input data were extensively validated by UK experts, the performed CEA is relevant to the patient population in England.

12.8.3. Main strengths and weaknesses of the analysis

Strengths

- Data from the pivotal RCT ENVISION and published natural history data highly relevant to the UK were used to inform the model.
- The model structure and its inputs were either validated by or elicited from UK clinical experts with extensive experience in treating AHP.
- The model was validated and quality-assured by a recognised model quality checklist methodology.

Weaknesses

- Long-term data on the natural history of AHP in patients receiving BSC are unavailable; as a conservative assumption, health state transitions in this arm are frozen after the first model cycle (matching available data from the double-blind period of ENVISION).
- No published data were available on prevalence of chronic conditions in the Severe health state; as a conservative assumption, prevalence was set to be the same as in the Recurrent health state.

12.8.4. Further analyses that could be undertaken to enhance the robustness/completeness of the results

The external validity of the model can be enhanced in the future by the incorporation of real-world data on the effectiveness and safety of givosiran in patients in routine clinical practice in the UK. No such data were available at the time this analysis was conducted.

13. Cost to the NHS and Personal Social Services

13.1. Number of patients eligible for treatment in England over the next five years

According to the National Acute Porphyria Service (NAPS), there are currently [redacted] people with severe recurrent AHP attacks in the UK, the majority of whom would be candidates for treatment with givosiran. All of these patients are under the care of the NAPS. Of these, [redacted] patients are included in trials or a compassionate use programme. According to NAPS expert opinion, it is assumed that there will be approximately [redacted] new (incident) patients with severe recurrent acute attacks each year. This is considered a worst-case scenario from the NHS perspective, as it is based on a very conservative assumption where the increase in new patients is not offset by the expected reduction in patients who no longer need treatment. Survival estimates for givosiran and BSC are incorporated into calculations of eligible patient numbers, in accordance with the base-case cost-effectiveness analysis presented in Section 12 of the core company submission of evidence. Five-year survival is predicted to be 99% regardless of whether or not patients receive givosiran. The total estimated number of patients eligible for treatment with givosiran over 5 years is presented in Table 75.

Table 75. Givosiran eligible patients per year

	Year 1	Year 2	Year 3	Year 4	Year 5
Total eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.2. Expected uptake of givosiran and the changes in its demand over the next five years

Table 76 shows the expected uptake of givosiran over the first 5 years after introduction, based upon the latest company market research.

Table 76: Uptake and market share

Technology	Current practice	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Givosiran	0%	55%	80%	85%	93%	97%
BSC	100%	45%	20%	15%	7%	3%

Note: [redacted] patients in the UK are currently receiving givosiran as part of a compassionate use programme or clinical trials but are included in the estimated number of patients who would receive givosiran in Year 1. The increase of [redacted] patients per year is a conservative approach that does not reflect the historic stable recurrent severe population size. BSC: Best Supportive Care.

13.3. Other significant costs associated with treatment

The budget impact analysis considers various costs, as summarised in Table 77, with the introduction of givosiran within its licensed terms. These costs are consistent with those used in the base-case CEA reported in Section 12.5. The 5-year projections for these cost components are shown in Table 77.

Table 77. Treatment, administration, and pre-medication costs

Category	Year				
Givosiran	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Treatment costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs (£)	219	204	188	171	154
Chronic symptoms/comorbidities (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attacks (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A&E costs (£)	7	6	6	5	5
Opioid addiction (£)	307	52	7	1	0
End-of-life costs (£)	4	4	4	4	5
BSC	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Treatment costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs (£)	0	0	0	0	0
Chronic symptoms/comorbidities (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attacks (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A&E costs (£)	2	2	2	2	2
Opioid addiction (£)	854	852	851	849	847
End-of-life costs (£)	4	4	5	5	6

A&E: accident and emergency department; BSC: Best Supportive Care.

Liver function tests should be performed prior to initiating givosiran treatment. These tests should be repeated monthly during the first 6 months of treatment, and as clinically indicated thereafter.

13.4. Estimates of resource savings associated with the use of the technology

The introduction of givosiran is expected to lead to savings of healthcare resource usage. This is primarily driven by the demonstrated ability of givosiran to reduce the accumulation of the precursors of porphyrin (and consequently the burden of acute attacks) across patients over time. As such, the NHS is expected to benefit from a disinvestment in resources and symptomatic treatments associated with management of acute attacks and AHP-related chronic conditions.

13.5. Other opportunities for resource savings or redirection of resources that it has not been possible to quantify

As givosiran treatment alleviates the overall burden of AHP disease, it is also likely to reduce the reliance on primary care support for the management of long-term and chronic conditions associated with AHP. The same applies for other forms of care and support for AHP patients such as rehabilitation costs associated with chronic conditions and patient counselling for stress and pain management.

13.6. Costs or savings associated with givosiran that are incurred outside of the NHS and PSS

Givosiran treatment is also expected to reduce costs for caregivers, and generally provide better life opportunities and higher lifetime income for AHP patients that are seriously affected by debilitating AHP disease, most of whom are of working or child-rearing age.

13.7. Estimated budget impact for the NHS and PSS over the first year of uptake of givosiran, and over the next 5 years

Introducing givosiran for the treatment of AHP in England is projected to add less than [redacted] to the NHS budget in the first year of uptake, and is anticipated to result in a net budget impact below [redacted] in each of the first 5 years after introduction (Table 78).

Table 78: Expected budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population (patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Population expected to receive givosiran (patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
World without givosiran: total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
World with givosiran: total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.8. Main limitations within the budget impact analysis

The budget impact model is consistent with the cost-effectiveness model for givosiran in patients with AHP. As such, the budget impact analysis is subject to the same limitations, and many of the same underlying assumptions that are made in the cost-effectiveness analysis.

It is assumed in the budget impact assessment that the NHS faces the additional cost of 20% value-added tax (VAT) on drug costs, administration costs, and all other healthcare resources. However, the company does not believe that VAT is applicable to all patients across all cost categories based on the service model agreed with clinical experts and patient representatives (see Sections 8 and 12). If some of the costs of administration are not subject to VAT, the present approach will overestimate the net budget impact of givosiran.

It should also be noted that givosiran will be subject to the VPAS from September 2021. This has not been included in the analysis as the final discount is yet to be confirmed between the negotiating parties, but is currently estimated to be between 8-10%. Thus, it is highly probable that drug acquisition costs from 2022 onwards have been significantly overestimated in this budget impact analysis.

Finally, as they are an estimate of future uptake, market shares are inherently uncertain. However, the company's best estimate of the uptake of givosiran has been used in the budget impact analysis.

Section E – Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.
It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14. Impact of the technology beyond direct health benefits

14.1. Impact on costs incurred outside of the NHS and personal social services and on benefits other than health

Givosiran is anticipated to bring significant economic benefits outside the NHS in terms of improved patient and caregiver productivity, mental health and the ability to participate in activities of daily living. Although these wider economic benefits have not been quantified, the magnitude of the current burden in the absence of givosiran therapy is impacting all domains of AHP patients' QoL, including social life, relationships, psychological wellbeing, personal finances, employment and the ability to study.[26]

AHP also has an impact on work productivity, particularly in AHP patients experiencing at least one attack per year.[26] In EXPLORE, 68% of AHP patients were not in full-time work after one year of follow-up, and 21% of AHP patients had received disability payments in the past 12 months.[11] In ENVISION, 45.7% of AHP patients were not working at all, and those that were in employment reported an annual mean of 63.7 work days lost. Similarly, AHP patients in education missed on average 53.3 study days per year due to their disease.[169]

Furthermore, female patients are disproportionately impacted, as AHP predominately affects women in their reproductive years, and in some cases, the porphyria disease manifestations make taking care of children impossible.[11,26,32,33]

AHP also has an impact on caregiver productivity. A survey study by the British Porphyria Association (BPA) found that caregivers spent an average of 16 hours per week caring for AHP patients. The heaviest care burden falls on the partners of patients with acute porphyria, as they reported spending an average of 27.7 hours per week on care, followed by parents of AHP patients, who spent an average of 8.3 hours per week on caring activities.[26] In ENVISION, AHP patient caregivers reported spending on average 639.6 hours on caregiver assistance every year.[169]

14.2. Costs and cost savings to government bodies other than the NHS.

Both acute attacks and chronic symptoms experienced by AHP patients affect their ability to work and/or study. Patients frequently report having to reduce their working hours due to chronic AHP symptoms, or give up work altogether.26 This reduction in work capacity is likely to lead to increased government expenditure on unemployment benefits and statutory sick pay and decreased government revenue from income tax and National Insurance contributions.

14.3. Costs borne by patients that are not reimbursed by the NHS.

AHP patients and their caregivers face many additional costs not reimbursed by the NHS. Some of the financial costs typically borne by patients and caregivers and families that are not reimbursed by the NHS include:

- *The cost of transportation to and from hospitals to access specialised services and care, parking charges, and overnight accommodation/meals*

AHP is a rare disease and few healthcare professionals in the UK have the specialised expertise needed to treat it, with existing NAPS Highly Specialised Services located in London and Cardiff (King's College Hospital NHS Foundation Trust; University Hospital of Wales), complemented by a small number of outreach clinics.[95,96] For patients who live at a considerable distance, every visit may involve substantial travel time and transportation costs including overnight stays. The costs of the cumulative visits may be considerable and will be especially burdensome for patients who are unable to work full-time due to their disease.

- *Loss of income*

As discussed in more detail in section 14.1, AHP patients frequently report a reduction in work productivity, leading to loss of income and in approximately one fifth of cases, disability payments.[11,26]

14.4. Estimates of time spent by family members providing care.

A survey study by the BPA reports that caregivers spend an average of 16 hours per week caring for AHP patients. The heaviest care burden falls on the partners of patients with acute porphyria, who reported spending an average of 27.7 hours per week on care, followed by the parents of AHP patients, who spent an average of 8.3 hours per week on caring activities.[26]

In the EXPLORE study, 52% of caregivers holding a paying job reported losing work days due to patient's AHP, with an average of 17 work days lost in the past 12 months.[170] In ENVISION, AHP patient caregivers reported spending on average 639.6 hours on caregiver assistance every year.[171]

14.5. Impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area.

The ENVISION study was the first ever adequately powered RCT in AHP, and demonstrated superior outcomes with givosiran treatment compared to BSC.[14] The ongoing ENVISION and phase 1/2 OLEs have to date demonstrated sustained efficacy of givosiran, with no new safety signals, over more than 3 years of treatment follow-up.[51,101,102]

ELEVATE, a global, observational, longitudinal prospective registry of patients with AHP, is currently being planned. This study aims to characterise the long-term real-world safety of givosiran in patients with all types of AHP, including AHP patients with hepatic and/or renal impairment, adolescents (≥12 to <18 years of age), elderly patients (>65 years of age), and pregnant or lactating women. The NAPS will be included as a 'wave 1' site in ELEVATE.54

14.6. Anticipated impact of the technology on innovation in the UK.

Givosiran is the second member of the siRNA drug class ever approved by both EMA and FDA.[172] As a proof-of-concept of the potential of how an siRNA drug can be used to treat a rare and serious condition, givosiran is likely to inspire further research and clinical development of other siRNA drugs aimed at other medical conditions that can be treated through the silencing of disease-causing genes and proteins.

14.7. Plans for the creation of a patient registry or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

A global, observational, longitudinal prospective registry of patients with AHP (ELEVATE) is currently being planned. This study will include the NAPS as a 'wave 1' site.54

14.8. Plans on how the clinical effectiveness of the technology will be reviewed.

Givosiran has been approved by both the FDA and EMA.[1,48] No review of the clinical effectiveness of givosiran in the UK is planned outside of this submission.

14.9. Level of expertise in the relevant disease area required to ensure safe and effective use of the technology.

As directed in the product label, givosiran therapy should be initiated under the supervision of a physician knowledgeable in the management of porphyria.[2] Due to the rarity of severe recurrent AHP, givosiran treatment will be initiated exclusively within the existing highly specialised service (NAPS). A detailed patient care pathway is outlined in Sections 8.4 and 8.6.

14.10. Additional infrastructure requirements to ensure the safe and effective use of the technology and equitable access for all eligible patients.

Treatment with givosiran will be implemented within the existing highly specialised service (NAPS). No additional infrastructure will be required to ensure the safe and effective use of the technology and equitable access for all eligible patients.

15. Section F - Managed Access Arrangements

15.1. Level of engagement with clinical and patient groups to develop the MAA

Alnylam has been informed by clinical experts from the NAPS, in consultation with the BPA, of their intention to collect data on the real-world use of givosiran in UK practice. [redacted]

The main evidence base for use of givosiran in patients with AHP is the ENVISION RCT and the subsequent OLE which follow treatment rules that were pre-specified in the study protocols where monthly dosing was required continuously throughout the trials. [redacted]

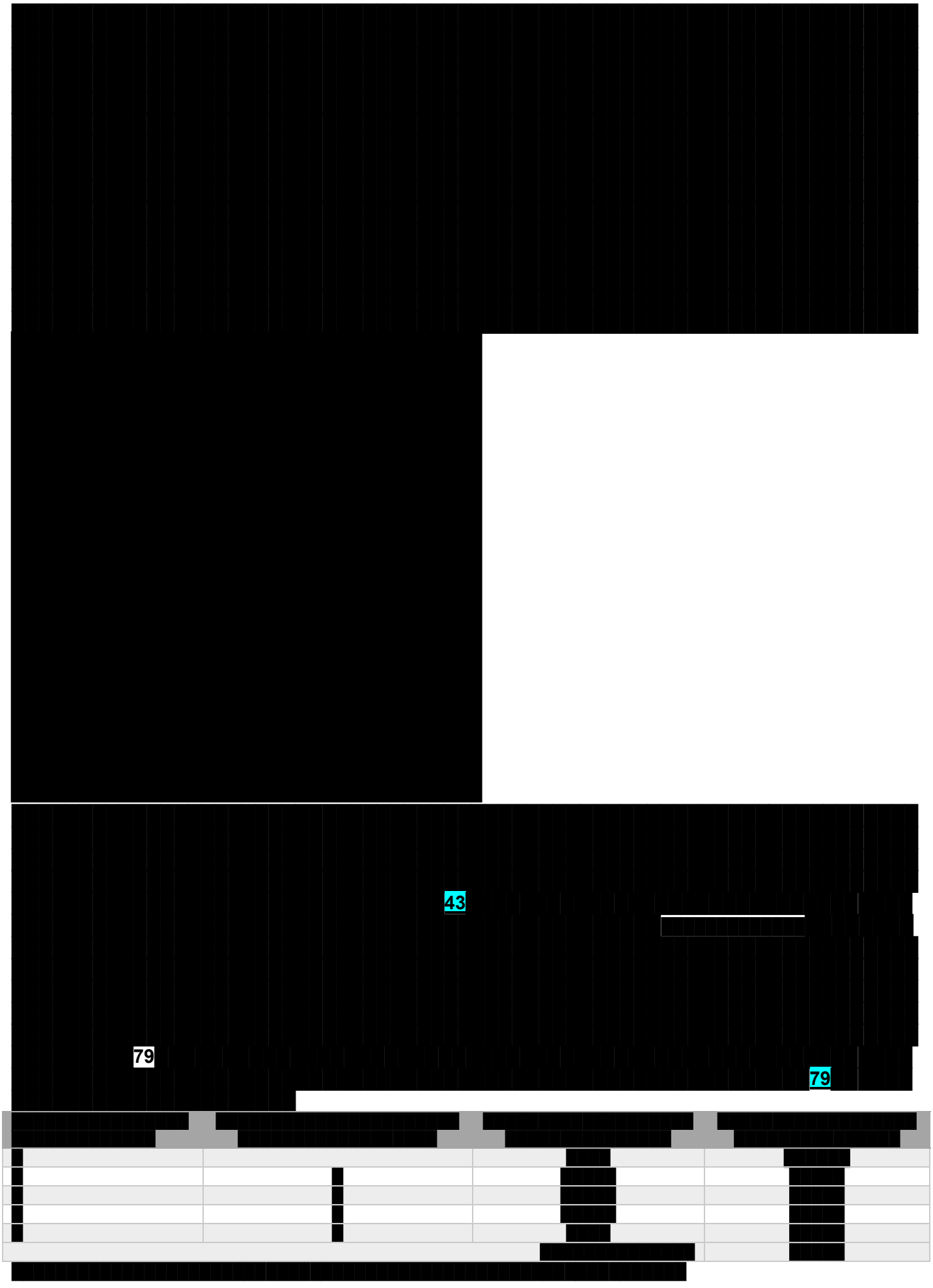
15.2. Details of the MAA proposal

[redacted]

In the event that a restricted or negative recommendation is issued after the guidance has been reviewed, patients who are no longer eligible to receive givosiran should be informed of the decision and reasoning, and continuation of treatment should be considered on compassionate grounds if warranted or feasible. It should be emphasised that givosiran is only the second product that Alnylam has ever brought to market. Thus, the considerable development and production costs of givosiran may preclude Alnylam supplying the drug at no charge in the event of a restricted or negative recommendation.

15.3. Effect of the MAA proposal on value for money

[redacted]


43
79
79

Therefore, implementation of the MAA is estimated to yield an [redacted] reduction in the use of givosiran over [redacted]. Incorporating [redacted] would decrease the net budget impact each year of the MAA [redacted] (Table 80).

Table 80. Expected budget impact with and without application of the MAA

Net budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
Without MAA, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With MAA, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MAA, Managed Access Arrangement

As shown in Table 81, application of the MAA [redacted] is calculated to reduce the ICER for givosiran vs BSC to [redacted]/QALY, compared with [redacted]/QALY in the base-case scenario, representing a [redacted] reduction in the ICER. [redacted]

Table 81. Cost-effectiveness of givosiran vs BSC in the base-case scenario and under the MAA

	Total costs (£)		Incremental costs (£)			Incre-mental	ICER (£/QALY)	
Technologies	Base-case	MAA	Base-case	MAA	QALYs	QALYs	Base-case	MAA
Undiscounted								
Givosiran	[redacted]	[redacted]	[redacted]	[redacted]	24.36	17.28	[redacted]	[redacted]
BSC	[redacted]	[redacted]			7.07			
Discounted								
Givosiran	[redacted]	[redacted]	[redacted]	[redacted]	13.37	9.32	[redacted]	[redacted]
BSC	[redacted]	[redacted]			**4.05**			

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; MAA: Managed Access Arrangement; QALY: quality-adjusted life-year.

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17. Appendices

17.1. Appendix 1: Search strategy for clinical evidence

17.1.1. The specific databases searched and the service provider used

A comprehensive literature search consisted of retrieving references from Pubmed, Embase, the Cochrane Library, the International Network of Agencies for Health Technology Assessment (INAHTA HTA) Database, PsycInfo, and Econlit. The search strategy comprised of both selected subject headings and keywords relating to AHP, including HCP, AIP, VP, and ADP. No restriction on language was made. The search strategy removed non-human studies, in-vitro studies, case studies, letters, and editorials.

17.1.2. The date on which the search was conducted.

The searches were conducted 11–13 September 2020.

17.1.3. The date span of the search.

No date span restrictions were applied to the searches.

17.1.4. The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search terms used for the main database searches are listed in Table 82.

Table 82. Search terms used for main database searches

Search Number	Search Terms	Yield
Pubmed Medline		
#1	Coproporphyria, Hereditary[MeSH Terms]	76
#2	Porphyria, Acute Intermittent[MeSH Terms]	1134
#3	Porphyria, Variegate[MeSH Terms]	95
#4	Porphyria, Acute Hepatic[Supplementary Concept]	25
#5	acute intermittent porphyria	2200
#6	acute porphyria*	3192
#7	variegate porphyria	412
#8	hereditary coproporphyria	307
#9	delta aminolevulinic acid dehydratase deficiency porphyria	216
#10	ALA dehydratase porphyria	82
#11	ALAD Porphyria	64
#12	ALAD deficiency	40
#13	ALA dehydratase deficient porphyria	40
#14	delta aminolevulinate dehydratase deficiency	31
#15	doss porphyria	34
#16	hereditary deficit of delta aminolevulinic acid dehydratase	1
#17	porphobilinogen synthase deficiency	99
#18	acute hepatic porphyria*	633
#19	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)	3595
#20	#19 NOT (Animals[MeSH Terms] NOT Humans[MeSH Terms])	3387
#21	((#20 NOT Case Reports[Publication Type]))	2256
#22	((case report*[Title] or case stud*[Title]))	299496
#23	(#21 NOT #22)	2229
#24	#20 AND Case Reports[Publication Type]	1131
#25	#20 AND #22	120
#26	(#24 OR #25)	1158
#27	((#23 NOT (Comment[Publication Type] OR Editorial[Publication Type] OR Letter[Publication Type] OR in vitro techniques[MeSH]))	2078
#28	2019/06/09:2020/09[crdt]	1705682
#29	#27 AND #28	71

#30	2019/06/09:2020/09[edat]	1666060
#31	#27 AND #30	70
#32	#29 OR #31	71
Embase		
#1	'coproporphyria'/de	278
#2	'acute intermittent porphyria'/de	2194
#3	'porphyria variegata'/de	519
#4	'acute hepatic porphyria'/de	22
#5	porphyria* NEAR/3 (intermittent OR hepatic OR variegat* OR dehydratase OR ala OR alad OR doss OR acute)	4645
#6	'hereditary coproporphyria':ab,kw,ti	344
#7	((deficiency OR deficit) NEAR/5 (alad OR dehydratase OR porphobilinogen)):ab,kw,ti	188
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	4824
#9	'animal'/exp NOT 'human'/exp	5,489,447
#10	#8 NOT #9	4438
#11	#10 AND ('animal cell'/de OR 'animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'cell culture'/de OR 'in vitro study'/de OR 'in vivo study'/de OR 'mouse model'/de OR 'nonhuman'/de)	336
#12	#10 NOT #11	4102
#13	#12 AND ('editorial'/it OR 'letter'/it)	280
#14	#12 NOT #13	3822
#15	#14 AND ('case report'/de OR 'case study'/de)	1231
#16	#14 NOT #15	2591
#17	#16 AND ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)	335
#18	#16 NOT #17	2256
#19	#18 AND [9-6-2019]/sd NOT [12-9-2020]/sd	72
#20	#17 AND [9-6-2019]/sd NOT [12-9-2020]/sd	32
Cochrane Library		
#1	MeSH descriptor: [Coproporphyria, Hereditary]	2
#2	MeSH descriptor: [Porphyria, Acute Intermittent]	10
#3	MeSH descriptor: [Porphyria, Variegate]	3
#4	(porphyria* NEAR/3 (intermittent OR hepatic OR variegat* OR dehydratase OR ala OR alad OR doss OR acute)):ti,ab,kw	57
#5	(hereditary coproporphyria):ti,ab,kw	6
#6	((deficiency OR deficit) NEAR/5 (alad OR dehydratase OR porphobilinogen)):ti,ab,kw	1
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6 with Cochrane Library publication date from Jun 2019 to Sep 2020	13
International Health Technology Assessment database		
#1	porphyria* limited to Year 2019 - 2020	0
#2	(deficiency OR deficit) AND (alad OR dehydratase OR porphobilinogen)	0
#3	"Coproporphyria, Hereditary"[mh]	0
#4	"Porphyria, Acute Intermittent"[mh]	0
#5	hereditary coproporphyria	0
#6	"Porphyria, Variegate"[mh]	0
Econlit via the American Economic Association Website		
#1	porphyria OR porphyrias	0
PsycINFO via APA PsychNet		
#1	((Any Field: (hereditary coproporphyria))) OR ((Any Field: (deficiency) OR Any Field: (deficit)) NEAR/5 (Any Field: (alad) OR Any Field: (dehydratase) OR Any Field: (porphobilinogen)))) OR ((AnyField:(porphyria* NEAR/3) (AnyField:(intermittent) OR AnyField:(hepatic) OR AnyField:(variegat*) OR AnyField:(dehydratase) OR AnyField:(ala) OR AnyField:(alad) OR AnyField:(doss) OR AnyField:(acute)))) limited to 2019 OR 2020	3

APA: American Psychological Association

17.1.5. Details of any additional searches, such as searches of company or professional organisation databases.

The search terms used for grey literature database searches are listed in Table 83.

Table 83. Grey literature database search terms

Search number	Search terms	Yield
Clinical trials.gov		
#1	porphyria AND (intermittent OR hepatic OR variegate OR dehydratase OR ala OR alad OR doss OR acute) | First posted from 06/09/2019 to 09/13/2020	3
#2	porphyria AND (intermittent OR hepatic OR variegate OR dehydratase OR ala OR alad OR doss OR acute) | Last update posted from 06/09/2019 to 09/13/2020	19
#3	hereditary coproporphyria | Results first posted from 06/09/2019 to 09/13/2020	1
#4	hereditary coproporphyria | Last update posted from 06/09/2019 to 09/13/2020	7
WHO ICTRP		
#1	Porphyria OR porphyrias in title OR porphyria in condition	40
FDA		
#1	Using Google advanced: porphyria site:https://www.fda.gov filetype:pdf	1
EMA		
#1	Using Google advanced: porphyria intermittent OR hepatic OR variegate OR dehydratase OR ala OR alad OR doss OR coproporphyria OR acute site:http://www.ema.europa.eu/ filetype:pdf	5
CADTH		
#1	Using Google advanced: porphyria intermittent OR hepatic OR variegate OR dehydratase OR ala OR alad OR doss OR coproporphyria OR acute site:https://www.cadth.ca/ filetype:pdf	2
NICE		
#1	Using Google advanced: porphyria intermittent OR hepatic OR variegate OR dehydratase OR ala OR alad OR doss OR coproporphyria OR acute site:https://www.nice.org.uk/ filetype:pdf	1
SMC		
#1	Using Google advanced: porphyria intermittent OR hepatic OR variegate OR dehydratase OR ala OR alad OR doss OR coproporphyria OR acute site:https://www.scottishmedicines.org.uk/ filetype:pdf	0
AWMSG		
#1	Using Google advanced: porphyria intermittent OR hepatic OR variegate OR dehydratase OR ala OR alad OR doss OR coproporphyria OR acute site:http://www.awmsg.org/ filetype:pdf	0

AWMSG: All Wales Medicines Strategy Group; CADTH: Canadian Agency for Drugs and Technologies in Health; EMA: European Medicines Agency; FDA: Food and Drug Administration; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium; WHO ICTRP: World Health Organisation International Clinical Trials Registry Platform

17.1.6. The inclusion and exclusion criteria.

The SLR selection criteria for published studies are summarised in Table 10.

17.1.7. The data abstraction strategy.

A summary of the number of reports identified by the literature search (total and de-duplicated) is provided in Table 84.

Table 84. Summary of literature search results: number of citations identified

Database	Total Hits	De-duplicated
Medline (Pubmed)	71	69
Embase	72	41
Embase (Conference abstracts)	32	28
INAHTA HTA	0	0
Cochrane Library	13	9

Database	Total Hits	De-duplicated
Econlit	0	0
PsychInfo	3	2
ClinicalTrials.gov	30	23
WHO ICTRP	40	40
FDA	1	1
EMA	5	5
NICE	1	1
SMC	0	0
CADTH	2	2
AWMSG	0	0
TOTAL	**270**	**221**

AWMSG: All Wales Medicines Strategy Group; CADTH: Canadian Agency for Drugs and Technologies in Health; EMA: European Medicines Agency; FDA: Food and Drug Administration; HTA: Health technology assessment; ICTRP: International Clinical Trials Registry Platform; INAHTA: International Network of Agencies for Health Technology Assessment; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium; WHO: World Health Organisation.

The search was fully documented, and results were saved in a dedicated EndNote library as well as in a Microsoft Excel workbook. The first step of the screening process involved study selection based on title and abstract, including a full-text screening for articles that were not definitively categorised via title and abstract. The second stage of screening involved a full-text screening of all citations that were identified for further evaluation and scrutiny. One reviewer screened all abstracts and articles for inclusion or exclusion. Reasons for study exclusion were documented in the Microsoft Excel workbook. A listing of the 40 identified reports, an indicator for the evidence they contain (i.e., clinical, economic, health-related quality-of-life), and details on new content published since the original SLR is provided in Table 85.

Table 85. Listing of the evidence identified in the AHP literature scan

Author (year)	Publication type	Country	Study name	Treatment	Included evidence			
					Clinical	Economic	QoL	New Information
Agarwal (2020a)[173]	Abstract	International	Phase 1	Givosiran	Yes	No	No	
Agarwal (2020b)[174]	Abstract	Sweden	DDI Study	Givosiran	Yes	No	No	Drug-drug interaction study that reported maximum PD effect of givosiran on ALA
Anderson (2019a)[175]	Abstract	International	ENVISION	Givosiran	No	No	Yes	Description of comorbidities among patients enrolled in ENVISION that affect QoL
Anderson (2019b)[176]	Abstract	International	EXPLORE	NA	No	No	Yes	Symptoms associated with impacts on QoL
Balwani (2019)[177]	Abstract	International	ENVISION	Givosiran	No	No	Yes	Description of complications that impact QoL
Balwani (2020a)[178]	Abstract	International	ENVISION	Givosiran	Yes	No	No	
Balwani (2020b)[179]	Paper	International	ENVISION	Givosiran	Yes	No	Yes	Primary report of ENVISION published in New Engl J Med
Baravelli (2020)[81]	Paper	Norway	NA	NA	No	Yes	No	Long-term sick-leave and disability pension risk
Bissell (2019a)[180]	Abstract	International	ENVISION	Givosiran	Yes	No	No	
Bissell (2019b)[181]	Abstract	International	Phase 1/2 OLE	Givosiran	Yes	No	No	
Blaylock (2020a)[182]	Paper	USA	NA	Hemin	No	Yes	No	Healthcare resource utilisation and expenditure
Blaylock (2020b)[183]	Abstract	USA	NA	Hemin	No	Yes	No	Healthcare resource utilisation
Bonkovsky (2019)[51]	Abstract	International	Phase 1/2 OLE	Givosiran	Yes	No	No	AAR, hemin use, 19April2019 data cut
Bronisch (2019)[88]	Paper	Germany	NA	NA	No	No	Yes	Description of signs and symptoms of AIP that affect QoL
CADTH (2019)[184]	HTA report	Canada	NA	Panhematin	No	Yes	No	Budget impact analysis for Panhematin in Canada (redacted)
Erwin (2020)[185]	Abstract	USA	NA	Hemin	No	Yes	No	Healthcare resource utilisation and expenditure
Gill (2019a)[186]	Abstract	United Kingdom	NA	NA	No	Yes	No	Delay in diagnosis, specialist care, hospitalisation, treatment
Gill (2019b)[26]	Abstract	United Kingdom	NA	NA	No	Yes	Yes	Symptoms and impact on QoL, impacts on employment, finances, caregiver time
Gouya (2019a)[101]	Abstract	International	ENVISION	Givosiran	Yes	No	Yes	
Gouya (2019b)[11]	Paper	International	EXPLORE	None or Hemin	Yes	Yes	Yes	Primary report of EXPLORE, published in Hepatology
Kauppinen (2020)[187]	Abstract	International	ENVISION	Givosiran	Yes	Yes	Yes	Reduction in pain during and between attacks; analgesic use; SF-12 bodily pain domain
Ko (2019)[188]	Abstract	International	NA	NA	No	Yes	Yes	Frequency of hospitalisation; common chronic symptoms of AHP affecting QoL
Ko (2020)[189]	Abstract	International	ENVISION	Givosiran Hemin prophylaxis	Yes	Yes	Yes	Healthcare resource utilisation and expenditure; hemin prophylaxis prior to study entry with rate of AHP attack

Author (year)	Publication type	Country	Study name	Treatment	Included evidence			
					Clinical	Economic	QoL	New Information
				prior to study entry				
Lakhoo (2019)[190]	Abstract	USA	NA	NA	No	Yes	Yes	Description of signs and symptoms of AHP that affect QoL; healthcare resource utilisation
Lombardelli (2019)[191]	Abstract	International (Europe)	NA	NA	No	Yes	Yes	Frequency of hospitalisation; common chronic symptoms affecting QoL
Meninger (2019)[192]	Abstract	USA	NA	NA	No	Yes	Yes	Unemployment, disability, ADL, symptoms affecting QoL, healthcare resource utilisation
Naik (2019a)[193]	Abstract	International	EXPLORE	None or Hemin	No	Yes	Yes	Hemin use and attack treatment location; symptoms of AHP affecting QoL
Naik (2019b)[194]	Abstract	USA	PROMIS	NA	No	No	Yes	PROMIS scores in AIP
Naik (2020a)[195]	Abstract	International	EXPLORE	None or Hemin	No	Yes	Yes	Hemin use and attack treatment location; symptoms of AHP affecting QoL
Naik (2020b)[18]	Paper	USA	PROMIS	NA	No	No	Yes	PROMIS scores in AIP
Rudnick (2019)[196]	Abstract	USA	NA	NA	No	Yes	Yes	Description of symptoms of AIP that affect QoL; healthcare utilisation
Salameh (2019)[197]	Abstract	International (Europe)	NA	NA	No	Yes	Yes	Frequency of hospitalisation; common chronic symptoms affecting QoL
Sardh (2019)[198]	Abstract	International	ENVISION	Givosiran	No	Yes	Yes	QoL, work productivity, caregiver burden
Sardh (2020a)[102]	Abstract	International	ENVISION OLE	Givosiran	Yes	No	No	ALA, PBG, AAR safety up to 30 months after ENVISION RCT
Sardh (2020b)[199]	Abstract	International	ENVISION	Givosiran	Yes	No	Yes	
Stein (2020)[200]	Abstract	International	Phase 1/2 OLE	Givosiran	Yes	No	No	ALA, PBG, AAR, safety after median of 24.7 months
Stölzel (2019a)[201]	Abstract	Germany	EXPLORE	NA	No	No	Yes	European and German subset of patients; chronic symptoms affecting QoL, healthcare utilisation; EQ-5D dimensions
Stölzel (2019b)[202]	Abstract	Germany	EXPLORE	NA	No	No	Yes	European and German subset of patients; chronic symptoms affecting QoL, healthcare utilisation; EQ-5D dimensions
Vassiliou (2019)[203]	Abstract	Sweden	DDI study	Givosiran	Yes	No	No	Drug-drug interaction study that assessed maximum PD effect of givosiran on ALAS1, ALA and PBG
Wang (2019)[204]	Paper	China	NA	NA	No	No	Yes	Description of clinical characteristics of AIP that affect QoL

AAR: Annualised attack rate; AHP: Acute hepatic porphyria; AIP: Acute intermittent porphyria; ALA: aminolevulinic acid; ALAS1; aminolevulinic acid synthase 1; DDI: Drug-drug interaction; EQ-5D: EuroQol 5-Dimension Questionnaire; HTA: Health technology assessment; NA: Not applicable; OLE: Open label extension; PBG: Porphobilinogen; PD: Pharmacodynamic; PROMIS: Porphyrias Consortium's Longitudinal Study; QoL: Quality of life; SF-12: 12-Item Short-Form Health Survey; USA: United States of America.

The following studies were excluded due to a lack of results reporting, study design, or because they were duplicates of included studies:

- Alnylam Pharmaceuticals. Expanded access protocol of givosiran for patients with acute hepatic porphyria. In: https://ClinicalTrials.gov/show/NCT04056481; 2020.(results not reported)
- de Paula Brandão PR, Titze-de-Almeida SS, Titze-de-Almeida R. Leading RNA interference therapeutics part 2: Silencing delta-aminolevulinic acid synthase 1, with a focus on givosiran. Mol Diagn Ther. 2020;24(1):61-68. (Study design)
- Gouya L, Ventura P, Balwani M, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. Hepatology. 2019;0(0):1-13. (Duplicate)
- Makosi DM. Knocking down the genes: Active substance givosiran take effect by means of RNA interference against acute hepatic porphyrias. Deutsche Apotheker Zeitung. 2020;160(20). (Study design)
- Siegmund-Schultze N. Acute hepatic porphyria: The RNA interference molecule givosiran is clinically highly effective. Deutsches Arzteblatt International. 2020;117(31-32):A1509. (Study design – secondary report of published study)
- Stölzel U. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. Z Gastroenterol. 2020;58(8):785. (Study design – commentary on a presentation)

17.2. Appendix 2: Search strategy for adverse events

The search strategy for AEs was identical to the one outlined in Appendix 1.

17.3. Appendix 3: Search strategy for economic evidence

The search strategy for economic evidence was identical to the one outlined in Appendix 1.

17.4. Appendix 4: Resource identification, measurement and valuation

The search strategy for Resource identification, measurement and valuation was identical to the one outlined in Appendix 1.

17.5. Appendix 5: Supplemental data

Table 86. Detailed frequencies of chronic symptoms in AIP

Symptom	Recurrent cases (n=11) (%)	Symptomatic cases (n=24) (%)	Asymptomatic controls (n=53) (%)	Linear-by-linear Chi^2 association test
Pain	100.0	91.7	30.2	P<0.001
Abdomen	90.9	79.2	28.3	
Headaches	36.4	29.2	13.2	
Chest	9.1	4.2	1.9	
Back	45.5	33.3	7.5	
Upper extremities	36.4	25.0	3.8	
Lower extremities	45.5	25.0	5.7	
Genitalia	0.0	8.3	0.0	
Neurological	81.8	45.8	17.0	P<0.001
Paraesthesia	36.4	8.3	7.5	
Motor weakness	45.5	20.8	7.5	
Paralysis	9.1	20.8	1.9	
Urinary incontinence	0.0	4.2	0.0	

Symptom	Recurrent cases (n=11) (%)	Symptomatic cases (n=24) (%)	Asymptomatic controls (n=53) (%)	Linear-by-linear Chi^2 association test
Advanced neuropathy /coma/respiratory failure	27.3	20.8	0.0	
Psychiatric	81.8	33.3	18.9	P<0.001
Anxiety	45.5	20.8	5.7	
Depression	36.4	12.5	9.4	
Psychosis/Hallucinations	36.4	4.2	9.4	
Insomnia	27.3	20.8	11.3	
Suicidality	18.2	0.0	1.9	

Note: Recurrent cases were defined as having >4 attacks per year, Symptomatic cases had at least one attack in any year that they were followed but did not meet that criteria for a Recurrent case, and Asymptomatic controls were mutation carriers who did not experience attacks. AIP: acute intermittent porphyria. Source: Neeleman et al. (2018)[19]

Table 87. Healthcare Resource Group (HRG) and PbR cost codes used in the CE model

Currency Code	Currency Description
Source for Ambulance cost	
ASC1	Calls
ASH1	Hear and treat or refer
ASS01	See and treat or refer
ASS02	See and treat and convey
Source for emergency admission cost	
VB03Z	Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment
Source for hospital stay cost	
WH08A	Unspecified Pain with CC Score 1+
Source for ICU cost	
XC01Z	Adult Critical Care, 6 or more Organs Supported
XC02Z	Adult Critical Care, 5 Organs Supported
XC03Z	Adult Critical Care, 4 Organs Supported
XC04Z	Adult Critical Care, 3 Organs Supported
XC05Z	Adult Critical Care, 2 Organs Supported
XC06Z	Adult Critical Care, 1 Organ Supported
XC07Z	Adult Critical Care, 0 Organs Supported
Source of diagnostic tests	
DAPS01	Cytology
DAPS02	Histopathology and histology
DAPS03	Integrated Blood Services
DAPS04	Clinical Biochemistry
DAPS05	Haematology
DAPS06	Immunology
DAPS07	Microbiology
DAPS08	Phlebotomy
DAPS09	Other
Source of liver function test*	
DZ52Z	Full Pulmonary Function Testing
Source of diagnostic imaging (x-ray, liver imaging and ultrasound scan)	
PF	Plain Film
RD01A	Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over
RD02A	Magnetic Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over
RD03Z	Magnetic Resonance Imaging Scan of One Area, with Pre- and Post-Contrast
RD41Z	Ultrasound Scan with duration of less than 20 minutes, with Contrast
RD43Z	Ultrasound Scan with duration of 20 minutes and over, with Contrast
Source of adverse events hemin	
HE81A	Infection or Inflammatory Reaction, due to, Internal Orthopaedic Prosthetic Devices, Implants or Grafts, with CC Score 6+
HE81B	Infection or Inflammatory Reaction, due to, Internal Orthopaedic Prosthetic Devices, Implants or Grafts, with CC Score 3-5
HE81C	Infection or Inflammatory Reaction, due to, Internal Orthopaedic Prosthetic Devices, Implants or Grafts, with CC Score 0-2

*The pulmonary function test was used a proxy because liver function test was not identified in NHS tariffs.

17.6. Appendix 6: Cost-effectiveness Model – Contains Confidential Information

17.7. Appendix 7: Budget Impact Model Report – Contains Confidential Information

17.8. Appendix 8: Budget Impact Model – Contains Confidential Information

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Givosiran for treating acute hepatic porphyria [ID1549]

Company response to ERG clarification questions

January 2021

File name	Version	Contains confidential information	Date
ID1549 Alnylam Givosiran HST Response to ERG v6.0.doc	6.0	Yes	12 January 2020

Preamble

Alnylam would like to express our sincere appreciation for the careful review by the ERG of our company submission (CS) for givosiran for treating acute hepatic porphyria (AHP). We welcome this opportunity to provide additional information to support an informed assessment of the value of givosiran in adults and young people aged 12 years or older with recurrent severe attacks of acute hepatic porphyria, per the final NICE scope.[1]

We hope that we have addressed each of the questions to the ERG's satisfaction, and would be pleased to provide any additional information that may be required. We wish to note that some of our responses contain confidential information that has been marked accordingly.

Response to ERG clarification questions

The ERG notes that a request was made on receipt of the CS for the RIS file to accompany the company's report, as well as in respect of the following evidence from the company's clinical effectiveness review:

- Baseline characteristics for the included trials
- Methodology, results, and critical appraisal of included non-randomised studies (except those evaluating acute hemin)

Response: Alnylam sent on 17 December 2020 the RIS files for the references in the CS and in the systematic literature review (SLR), along with the SLR report and appendices providing the requested evidence. We would be happy to provide any additional documentation that ERG may find helpful.

Section A: Clarification on effectiveness data

Clinical evidence

A1. The ERG understands that gonadotrophin-releasing hormone (GnRH) analogues are used as prophylactic therapy to prevent acute attacks in a sub-population of AHP patients. Please confirm whether studies evaluating these treatments were relevant for inclusion in the clinical effectiveness review? If so, please confirm that none were identified in the searches.

Response: Alnylam determined that GnRH analogue prophylaxis was not relevant for explicit inclusion in the givosiran HST submission because it is applicable only for a small number of female patients with repeated premenstrual acute attacks.[2] Thus, neither the original systematic literature review for the submission (May 2020)[3] nor the updated literature review (October 2020)[4] included specific search terms for GnRH analogues, and no studies of this therapy were identified in the searches. Clinical experts at the UK National Acute Porphyria Service (NAPS) have noted that no randomised controlled trial data exist to support GnRH analogue prophylaxis for patients with AHP.[2]

Although hormonal therapy with a GnRH analogue has been prescribed off-label for some women whose acute porphyria attacks are associated with the menstrual cycle, the relevance of this management strategy to even the subset of women for whom a GnRH analogue appears effective is limited by the requirement for long-term use in this chronic disease and because

prolonged use is associated with serious side effects, including osteoporosis and endometrial dysplasia.[5] Furthermore, a recent review by NAPS experts Dr. Stein, Dr. Badminton, and Prof. Rees noted that the strategy of add-back low-dose oestrogen to offset menopausal side effects may increase the risk of acute attacks and uterine carcinoma.[6]

Due to these major shortcomings of GnRH analogue prophylaxis in AHP, women receiving this therapy are a very limited subset of the overall AHP patient population. In the EXPLORE natural history study, only 6.3% of all patients were on a GnRH analogue for prophylaxis of attacks.[7] In the ENVISION phase 3 trial of givosiran, patients receiving GnRH analogue prophylaxis at screening could enrol if they met the inclusion criteria for porphyria attacks (≥2 in the 6 months prior to screening) and agreed to remain on GnRH treatment throughout the 6-month double-blind period.[8] However, only 4.3% all patients in ENVISION used GnRH analogues.[8]

Use of GnRH analogue prophylaxis in clinical practice for AHP patients in the UK is similarly limited. As reported at the NAPS–NHS England Commissioning for Quality and Innovation (CQUIN) meeting on 6 November 2020, only one NAPS patient was on GnRH analogue therapy in 2020. An audit of the NAPS database identified only 20 women with recurrent acute attacks who tried GnRH analogue therapy between 2000 and 2015.[2] Of the 22 courses of GnRH analogue therapy available for analysis in this audit, only 8 (36%) were deemed by the patient and clinician to have successfully reduced attack frequency. The audit also demonstrated wide variation in UK clinical practice for AHP patients in terms of the indication, duration, and monitoring of GnRH analogue use, the specific drugs used, and the treatment of side effects.[2] Therefore, not only is GnRH analogue prophylaxis not relevant to include in the clinical effectiveness review, but also the variability in its use precludes incorporating this therapy as a comparator in the cost-effectiveness model (CEM).

A2. Please clarify the statistical methods used for analysis of primary outcomes. For example, whereas the Balwani publication specifies that annualised attack rate (ARR) for attacks was analysed using a standard negative binomial regression model, the CS states that ARR was analysed using a mixed-effects regression model.

Response: Thank you for identifying this discrepancy in reporting of the statistical analysis of the ENVISION primary endpoint. Table 18 in the CS incorrectly indicates that mean composite annualised attack rate (AAR) was analysed using a mixed-effects repeated measures model, but in fact this primary endpoint was analysed using a negative binomial regression model as prespecified in the statistical analysis plan (SAP) and reported in the clinical study report (CSR) and *New England Journal of Medicine* (NEJM) publication by Balwani et al. (2020).[8-10] The rate ratios for givosiran vs. placebo on the AAR endpoints are correctly reported in CS Table 18.[8]

Furthermore, CS Table 18 incorrectly states that t-tests were used to compare givosiran vs. placebo for change in urinary levels of aminolevulinic acid (ALA) and porphobilinogen (PBG), as well as the Physical Component Summary (PCS) of the 12-item Short-Form Health Survey (SF-12), when in fact these analyses were based on a mixed-effects repeated measures model. CS Table 18 also states that a t-test was used to compare hemin use but this endpoint was actually analysed using a negative binomial regression model. Finally, results in CS Table 18 were transposed for daily worst fatigue and daily worst nausea.

The following Table 1 clarifies the statistical reporting in CS Table 18 to align with the CSR. P-values in Table 1 are as reported in the ENVISION CSR, which presents P-values to greater precision than Balwani et al. (2020), because NEJM mandates rounding up of all P-values smaller than 0.001 as P<0.001.

Table 1. Corrections to statistical reporting in CS Table 18

Outcome name (unit)	Effect Size		Statistical test	
	Value	95%CI	Type	P-value
Mean composite AAR in AIP (RR)	0.26	(0.16, 0.41)	**Negative binomial regression**	6.04×10^{-9}
LS mean urinary ALA in AIP at 3 months (mmol/mol Cr)	-18.**2**	(-22.3, -14.2)	**MMRM**	8.74×10^{-14}
LS mean urinary ALA in AIP at 6 months (mmol/mol Cr)	-19.**1**	(-26.0, -12.2)	**MMRM**	6.24×10^{-7}
LS mean urinary PBG in AIP at 6 months (mmol/mol Cr)	-36.**2**	(-49.7, -22.7)	**MMRM**	8.80×10^{-7}
Mean annualised days of hemin usage in AIP	0.23	(0.11, 0.45)	**Negative binomial regression**	2.36×10^{-5}
Mean composite AAR in AHP (RR)	0.27	(0.17, 0.43)	**Negative binomial regression**	1.36×10^{-8}
Daily worst pain (BPI-SF-NRS, range 0–10 points) **in AIP, median** AUC change from baseline**	**-10.067**	**(-22.833, 0.936)**	**Wilcoxon**	**0.0455***
Daily worst fatigue (BFI-SF NRS, range 0–10) in AIP, AUC change from baseline**	-6.940	(-19.837, 5.957)	ANCOVA	0.2876
Daily worst nausea (NRS, range: 0–10) in AIP, AUC change from baseline**	5.492	(-4.000, 14.984)	ANCOVA	0.2532
Mean proportion of days with opioid use **in AIP** over 6 months	Givosiran: 23% Placebo: 38%	NR	NR	NR
PCS of SF-12 (range 0–100) in AIP, **LS mean** change from baseline***	3.939	(0.592, 7.285)	**MMRM**	0.0216
EQ-5D-5L VAS (range 0–100) **in AIP**, **LS mean** change from baseline***	**5.8**	**(-1.5, 13.2)**	**MMRM**	**0.1186**
PGIC **in AHP** at 6 months†	Givosiran: **59.5%** Placebo: 18.4%	NR	NR	NR
PPEQ **in AHP** at 6 months (Givosiran vs Placebo, % patients)‡				
1. Travelling >1 day for work or pleasure	35.1 vs 13.2	NR	NR	NR
2. Participating in social activities	35.1 vs 7.9	NR	NR	NR
3. Planning future events	35.1 vs 10.5	NR	NR	NR
4. Doing household chores	35.1 vs 5.3	NR	NR	NR
5. Exercising moderately	32.4 vs 5.3	NR	NR	NR
6. Convenience of current porphyria treatment	72.2 vs 8.1	NR	NR	NR
7. Overall satisfaction with porphyria treatment	72.2 vs 13.5	NR	NR	NR
8. Study drug helping more normal life	66.7 vs 10.8	NR	NR	NR
Days of **work** missed **in past 4 weeks** at 6 months **in AIP** (Givosiran vs Placebo, mean)	2.4 vs 6.9	NR	NR	NR

Note: Updates to CS Table 18 are indicated by bold text.
Source: ENVISION CSR1.[8]
AAR: annualised attack rate; AHP: acute hepatic porphyria; AIP: acute intermittent porphyria; ALA: aminolevulinic acid; ANCOVA: analysis of covariance; AUC: area under the curve; BFI-SF: Brief Fatigue Inventory-Short Form; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; Cr: creatinine; CS: company submission; EQ-5D-5L: EuroQol 5-Dimension 5-Level Questionnaire; LS: least square; mmol: millimole; MMRM: mixed-effects model repeated measures; mol: mole; NR: not reported; NRS: numeric rating scale; PBG: porphobilinogen; PCS: Physical Component Summary; PGIC: Patient Global Impression of Change Questionnaire; PPEQ: Porphyria Patient Experience Questionnaire; RR: rate ratio; SF-12: 12-Item Short Form Health Survey; VAS: visual analogue scale.
*Pain data not normally distributed; ANCOVA method not valid. Post-hoc analysis using non-parametric stratified Wilcoxon method.
**A higher score indicates worse manifestation.
***A higher score indicates better physical health and functioning.

†Proportion of patients reporting “much improved” or “very much improved”. None of the placebo patients reported that their condition was “very much improved”.
‡Percentage of patients with response “Much Better” for Q1–7 or with response “Always” or “Most of the time” for Q8 at Month 6.

A3. Please provide the following data for the endpoints of ENVISION at all measured timepoints (including during the OLE):

Response: We are presenting the requested data at all 6-monthly analysis intervals, including the ENVISION double-blind period and the OLE up to Month 18, allowing us to remain in alignment with prespecified statistical analyses and quality-controlled results in the CSRs. Final OLE data are not yet available for these endpoints. In addition, OLE data were not collected at all assessment times for some endpoints, per the prespecified study protocol (e.g., pain scores were collected via eDiary only up to Month 12).

- **[A3, contd.]** Absolute and relative rate of all types of the ARR in acute intermittent porphyria (AIP) and acute hepatic porphyria (AHP) cohorts (i.e. overall (OLE only), hospitalisation, urgent healthcare visit, intravenous (IV) hemin, and treated at home without hemin)

Response: The requested AAR data, showing consistent outcomes between the AIP and AHP cohorts, are presented in Table 2. All patients in the OLE received givosiran, so relative rates for the OLE are presented as rate ratios for intra-patient comparisons of AAR between Month 6 (i.e., during the double-blind period) and either Month 12 or Month 18 in the OLE in patients who were randomised to placebo in the double-blind period.

Table 2. Annualised rate of porphyria attacks in ENVISION: composite endpoint and endpoint components in the DB period and OLE in the AIP and AHP cohorts

	AIP		AHP	
Month 6 (DB period)	**Placebo (n=43)**	**Givosiran (n=46)**	**Placebo (N=46)**	**Givosiran (N=48)**
Composite AAR				
Total attacks, n	284	83	297	90
Mean AAR (95% CI)	12.52 (9.35, 16.76)	3.22 (2.25, 4.59)	12.26 (9.22, 16.29)	3.35 (2.37, 4.74)
Rate ratio (95% CI)		0.26 (0.16, 0.41)		0.27 (0.17, 0.43)
Attacks requiring hospitalisation				
Total attacks, n	68	43	69	50
Mean AAR (95% CI)	3.21 (1.98, 5.20)	1.65 (0.98, 2.78)	3.06 (1.90, 4.94)	1.74 (1.04, 2.92)
Rate ratio (95% CI)		0.51 (0.25, 1.04)		0.57 (0.28, 1.15)
Attacks requiring urgent healthcare visit				
Total attacks, n	184	37	196	37
Mean AAR (95% CI)	7.53 (5.13, 11.05)	1.22 (0.73, 2.05)	7.51 (5.21, 10.83)	1.19 (0.72, 1.97)
Rate ratio (95% CI)		0.16 (0.09, 0.31)		0.16 (0.08, 0.30)
Attacks requiring IV hemin administration at home				
Total attacks, n*	32	3	32	3
Month 12 (OLE)	**Placebo DB/Givosiran OLE**		**Placebo DB/Givosiran OLE**	
	Month 6 (n=43)	**Month 12 (n=43)**	**Month 6 (N=46)**	**Month 12 (n=45†)**
Composite AAR (N)				
Total attacks, n	284	79	297	80
Mean individual AAR	14.33	3.51	14.01	3.39
Rate ratio (95% CI)‡		0.24 (0.18, 0.34)		0.24 (0.18, 0.34)

	AIP		AHP	
Attacks requiring hospitalisation				
Total attacks, n	68	25	69	25
Mean individual AAR	3.46	1.15	3.28	1.10
Rate ratio (95% CI)‡		0.33 (0.20, 0.54)		0.32 (0.19, 0.54)
Attacks requiring urgent healthcare visit				
Total attacks, n	184	50	196	51
Mean individual AAR	9.27	2.19	9.24	2.13
Rate ratio (95% CI)‡		0.24 (0.15, 0.36)		0.24 (0.16, 0.36)
Attacks requiring IV hemin administration at home				
Total attacks, n	32	4	32	4
Mean individual AAR	1.59	0.17	1.49	0.16
Rate ratio (95% CI)‡		0.11 (0.02, 0.53)		0.11 (0.02, 0.53)
Month 18 (OLE)	**Placebo DB/Givosiran OLE**		**Placebo DB/Givosiran OLE**	
	Month 6 (n=43)	**Month 18 (n=43)**	**Month 6 (N=46)**	**Month 18 (n=45†)**
Composite AAR				
Total attacks, n	284	119	297	121
Mean individual AAR	14.33	2.56	14.01	2.49
Rate ratio (95% CI)‡		0.18 (0.13, 0.25)		0.18 (0.13, 0.25)
Attacks requiring hospitalisation				
Total attacks, n	68	41	69	41
Mean individual AAR	3.46	0.94	3.28	0.90
Rate ratio (95% CI)‡		0.27 (0.16, 0.43)		0.26 (0.16, 0.43)
Attacks requiring urgent healthcare visit				
Total attacks, n	184	74	196	76
Mean individual AAR	9.27	1.56	9.24	1.53
Rate ratio (95% CI)‡		0.17 (0.11, 0.25)		0.17 (0.12, 0.25)
Attacks requiring IV hemin administration at home				
Total attacks, n	32	4	32	4
Mean individual AAR	1.59	0.06	1.49	0.06
Rate ratio (95% CI)‡		0.04 (0.01, 0.19)		0.04 (0.01, 0.19)

Sources: ENVISION CSR1[8]; ENVISION CSR2[11]; Alnylam, ENVISION data on file
AAR: annualised attack rate; AHP acute hepatic porphyria; AIP: acute intermittent porphyria; CI: confidence interval; DB: double-blind; OLE: open-label extension
*Negative binomial regression analysis was not performed for this component because <10 patients had this type of attack.
†One patient with follow-up duration after taking givosiran <85 days is excluded from the descriptive summaries, but is included in the negative binomial regression analysis.
‡Intra-patient comparison of AAR in OLE vs. DB period. The rate ratio and corresponding 95% CI for comparing AAR during the DB period vs during the OLE (Month 12 or Month 18 as indicated) were derived from a negative binomial regression model with period as a fixed effect and patient as a random effect with exchangeable working correlation matrix, and the logarithm of the follow-up time as an offset variable. A rate ratio <1 represents a favourable outcome for the OLE period compared with the DB period.

- **[A3, contd.]** Absolute and relative rate of analgesic use (non-opioid) in AIP and AHP cohorts

- Absolute and relative rate of opioid use in AIP cohort

Response: We report in Table 3 the absolute and relative rate of opioid and non-opioid analgesic use during the 6-month double-blind period. Results were similar in the AIP and AHP cohorts. Analysing this exploratory endpoint is complex and time-consuming because the data have to be extracted from concomitant medication records and the patient-reported eDiary, which was only used up to Month 12. Given the complexity of running the analyses and the limited time available due to the combination of the deadline, the holidays, regulatory interactions, and pandemic-related disruptions, it was not possible for the biostatisticians to

perform the Month-12 OLE analysis in time for this response. It should be noted that the ENVISION analgesia endpoint is not used to set CEM parameters, because analgesics are explicitly considered only in the context of treating acute attacks and their utilisation in this context is not derived from ENVISION but rather from UK-specific sources as explained in CS Section 12.3.3. Analgesics would also be subsumed in the cost of chronic pain management for the health-state costs, but again these parameters are not derived from ENVISION but from sources reporting costs for chronic conditions as described in CS Section 12.3.4.

Table 3. Analgesic use in the ENVISION DB period in the AIP and AHP cohorts

	AIP		AHP	
	Placebo (n=43)	Givosiran (n=46)	Placebo (N=46)	Givosiran (N=48)
Either opioid or non-opioid				
Patients with use, n (%)	43 (100.0)	41 (89.1)	45 (97.8)	43 (89.6)
Rate ratio (95% CI)		0.891 (0.805, 0.986)		0.913 (0.821, 1.014)
Opioid				
Patients with use, n (%)	38 (88.4)	31 (67.4)	38 (82.6)	32 (66.7)
Rate ratio (95% CI)		0.756 (0.602, 0.949)		0.798 (0.628, 1.014)
Non-opioid				
Patients with use, n (%)	32 (74.4)	30 (65.2)	34 (73.9)	32 (66.7)
Rate ratio (95% CI)		0.873 (0.657, 1.160)		0.899 (0.684, 1.181)

Source: Alnylam, ENVISION data on file
AHP acute hepatic porphyria; AIP: acute intermittent porphyria; CI: confidence interval; DB: double-blind

- **[A3, contd.]** Final follow-up data for monthly attack rate, urinary aminolevulinic acid (ALA), and porphobilinogen (PBG; to accompany Figures 20-22)

Response: We do not yet have final follow-up source data verification for the ENVISION OLE, and thus the graphs presented as Figures 20–22 in the CS are still the latest versions available. In these three figures, all patients have reached the Month-18 timepoint. Pandemic impacts precluded performing additional *ad hoc* interim analyses of these data at this time.

- **[A3, contd.]** Pain scores between and during acute attacks (i.e. to support the trend shown in Figure 16).

Response: The data to support CS Figure 16 (Median change from baseline in pain score by study period and all attack status in AIP patients) are presented in Table 4, along with data for AHP patients and mean daily worst pain scores in both cohorts. Because pain was captured via the daily eDiary, rather than on a schedule with many months between assessments as for the EQ-5D, many pain scores overlapped with attacks. As previously mentioned, the eDiary was completed only through Month 12, so pain scores are only available in the OLE up to that timepoint.

Table 4. Change from baseline in daily worst pain scores in the ENVISION DB period and OLE in the AIP and AHP cohorts

	AIP				AHP			
Month 6 (DB period)	Placebo (n=43)		Givosiran (n=46)		Placebo (N=46)		Givosiran (N=48)	
	During attacks	Not during attacks	During attacks	Not during attacks	During attacks	Not during attacks	During attacks	Not during attacks
n	38	43	28	46	40	46	29	48
Mean (SD)	1.63 (1.905)	-0.49 (1.514)	1.89 (2.072)	-0.66 (1.192)	1.58 (1.867)	-0.46 (1.467)	1.91 (2.038)	-0.63 (1.179)
Median (IQR)	1.75 (0.49, 2.67)	-0.41 (-1.30, 0.25)	1.37 (0.79, 3.02)	-0.59 (-1.46, 0.02)	1.56 (0.51, 2.62)	-0.39 (-1.29, 0.19)	1.41 (0.86, 2.99)	-0.51 (-1.39, 0.02)
Month 12 (OLE)	Placebo DB/Givosiran OLE		Givosiran DB/Givosiran OLE		Placebo DB/Givosiran OLE		Givosiran DB/Givosiran OLE	
	During attacks	Not during attacks	During attacks	Not during attacks	During attacks	Not during attacks	During attacks	Not during attacks
n	28	43	23	46	30	46	24	47
Mean (SD)	0.86 (2.350)	-0.73 (1.845)	1.86 (2.484)	-0.86 (1.605)	0.94 (2.288)	-0.69 (1.794)	1.90 (2.435)	-0.83 (1.603)
Median (IQR)	0.27 (-0.97, 2.41)	-0.75 (-1.73, 0.01)	0.47 (0.18, 2.71)	-0.90 (-1.77, 0.24)	0.68 (-0.86, 2.36)	-0.75 (-1.69, 0.01)	0.65 (0.21, 2.68)	-0.81 (-1.77, 0.26)

Source: Alnylam, ENVISION data on file

AHP acute hepatic porphyria; AIP: acute intermittent porphyria; DB: double-blind; IQR: interquartile range; OLE: open-label extension; SD: standard deviation

Changes <0 indicate improvement. All investigator-adjudicated attacks are included.

- **[A3, contd.]** The Porphyria Patient Experience Questionnaire (PPEQ) and Patients' Global Impression of Change (PGIC) data in AIP and AHP cohorts

Response: PPEQ results at Months 6, 12, and 18 are reported in Table 5. For additional context regarding the PPEQ, please see our response to question A6. These PPEQ results extend our understanding of the wider impact of givosiran treatment beyond improvement in proximal symptoms and current health status. PGIC data at Months 6 and 12 are reported in Table 6 (the PGIC was not administered at Month 18). For both instruments, responses were consistent in the AIP and AHP cohorts.

Table 5. PPEQ results in the ENVISION DB period and OLE in the AIP and AHP cohorts

	AIP		AHP	
	Placebo DB/ Givosiran OLE (n=43)	Givosiran DB/ Givosiran OLE (n=46)	Placebo DB/ Givosiran OLE (N=46)	Givosiran DB/ Givosiran OLE (N=48)
Q1. Traveling >1 day for work or pleasure				
Month 6 (DB period)				
Much better	5/35 (14.3)	13/36 (36.1)	5/38 (13.2)	13/37 (35.1)
Minimally better	3/35 (8.6)	5/36 (13.9)	3/38 (7.9)	6/37 (16.2)
No change	23/35 (65.7)	10/36 (27.8)	24/38 (63.2)	10/37 (27.0)
Minimally worse	2/35 (5.7)	4/36 (11.1)	2/38 (5.3)	4/37 (10.8)
Much worse	1/35 (2.9)	1/36 (2.8)	2/38 (5.3)	1/37 (2.7)
Not applicable	1/35 (2.9)	3/36 (8.3)	2/38 (5.3)	3/37 (8.1)
Month 12 (OLE)				
Much better	22/40 (55.0)	29/45 (64.4)	22/42 (52.4)	30/46 (65.2)
Minimally better	9/40 (22.5)	8/45 (17.8)	9/42 (21.4)	8/46 (17.4)
No change	5/40 (12.5)	7/45 (15.6)	7/42 (16.7)	7/46 (15.2)
Minimally worse	3/40 (7.5)	0	3/42 (7.1)	0
Much worse	1/40 (2.5)	0	1/42 (2.4)	0
Not applicable	0	1/45 (2.2)	0	1/46 (2.2)
Month 18 (OLE)				
Much better	24/37 (64.9)	33/45 (73.3)	25/39 (64.1)	33/45 (73.3)
Minimally better	6/37 (16.2)	4/45 (8.9)	7/39 (17.9)	4/45 (8.9)
No change	6/37 (16.2)	5/45 (11.1)	6/39 (15.4)	5/45 (11.1)
Minimally worse	0	1/45 (2.2)	0	1/45 (2.2)
Much worse	0	1/45 (2.2)	0	1/45 (2.2)
Not applicable	1/37 (2.7)	1/45 (2.2)	1/39 (2.6)	1/45 (2.2)
Q2. Participating in social activities				
Month 6 (DB period)				
Much better	3/35 (8.6)	13/36 (36.1)	3/38 (7.9)	13/37 (35.1)
Minimally better	5/35 (14.3)	12/36 (33.3)	5/38 (13.2)	13/37 (35.1)
No change	23/35 (65.7)	5/36 (13.9)	25/38 (65.8)	5/37 (13.5)
Minimally worse	3/35 (8.6)	3/36 (8.3)	3/38 (7.9)	3/37 (8.1)
Much worse	1/35 (2.9)	2/36 (5.6)	2/38 (5.3)	2/37 (5.4)
Not applicable	0	1/36 (2.8)	0	1/37 (2.7)
Month 12 (OLE)				
Much better	15/40 (37.5)	24/45 (53.3)	15/42 (35.7)	24/46 (52.2)
Minimally better	14/40 (35.0)	14/45 (31.1)	15/42 (35.7)	15/46 (32.6)
No change	8/40 (20.0)	7/45 (15.6)	9/42 (21.4)	7/46 (15.2)
Minimally worse	2/40 (5.0)	0	2/42 (4.8)	0
Much worse	1/40 (2.5)	0	1/42 (2.4)	0
Not applicable	0	0	0	0

	AIP		AHP	
	Placebo DB/ Givosiran OLE (n=43)	Givosiran DB/ Givosiran OLE (n=46)	Placebo DB/ Givosiran OLE (N=46)	Givosiran DB/ Givosiran OLE (N=48)
Month 18 (OLE)				
Much better	18/37 (48.6)	24/45 (53.3)	19/39 (48.7)	24/45 (53.3)
Minimally better	9/37 (24.3)	10/45 (22.2)	10/39 (25.6)	10/45 (22.2)
No change	10/37 (27.0)	10/45 (22.2)	10/39 (25.6)	10/45 (22.2)
Minimally worse	0	0	0	0
Much worse	0	0	0	0
Not applicable	0	1/45 (2.2)	0	1/45 (2.2)
Q3. Planning future events				
Month 6 (DB period)				
Much better	4/35 (11.4)	13/36 (36.1)	4/38 (10.5)	13/37 (35.1)
Minimally better	5/35 (14.3)	11/36 (30.6)	5/38 (13.2)	11/37 (29.7)
No change	20/35 (57.1)	7/36 (19.4)	22/38 (57.9)	8/37 (21.6)
Minimally worse	5/35 (14.3)	3/36 (8.3)	5/38 (13.2)	3/37 (8.1)
Much worse	1/35 (2.9)	1/36 (2.8)	2/38 (5.3)	1/37 (2.7)
Not applicable	0	1/36 (2.8)	0	1/37 (2.7)
Month 12 (OLE)				
Much better	20/40 (50.0)	25/45 (55.6)	20/42 (47.6)	25/46 (54.3)
Minimally better	11/40 (27.5)	15/45 (33.3)	11/42 (26.2)	16/46 (34.8)
No change	5/40 (12.5)	3/45 (6.7)	7/42 (16.7)	3/46 (6.5)
Minimally worse	2/40 (5.0)	1/45 (2.2)	2/42 (4.8)	1/46 (2.2)
Much worse	1/40 (2.5)	0	1/42 (2.4)	0
Not applicable	1/40 (2.5)	1/45 (2.2)	1/42 (2.4)	1/46 (2.2)
Month 18 (OLE)				
Much better	19/37 (51.4)	29/45 (64.4)	20/39 (51.3)	29/45 (64.4)
Minimally better	10/37 (27.0)	9/45 (20.0)	11/39 (28.2)	9/45 (20.0)
No change	6/37 (16.2)	6/45 (13.3)	6/39 (15.4)	6/45 (13.3)
Minimally worse	2/37 (5.4)	0	2/39 (5.1)	0
Much worse	0	0	0	0
Not applicable	0	1/45 (2.2)	0	1/45 (2.2)
Q4. Doing household chores				
Month 6 (DB period)				
Much better	2/35 (5.7)	13/36 (36.1)	2/38 (5.3)	13/37 (35.1)
Minimally better	6/35 (17.1)	9/36 (25.0)	7/38 (18.4)	10/37 (27.0)
No change	21/35 (60.0)	8/36 (22.2)	22/38 (57.9)	8/37 (21.6)
Minimally worse	5/35 (14.3)	3/36 (8.3)	5/38 (13.2)	3/37 (8.1)
Much worse	1/35 (2.9)	2/36 (5.6)	2/38 (5.3)	2/37 (5.4)
Not applicable	0	1/36 (2.8)	0	1/37 (2.7)
Month 12 (OLE)				
Much better	15/40 (37.5)	21/45 (46.7)	15/42 (35.7)	22/46 (47.8)
Minimally better	8/40 (20.0)	13/45 (28.9)	9/42 (21.4)	13/46 (28.3)
No change	13/40 (32.5)	9/45 (20.0)	13/42 (31.0)	9/46 (19.6)
Minimally worse	2/40 (5.0)	1/45 (2.2)	3/42 (7.1)	1/46 (2.2)
Much worse	2/40 (5.0)	0	2/42 (4.8)	0
Not applicable	0	1/45 (2.2)	0	1/46 (2.2)
Month 18 (OLE)				
Much better	18/37 (48.6)	24/45 (53.3)	19/39 (48.7)	24/45 (53.3)
Minimally better	9/37 (24.3)	10/45 (22.2)	10/39 (25.6)	10/45 (22.2)
No change	8/37 (21.6)	10/45 (22.2)	8/39 (20.5)	10/45 (22.2)
Minimally worse	2/37 (5.4)	0	2/39 (5.1)	0
Much worse	0	0	0	0
Not applicable	0	1/45 (2.2)	0	1/45 (2.2)

	AIP		AHP	
	Placebo DB/ Givosiran OLE (n=43)	Givosiran DB/ Givosiran OLE (n=46)	Placebo DB/ Givosiran OLE (N=46)	Givosiran DB/ Givosiran OLE (N=48)
Q5. Exercising moderately				
Month 6 (DB period)				
Much better	2/35 (5.7)	12/36 (33.3)	2/38 (5.3)	12/37 (32.4)
Minimally better	5/35 (14.3)	9/36 (25.0)	5/38 (13.2)	9/37 (24.3)
No change	23/35 (65.7)	7/36 (19.4)	25/38 (65.8)	8/37 (21.6)
Minimally worse	4/35 (11.4)	4/36 (11.1)	4/38 (10.5)	4/37 (10.8)
Much worse	1/35 (2.9)	2/36 (5.6)	1/38 (2.6)	2/37 (5.4)
Not applicable	0	2/36 (5.6)	1/38 (2.6)	2/37 (5.4)
Month 12 (OLE)				
Much better	15/40 (37.5)	23/45 (51.1)	15/42 (35.7)	23/46 (50.0)
Minimally better	8/40 (20.0)	8/45 (17.8)	8/42 (19.0)	9/46 (19.6)
No change	12/40 (30.0)	11/45 (24.4)	13/42 (31.0)	11/46 (23.9)
Minimally worse	2/40 (5.0)	2/45 (4.4)	3/42 (7.1)	2/46 (4.3)
Much worse	2/40 (5.0)	0	2/42 (4.8)	0
Not applicable	1/40 (2.5)	1/45 (2.2)	1/42 (2.4)	1/46 (2.2)
Month 18 (OLE)				
Much better	18/37 (48.6)	24/45 (53.3)	19/39 (48.7)	24/45 (53.3)
Minimally better	7/37 (18.9)	9/45 (20.0)	8/39 (20.5)	9/45 (20.0)
No change	8/37 (21.6)	9/45 (20.0)	8/39 (20.5)	9/45 (20.0)
Minimally worse	3/37 (8.1)	1/45 (2.2)	3/39 (7.7)	1/45 (2.2)
Much worse	1/37 (2.7)	1/45 (2.2)	1/39 (2.6)	1/45 (2.2)
Not applicable	0	1/45 (2.2)	0	1/45 (2.2)
Q6. Convenience of current porphyria treatment				
Month 6 (DB period)				
Much better	3/34 (8.8)	26/35 (74.3)	3/37 (8.1)	26/36 (72.2)
Minimally better	4/34 (11.8)	5/35 (14.3)	5/37 (13.5)	5/36 (13.9)
No change	21/34 (61.8)	3/35 (8.6)	22/37 (59.5)	4/36 (11.1)
Minimally worse	3/34 (8.8)	0	4/37 (10.8)	0
Much worse	3/34 (8.8)	1/35 (2.9)	3/37 (8.1)	1/36 (2.8)
Month 12 (OLE)				
Much better	33/40 (82.5)	36/44 (81.8)	33/42 (78.6)	36/45 (80.0)
Minimally better	2/40 (5.0)	3/44 (6.8)	4/42 (9.5)	4/45 (8.9)
No change	5/40 (12.5)	3/44 (6.8)	5/42 (11.9)	3/45 (6.7)
Minimally worse	0	2/44 (4.5)	0	2/45 (4.4)
Much worse	0	0	0	0
Month 18 (OLE)				
Much better	32/37 (86.5)	39/45 (86.7)	33/39 (84.6)	39/45 (86.7)
Minimally better	1/37 (2.7)	3/45 (6.7)	2/39 (5.1)	3/45 (6.7)
No change	4/37 (10.8)	2/45 (4.4)	4/39 (10.3)	2/45 (4.4)
Minimally worse	0	1/45 (2.2)	0	1/45 (2.2)
Much worse	0	0	0	0
Q7. Overall satisfaction with porphyria treatment				
Month 6 (DB period)				
Much better	5/34 (14.7)	26/35 (74.3)	5/37 (13.5)	26/36 (72.2)
Minimally better	6/34 (17.6)	5/35 (14.3)	7/37 (18.9)	5/36 (13.9)
No change	18/34 (52.9)	2/35 (5.7)	19/37 (51.4)	3/36 (8.3)
Minimally worse	2/34 (5.9)	1/35 (2.9)	3/37 (8.1)	1/36 (2.8)
Much worse	3/34 (8.8)	1/35 (2.9)	3/37 (8.1)	1/36 (2.8)
Month 12 (OLE)				
Much better	32/40 (80.0)	38/44 (86.4)	32/42 (76.2)	38/45 (84.4)
Minimally better	3/40 (7.5)	4/44 (9.1)	5/42 (11.9)	5/45 (11.1)
No change	4/40 (10.0)	1/44 (2.3)	4/42 (9.5)	1/45 (2.2)
Minimally worse	1/40 (2.5)	1/44 (2.3)	1/42 (2.4)	1/45 (2.2)
Much worse	0	0	0	0

	AIP		AHP	
	Placebo DB/ Givosiran OLE (n=43)	Givosiran DB/ Givosiran OLE (n=46)	Placebo DB/ Givosiran OLE (N=46)	Givosiran DB/ Givosiran OLE (N=48)
Month 18 (OLE)				
Much better	34/37 (91.9)	40/45 (88.9)	35/39 (89.7)	40/45 (88.9)
Minimally better	0	5/45 (11.1)	1/39 (2.6)	5/45 (11.1)
No change	2/37 (5.4)	0	2/39 (5.1)	0
Minimally worse	1/37 (2.7)	0	1/39 (2.6)	0
Much worse	0	0	0	0
Q8. Study drug helping return to more normal life				
Month 6 (DB period)				
Always	2/34 (5.9)	15/35 (42.9)	2/37 (5.4)	15/36 (41.7)
Most of the time	1/34 (2.9)	9/35 (25.7)	2/37 (5.4)	9/36 (25.0)
Sometimes	5/34 (14.7)	3/35 (8.6)	5/37 (13.5)	3/36 (8.3)
Rarely	8/34 (23.5)	4/35 (11.4)	8/37 (21.6)	5/36 (13.9)
Never	18/34 (52.9)	4/35 (11.4)	20/37 (54.1)	4/36 (11.1)
Month 12 (OLE)				
Always	13/40 (32.5)	25/44 (56.8)	13/42 (31.0)	25/45 (55.6)
Most of the time	14/40 (35.0)	9/44 (20.5)	14/42 (33.3)	9/45 (20.0)
Sometimes	8/40 (20.0)	9/44 (20.5)	8/42 (19.0)	10/45 (22.2)
Rarely	3/40 (7.5)	1/44 (2.3)	5/42 (11.9)	1/45 (2.2)
Never	2/40 (5.0)	0	2/42 (4.8)	0
Month 18 (OLE)				
Always	14/37 (37.8)	21/45 (46.7)	14/39 (35.9)	21/45 (46.7)
Most of the time	18/37 (48.6)	15/45 (33.3)	20/39 (51.3)	15/45 (33.3)
Sometimes	4/37 (10.8)	8/45 (17.8)	4/39 (10.3)	8/45 (17.8)
Rarely	1/37 (2.7)	0	1/39 (2.6)	0
Never	0	1/45 (2.2)	0	1/45 (2.2)

Source: Alnylam, ENVISION data on file
AHP acute hepatic porphyria; AIP: acute intermittent porphyria; DB: double-blind; OLE: open-label extension; PPEQ: Porphyria Patient Experience Questionnaire
Results are reported as n/N (%).

Table 6. PGIC results in the ENVISION DB period and OLE in the AIP and AHP cohorts

	AIP		AHP	
	Placebo DB/ Givosiran OLE (n=43)	Givosiran DB/ Givosiran OLE (n=46)	Placebo DB/ Givosiran OLE (N=46)	Givosiran DB/ Givosiran OLE (N=48)
Month 6 (DB period)				
Improved	13/35 (37.1)	32/36 (88.9)	14/38 (36.8)	33/37 (89.2)
Very Much Improved	0	10/36 (27.8)	0	10/37 (27.0)
Much Improved	7/35 (20.0)	12/36 (33.3)	7/38 (18.4)	12/37 (32.4)
Minimally Improved	6/35 (17.1)	10/36 (27.8)	7/38 (18.4)	11/37 (29.7)
No Change	15/35 (42.9)	1/36 (2.8)	16/38 (42.1)	1/37 (2.7)
Worse	7/35 (20.0)	3/36 (8.3)	8/38 (21.1)	3/37 (8.1)
Very Much Worse	0	1/36 (2.8)	0	1/37 (2.7)
Much Worse	1/35 (2.9)	0	2/38 (5.3)	0
Minimally Worse	6/35 (17.1)	2/36 (5.6)	6/38 (15.8)	2/37 (5.4)
Very Much Improved and Much Improved	7/35 (20.0)	22/36 (61.1)	7/38 (18.4)	22/37 (59.5)
Very Much Worse and Much Worse	1/35 (2.9)	1/36 (2.8)	2/38 (5.3)	1/37 (2.7)
Missing	8	10	8	11

	AIP		AHP	
	Placebo DB/ Givosiran OLE (n=43)	Givosiran DB/ Givosiran OLE (n=46)	Placebo DB/ Givosiran OLE (N=46)	Givosiran DB/ Givosiran OLE (N=48)
Month 12 (OLE)				
Improved	37/40 (92.5)	44/45 (97.8)	38/42 (90.5)	45/46 (97.8)
Very Much Improved	12/40 (30.0)	21/45 (46.7)	12/42 (28.6)	21/46 (45.7)
Much Improved	20/40 (50.0)	15/45 (33.3)	20/42 (47.6)	15/46 (32.6)
Minimally Improved	5/40 (12.5)	8/45 (17.8)	6/42 (14.3)	9/46 (19.6)
No Change	0	0	0	0
Worse	3/40 (7.5)	1/45 (2.2)	4/42 (9.5)	1/46 (2.2)
Very Much Worse	0	0	0	0
Much Worse	0	0	0	0
Minimally Worse	3/40 (7.5)	1/45 (2.2)	4/42 (9.5)	1/46 (2.2)
Very Much Improved and Much Improved	32/40 (80.0)	36/45 (80.0)	32/42 (76.2)	36/46 (78.3)
Very Much Worse and Much Worse	0	0	0	0
Missing	3	1	4	2

Source: Alnylam, ENVISION data on file
AHP acute hepatic porphyria; AIP: acute intermittent porphyria; DB: double-blind; OLE: open-label extension; PGIC: Patient Global Impression of Change
Results are reported as n/N (%).

- **[A3, contd.]** Variance data for the ARR in the Phase 1/2 OLE (p.60).

Response: In Table 7 we report the following measures of dispersion for the AAR data from the Phase 1/2 study and OLE: standard error, interquartile range, minimum, and maximum values. Data are presented for all patients as well as separately by treatment assignment in Study 001 to allow cross-referencing to the results reported on CS page 60.

Table 7. AAR results in the Phase 1/2 study and OLE

	Study 001 run-in period	Study 001 6-month treatment and follow-up period	Study 002 overall treatment period	Study 002 intended dose period*
All patients (N=16)				
Mean (SE)†	17.0 (3.5)	9.6 (1.9)	0.9 (0.3)	0.6 (0.2)
Median	14.8	7.5	0.6	0.3
IQR	8.2, 30.8	3.1, 15.0	0.0, 1.2	0.0, 0.8
Min, Max	0.0, 46.7	0.0, 27.8	0.0, 3.5	0.0, 3.1
Change from run-in, %‡		-43.2	-94.9	-96.7
Study 001 placebo/Study 002 givosiran (n=4)				
Mean (SE)†	20.2 (5.7)	16.6 (4.9)	0.8 (0.6)	0.3 (0.2)
Median	18.3	17.7	0.3	0.3
IQR	10.7, 27.9	10.7, 22.9	0.0, 1.5	0.0, 0.7
Min, Max	6.6, 34.0	4.0, 27.8	0.0, 2.4	0.0, 0.8
Change from run-in, %‡		-17.9	-96.3	-98.3
Study 001 givosiran/Study 002 givosiran (n=12)				
Mean (SE)†	16.2 (4.1)	7.3 (1.6)	0.9 (0.3)	0.6 (0.3)
Median	14.1	6.1	0.6	0.3
IQR	8.0, 31.2	2.2, 13.4	0.0, 1.2	0.0, 0.9
Min, Max	0.0, 46.7	0.0, 15.2	0.0, 3.5	0.0, 3.1
Change from run-in, %‡		-54.8	-94.4	-96.0

Source: Alnylam, Study 002 data on file
AAR: annualised attack rate; IQR: interquartile range; SE: standard error of the mean
*Intended dose period starts from the date the first givosiran dose was received in Study 002.
†Duration-weighted mean AAR; SE is calculated using Cochran's formula (1977).

‡Percent change from run-in in AAR is calculated based on the mean AAR from each post-treatment period compared to the mean AAR during run-in period.

- **[A3, contd.]** Please provide full data to support the statements about the results during the OLE period on p58 of the CS, where these have not been provided.

Response: Below we provide the requested data for the ENVISION OLE. Where applicable, the numbers from CS page 58 have been updated to reflect the Month-18 data cut.

- *CS p 58: An increase in the percentage of patients taking givosiran with zero days of hemin use from the RCT to the OLE period (54.3% vs 70.2%).*

Please refer to Table 8 below. This analysis is available only for the double-blind period and up to Month 12 in the OLE.

Table 8. Patients with 0 days of hemin use in the ENVISION DB and OLE periods, in patients randomised to givosiran in the DB period

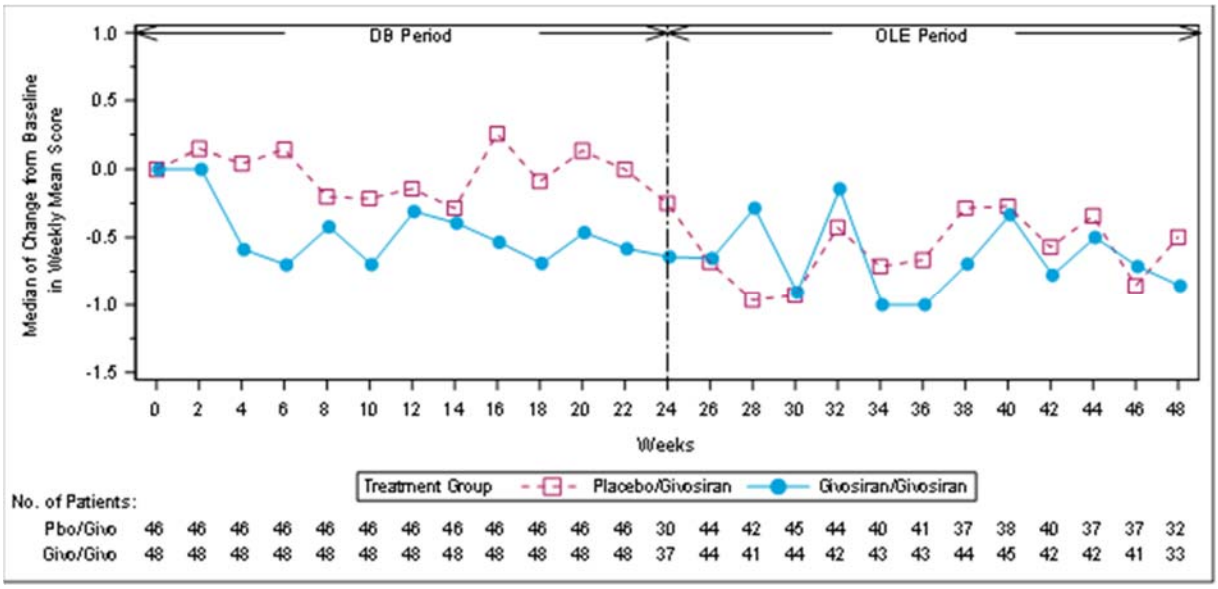
	DB period	OLE (Month 12)
Number of patients with 0 days of hemin use, n/N (%)	26/48 (54)	33/47 (70)

Sources: ENVISION CSR1[8]; Sardh et al. (2020)[12]
DB: double-blind; OLE: open-label extension

- *CS p 58: Maintenance of reductions in pain in givosiran-treated patients and decreased pain among patients crossing over from placebo:*

Please refer to Table 4 above and Figure 1 below.

Figure 1. Median change from baseline in weekly mean of daily worst pain scores during the ENVISION DB and OLE periods



Source: ENVISION CSR2[11]
DB: double-blind; OLE: open-label extension

- *CS p 58: Reductions in opioid or non-opioid analgesic use among patients crossing over to givosiran from placebo (28.5% of days reduced to 23.5% of days).*

These percentages appear to have been inadvertently carried over in the submitted CS from an early draft based only on interim ENVISION data. The described trend no longer applies to the updated percentages with the Month 18 OLE data as shown in Table 9. Comparison of results from different time periods is complicated by the fact that analgesic use was calculated from both eDiary records and concomitant medication forms up to Month 12 but only from the latter after Month 12 up to Month 18.

Table 9. Percentage of days with either opioid or non-opioid analgesic use in the ENVISION DB period and OLE

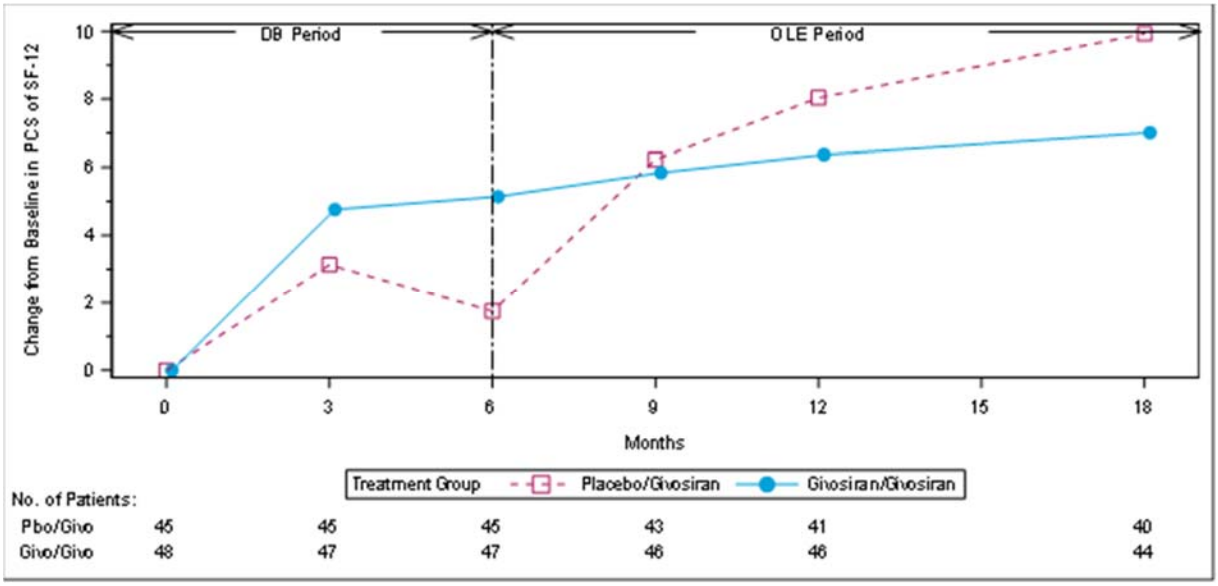
	Placebo DB/Givosiran OLE (N=46)	Givosiran DB/Givosiran OLE (N=48)
Mean (SD)		
DB period	44.97 (39.79)	32.08 (37.28)
OLE period		
Month 12	43.47 (40.47)	34.75 (35.11)
Month 18	55.46 (39.33)	51.69 (35.14)
Median (IQR)		
DB period	7.64 (0.58, 25.44)	2.42 (0, 16.00)
OLE period		
Month 12	19.01 (6.06, 86.73)	23.32 (2.65, 66.83)
Month 18	33.33 (2.18, 64.82)	44.93 (1.13, 63.80)

Source: ENVISION CSR2[11] (Appendix Tables 14.2.4.8.3, 14.2.4.8.3.1)
DB: double-blind; IQR: interquartile range; OLE: open-label extension; SD: standard deviation

- *CS p 58: Sustained levels of physical function (SF-12 PCS scores) among patients randomised to givosiran and improvement among patients crossing over from placebo.*

Please see Figure 2.

Figure 2. Mean change from baseline in Physical Component Summary of SF-12 by visit during the ENVISION DB period and OLE



Source: ENVISION CSR2[11]

DB: double-blind; OLE: open-label extension; PCS: Physical Component Summary; SF-12: 12-item Short Form Health Survey

- *CS p 58: Further increases to almost maximum PGIC scores (97.8%) among patients maintained on givosiran and similar improvements among patients crossing over from placebo (88.4%).*

This refers to the percentage of patients with “Improved” scores. The percentage is correct for patients on givosiran in the double-blind period and the updated percentage for patients crossing over from placebo is 90.5% rather than 88.4%. These data are reported in Table 6 above.

- *CS p 58: Further improvements with continued givosiran treatment in every category of the PPEQ, with patients crossing over from placebo showing improvements similar to those observed among givosiran-treated patients during the ENVISION RCT:*

Please see Table 5 above.

A4. Priority question: The ERG wish to clarify several points regarding chronic symptoms in the trial populations, as follows:

- The ERG understand that 48% of patients in ENVISION were not identified by study investigators as having chronic symptoms (i.e. daily or near daily symptoms). Is this correct?

Response: Yes, this is correct per the definition of chronic symptoms recorded at baseline in ENVISION. Regular chronic symptoms between attacks were reported at baseline in 47.9% of AHP patients in the givosiran group and 56.5% of AHP patients in the placebo group. This baseline characteristic was defined according to a field that investigators were asked to check at study entry, marking ”yes” or ”no” if patients experienced symptoms of porphyria when not having an attack daily or on most days prior to the study. However, we recognise there may be limitations to the conclusions we can draw solely using the data from this field since it may not fully represent the level or severity of chronic symptoms among patients in ENVISION. As one example, chronic opioid use was reported in 29.2% of givosiran and 28.3% of placebo patients. It would be expected that these patients receiving chronic opioid use suffer from chronic pain related to AHP. However, some of these patients reported chronic opioid use but did not report chronic symptoms, which suggests that there is an imperfect count of the proportion of patients with chronic symptoms. Also this question specified “daily or on most days”, which prompted the investigator to gauge the frequency of chronic symptoms rather than the severity of the symptoms.

In summary, while ENVISION reported chronic symptoms at baseline, the primary objective was to assess the efficacy and safety of givosiran, and thus this question about baseline chronic symptoms should not be misconstrued as being a comprehensive assessment of chronic symptom burden. Neeleman et al. (2018) more accurately represent the disease experience of AHP patients in their long-term natural history study.[13]

[A4, contd.] **Please provide a rationale for assuming that all patients in the model would experience chronic symptoms, despite their attack frequency health state?**

Response: The model does not assume that all patients in the model experience chronic symptoms of porphyria despite their health state. Instead the model uses the prevalence of chronic conditions categorised by the health states proposed by Neeleman et al. to capture the relationship between increased acute attack frequency and chronic conditions, which are both

key elements of disease burden. Table 58 in the CS shows that the proportion of patients with different chronic symptoms is dependent on health state as defined by attack frequency,

- **Please provide rates of chronic symptom for patients in ENVISION at baseline and at follow-up across all attack severity states?**

Response: This information is not available since chronic symptoms were not a study endpoint per se.

A5. Please provide the statistical analysis plan for ENVISION (CSR appendix 16.1.9)?

Response: We are enclosing the final ENVISION statistical analysis plan included as CSR Appendix 16.1.9, Amendment 2 dated 13 February 2019,[9] in the reference package accompanying this response.

A6. Please confirm whether the Porphyria Patient Experience Questionnaire has been validated (internally or externally) and provide related technical reports or publications.

Response: The Porphyria Patient Experience Questionnaire (PPEQ) is a *de novo* patient-reported outcome (PRO) instrument developed as an exploratory endpoint for the givosiran clinical development programme to assess treatment experience and impacts on patients' lives that are not collected by other health-related quality of life (HRQoL) assessments. The PPEQ is a simple eight-item measure of functional impacts, activities of daily living, and treatment convenience and satisfaction, with each item rated on a 5-point Likert scale (Figure 3).

Figure 3. Porphyria Patient Experience Questionnaire (PPEQ)

IMPACTS

Instructions: For each item below, mark the response that best describes how your ability to do the activity has changed **since before you started this study**.

Compared to before you started this study, how has your ability to do the following changed?						
	Much better	**Minimally better**	**No change**	**Minimally worse**	**Much worse**	**Not applicable**
1. Traveling more than a day for work or pleasure	□	□	□	□	□	□
2. Participating in social activities, such as visiting friends	□	□	□	□	□	□
3. Planning future events, such as work or personal appointments	□	□	□	□	□	□
4. Doing household chores, such as meal preparation or cleaning	□	□	□	□	□	□
5. Exercising moderately, such as walking more than 20 minutes	□	□	□	□	□	□

TREATMENT EXPERIENCE

Instructions: The following questions ask about your current study drug and the porphyria medication you used prior to the study. For each item below, please **mark** the response that best describes your experience.

Compared to your porphyria treatment prior to the study, how has your current study drug changed your view on the following items?					
	Much better	**Minimally better**	**No change**	**Minimally worse**	**Much worse**
6. Convenience of your current porphyria treatment	□	□	□	□	□
7. Your overall satisfaction with your porphyria treatment	□	□	□	□	□

Instructions: The following question asks about your current study drug. Please **mark** the response that best describes your experience.

In general, in the last four weeks, how *often did you feel*:					
	Always	**Most of the time**	**Sometimes**	**Rarely**	**Never**
8. That your study drug was helping you to return back to a more normal life?	□	□	□	□	□

Source: PRO Symptom and Quality of Life Report[14]

Although as an exploratory endpoint the PPEQ has not been formally validated (either internally or externally), the relevance of its five impact items to the AHP patient population is supported by multiple lines of evidence, including:

- Literature research described in the PRO Symptom and Quality of Life Report enclosed in the reference package accompanying this response[14]
- A burden-of-illness study developed with input from National Acute Porphyria Service (NAPS) experts (Dr Stein, Dr Badminton, and Prof Rees), comprising a survey and semi-structured interviews with adult patients with AHP in the UK[15]
- A Patient-Focused Drug Development (PFDD) meeting with AHP patients conducted for the US Food and Drug Administration (FDA) by the American Porphyria Foundation[16]

These sources document the negative impact of AHP on patients' ability to travel, participate in social activities, plan future events, perform household chores, and perform physical exercise, thus supporting the concept validity of the PPEQ Impact items.

As shown in Figure 3, the three Treatment Experience items of the PPEQ are simple direct questions on a global rating of change scale (which is appropriate since there is no baseline assessment for the PPEQ). While they ask patients to respond specifically about their porphyria treatment, their generic phrasing and response options would be valid to capture patient perceptions of treatment in essentially any disease.

Although there is no separate technical report or publication for the PPEQ, its rationale, structure, items, rating scale, and position in the PRO conceptual framework for ENVISION are described in the submitted PRO Symptom and Quality of Life Report.[14] Notably, there is no methodology for mapping from the PPEQ to any other PRO measure.

A7. In some cases, clinical data from the ENVISION trial are reported for only the AHP cohort rather than the AIP cohort, or vice versa. What was the rationale for selecting one cohort over the other for some clinical outcomes?

Response: In the clinical section of the CS we reported results for the AIP subgroup or the entire AHP patient population according to the hierarchy of endpoint definitions in the prespecified ENVISION investigational plan, which is summarised in Section 8 of the CSR.[8] In contrast, the CEM uses data for the entire AHP cohort, corresponding to the approved indication for givosiran.[17] No subgroup analyses were performed in the CEM for the different AHP subtypes because numbers of patients in ENVISION with subtypes other than AIP were too low for such analyses to be meaningful (n=1, 2, and 2 for hereditary coproporphyria [HCP], variegate porphyria [VP], and unidentified mutations, respectively[10]). Given that 95% of patients in ENVISION had AHP and key results were virtually identical in the AHP and AIP cohorts,[10] there would be no value in performing new analyses on every endpoint solely for the purposes of creating a comprehensive set of matching results for both of these cohorts.

Specification of AIP in the ENVISION primary endpoint and some secondary endpoints reflects the fact that Alnylam originally planned to perform this trial in AIP patients, since this is the most common AHP subtype. In line with advice received from the EMA Scientific Advice Working Party, non-AIP subtypes of AHP were subsequently included in the eligibility criteria for this pivotal trial. The low number of VP and HCP patients enrolled was expected based on the prevalence in the countries in which the study was conducted.

As explained in Section 12.6 of the CS, givosiran acts upstream of the steps that differentiate the AHP subtypes, and thus no difference in effect among subtypes is to be expected. The AHP subtypes have a common pathophysiologic basis of disease and thus a similar clinical presentation that includes acute porphyria attacks.[18,19] In all AHP subtypes, attacks are triggered by environmental or stress factors, such as certain drugs, the menstrual cycle, infection, inflammation, fasting, or low glucose levels, which lead to induction of hepatic ALA synthase 1 (*ALAS1*) mRNA transcription, resulting in accumulation of haem precursors.[20] Management of acute attacks is similar for all subtypes of AHP, and typically includes hemin, glucose, opioid analgesics, and antiemetics.[19,21-23] All non-AIP patients in ENVISION demonstrated reductions in ALA and PBG levels as early as 2 weeks after starting givosiran, similar to AIP patients treated with givosiran, accompanied by reductions in attacks and hemin usage. Thus, for all practical purposes, no distinction between AIP and non-AIP patients in ENVISION needs to be made.

A8. Page 33 of the CS states that no liver function tests will be required beyond six months on givosiran. Please clarify the reason that these tests would no longer be required after this time.

Response: The givosiran SmPC states that liver function tests (LFTs) should be performed prior to initiating treatment with givosiran, and these tests should be repeated monthly during the first 6 months of treatment, and as clinically indicated thereafter.[17] Notably, monthly LFTs after the first 6 months of treatment are not a standard requirement for givosiran, though they are recommended annually for all AHP patients,[5] as explained in more detail below. Transaminase elevations in ENVISION were mild to moderate in severity and transient, primarily occurring between 3 to 5 months following initiation of treatment.[8] No cases met Hy's Law criteria, signifying absence of hepatocellular injury. The absence of a requirement for LFTs after 6 months in the product label reflects the fact that transaminase elevations in ENVISION were confined to the first 3–5 months after initiating treatment. The monitoring regimen and recommendations in the label are appropriate for all patients, with and without hepatic

conditions, and no additional precautions are required for patients with pre-existing hepatic conditions.

Notably, the givosiran SmPC wording on LFTs does not preclude clinicians conducting these tests at their discretion after the first 6 months of treatment, and indeed LFTs are a routine assessment in current standard of care for AHP patients. Acute hepatic porphyria is associated with liver disease, including transaminase elevations, fibrosis, cirrhosis, hepatocellular carcinoma, and iron overload from chronic hemin administration as reported in the literature.[24-27] Serum aminotransferases are elevated in ~13% of patients during an acute attack, and in some clinically asymptomatic patients.[5] This is further evident in ENVISION, where ALT and aspartate transaminase (AST) values above the ULN were present during screening in 20.8% and 18.8% of patients in the givosiran group and 4.3% and 6.5% of patients in the placebo group, respectively.[8] Recommendations for the evaluation and long-term management of porphyria, published by the Porphyrias Consortium of the Rare Diseases Clinical Research Network in 2017, advise to monitor LFTs at baseline and annually thereafter regardless of treatment or attack rates.[5] Routine monitoring is included in both treatment arms of the CEM and has no impact on the results. Therefore, only LFTs during the first 6 months of givosiran treatment are included in the model.

A9. Please provide baseline characteristics for the EU cohort from ENVISION (i.e. the population used to inform the model).

Response: Table 10 shows the characteristics of the European (EU) population from ENVISION, along with the characteristics of the total AHP population as presented in the publication of the clinical trial by Balwani et al. (2020).[10] However, please note that only baseline average age, weight, and percentage of females in the model were estimated considering exclusively the EU population, and all other CEM inputs were informed by the overall AHP population.

Table 10. Population characteristics of the overall and EU AHP patients in ENVISION*

	Overall AHP patients (N=94)	EU AHP patients (N=42)
Age - yr	38.8±11.4	41.6±12.2
Female sex – no. (%)	84 (89)	36 (86)
Body-mass index †	24.9±5.8	23.8±3.4
Race – no. (%)‡		
White	73 (78)	39 (93)
Black	1 (1)	0 (0)
Asian	15 (16)	2 (5)
Other	5 (5)	1 (2)
Acute intermittent porphyria with identified mutation — no. (%)	89 (95)	40 (95)
Nonacute intermittent porphyria §		
All subtypes	5 (5)	2 (5)
Hereditary coproporphyria	1 (1)	0 (0)
Variegate coproporphyria	2 (2)	1 (2)
Acute hepatic porphyria without identified mutation	2 (2)¶	1 (2)
No. of yr since diagnosis	9.7±10.0	14.1±11.6
Previous hemin prophylaxis — no. (%)		
Yes	38 (40)	15 (36)
No	56 (60)	27 (64)
Historical annualized attack rate‖		
High — no. (%)	45 (48)	23 (55)
Low — no. (%)	49 (52)	10 (45)

	Overall AHP patients (N=94)	EU AHP patients (N=42)
Previous chronic symptoms — no. (%)**		
Yes	49 (52)	18 (43)
No	45 (48)	24 (57)
Previous long-term opioid use — no. (%)††		
Yes	27 (29)	11 (26)
No	67 (71)	31 (74)

Sources: Balwani et al. (2020)[10]; Alnylam, ENVISION data on file

*Plus–minus values are means ±standard deviation (SD). Percentages may not total 100 because of rounding.

† The body-mass index is the weight in kilograms divided by the square of the height in metres.

‡ Race was reported by the investigator after discussion with the patient.

§ Porphyria subtypes other than acute intermittent porphyria include hereditary coproporphyria, variegate porphyria, delta-aminolevulinic acid (ALA) dehydratase–deficiency porphyria with an identified mutation, and acute hepatic porphyria without an identified mutation. No patients with ALA dehydratase–deficiency porphyria were enrolled in this trial.

¶ The two patients with acute hepatic porphyria without an identified mutation were considered by the trial investigator to have acute intermittent porphyria on the basis of biochemical analysis.

‖ The historical annualised attack rate was calculated as the number of attacks resulting in a composite of hospitalisation, a visit to a health care facility, or hemin use at home during the 6 months before randomisation. For patients who were receiving hemin prophylaxis before the initiation of the trial, the attack rate was considered to be high if the historical annualised attack rate was 7 or more and low if the attack rate was less than 7 (attack rate of ≥12 and <12, respectively, for patients who were not receiving previous hemin prophylaxis).

** Symptoms were considered to be chronic if patients had symptoms of porphyria daily or on most days when they were not having an attack, as reported by the investigator. Information was reported on a screening questionnaire administered by trial staff members.

†† Opioid use was defined as long-term if patients reported taking an opioid for porphyria daily or most days when they were not having an attack, as reported on the screening questionnaire.

Section B: Clarification on cost-effectiveness data

Cycle length and model structure

B1. It appears that a six-month cycle length was selected on the basis that it reflected the duration of the ENVISION study. However, please outline whether a six-month cycle length adequately captures the frequency of clinically important events and monitoring requirements for patients with AHP?

Response: The 6-month cycle duration was selected for two main reasons. First, as ERG recognized, this duration aligns with the 6-month double-blind period of the ENVISION trial,[10] enabling us to parameterise the health-state transitions with the most robust data set available.

Second, this cycle duration matches the intervals between routine clinic visits for AHP patients, as set out in the AHP evaluation and management recommendations from Balwani et al. (2017).[5] In the schedule for follow-up assessments, most assessments occur at 6–12-month intervals. The exception is blood tests for ferritin levels, which could be obtained as frequently as every 3 months, but the recommendations specify that these should be obtained at least yearly. Specialist investigations and monitoring for AHP patients are also on a 6-monthly cycle in the NHS Standard Contract for Severe Acute Porphyria Service.[28] Monitoring can be considered as a good approximation for frequency of clinically important events, since intervals in follow-up visits/examinations are set to prevent disease worsening from going unidentified. In other words, routine monitoring is done at intervals which allow timely detection of clinically meaningful changes in disease status. Thus 6 months can be considered as the minimum amount of time to observe clinically meaningful events and therefore for the cohort to transition

from one health state to another. Consequently, we consider that the 6-month cycle duration corresponds to routine clinical practice for AHP patients.

B2. In terms of the choice of the model structure, please provide the rationale behind not choosing a combination of a short-term decision tree model for acute attacks and a long-term Markov model for the chronic complications?

Response: The current model considers four health states encompassing AHP disease severity (Severe, Recurrent, Symptomatic, and Asymptomatic). Health states are defined based on frequency of attacks and respective frequency of chronic symptoms/comorbidities as reported in the study by Neeleman et al. (2018).[13] The effectiveness of treatment is then measured in terms of changes in AAR from baseline over time, which are used to inform the transition probabilities between health states. Specifically, transition probabilities are estimated considering the number of patients in a given health state at the beginning and the end of 6-month intervals in the ENVISION trial (for placebo only in the double-blind period and for givosiran up to 18 months of the OLE). Each health state is associated with a mean attack rate, based on pooled observations in the ENVISION trial, and with prevalence of chronic conditions based on evidence reported by Neeleman et al. At each cycle, the model considers the one-off impact of attacks on costs and quality of life (disutility adjusted for the average attack duration) and the impact of chronic conditions on costs, quality of life and mortality.

If we were to model attacks using a decision-tree within each cycle, with end nodes corresponding to each of the modelled health states, we would need to account for the probability of having a first attack, then a second, a third, a fourth, etc., up to the maximum number of attacks observed in the ENVISION trial. If such recurrence of attacks were to be represented in a decision-tree analytic model, it would lead to a lengthy and complex structure which we believe would not add extra value since attacks are only associated with one-off disutility and one-off cost (i.e., no mortality), which can be more simply accounted for using the mean AAR in each health state at each cycle. Furthermore, no data exist to inform how the probability of an nth acute attack might vary depending on the number and timing of previous attacks (n-1, n-2, etc.), and thus any decision tree to model attacks would need to incorporate even more assumptions, decreasing its rigour as opposed to adding validity.

Moreover, the transitions between health states are defined based on shift tables representing the probability of falling within any of the health-state thresholds, thus not making any difference in terms of outcomes compared with the decision-tree approach described above. This would be different if the chronicity of the disease would be associated with having or not having the attack. In that case, we agree that a structure combining decision-tree and Markov model with shorter cycle length would have probably been the appropriate choice. However, in the case of AHP the presence of chronic symptoms/comorbidities is associated with the frequency of attacks during a given time period, as has been established for AHP health state categories by Neeleman et al. (2018).[13] Treatment effect is therefore measured based on changes in the number of attacks occurring in a 6-month interval, which may lead to transition to a different health state associated with a given prevalence of chronic conditions and mean number of attacks, as described above. As a result, we consider our current Markov model structure as the appropriate choice to represent the natural disease history in AHP and treatment effect.

Treatment and Comparator

B3. Please outline which treatments are considered within BSC in the model?

Response: BSC in the CEM can be considered to comprise the background therapies used by patients in ENVISION, which include on-label use of hemin and other drugs for treating acute attacks, medications to manage chronic symptoms of AHP, and GnRH analogue prophylaxis in a small number of patients (4.3%). A comprehensive list of concomitant medications used in ENVISION is presented in CSR Table 14.1.10.1, accompanying this reply.

However, other than hemin and other medications to manage acute attacks when they occur, the CEM does not need to explicitly consider the utilisation, costs, or health effects of BSC treatments because—as explained in our reply to question B4—these therapies are assumed to be used by patients in both arms of the model, and therefore cancel out.

Notably, the CEM does not base the utilisation of any BSC treatments on ENVISION data, instead using estimates for UK clinical practice from NAPS experts.[29]

B4. Please confirm that givosiran is modelled to be used as an add-on to BSC in clinical practice?

Response: We confirm that the CEM assumes givosiran will be used in addition to BSC in clinical practice, and thus the two treatment arms in the model can be considered as follows:

- Givosiran + BSC
- BSC

This approach is appropriate because patients receiving givosiran will still require BSC to treat any "break-through" acute attacks that occur, as well as to manage long-term complications of AHP.

B5. Haem arginate (in addition to BSC) appears to be used off-label for the prophylactic treatment of patients with AHP in the UK. Please outline why was haem arginate was not modelled as part of the comparator within the analysis.

Response: Alnylam invested considerable thought and discussion before ruling out off-label haem arginate prophylaxis as a relevant comparator to givosiran. Although NICE has considered off-label treatments as comparators in other appraisals, we believe it is inappropriate to do so in cases where such off-label use is specifically contraindicated in the approved product label—in other words, we assume that NICE guidance should not run counter to regulatory directives. Thus, prophylactic haem arginate is not included in the CEM because this off-label use is explicitly prohibited in the SmPC, which states, "NORMOSANG should not be used as a preventive treatment since available data is too limited and long term administration of regular infusions carries the risk of iron overload."[30]

Nevertheless, in correspondence received from NICE on 18 December 2020 we were requested to address hemin prophylaxis as a comparator. Since no clinical studies have directly compared givosiran vs. hemin prophylaxis, an indirect treatment comparison (ITC) would be the only way to obtain the necessary parameters to formally model haem arginate prophylaxis as a comparator. Alnylam has commissioned the consultancy Analysis Group to conduct an independent ITC feasibility assessment, and we anticipate their report being finalised and ready for delivery to NICE later this week. In the meantime, we provide below our current understanding of the feasibility of performing an ITC of givosiran vs. haem arginate prophylaxis.

We are aware that NAPS experts have prescribed haem arginate to some patients with AHP with a view to preventing recurrent attacks, and their experience has been reported in the peer-reviewed literature by Marsden et al. (2015).[31] There are numerous important differences between the patient populations included in the ENVISION phase 3 randomised trial and the retrospective case series reported by Marsden et al. The ENVISION trial included patients with more severe disease at baseline, as it enrolled only patients meeting strict criteria for repeated attacks whereas the study by Marsden et al. was not restricted to this population, and on average the patients in ENVISION had longer disease duration.

There are also important differences in the definition and collection of attack data between ENVISION and Marsden et al. (2015). Unlike in ENVISION, the definition of an acute attack was not clearly reported by Marsden et al., and the completeness of attack reporting in their case series is questionable given the reliance on retrospective data collection from medical charts.[31] It is obvious that retrospective extraction of attack data from medical charts over a multi-year period prior to study conduct cannot be a reliable basis for comparison with data gathered in a prospective, systematic, and adjudicated manner in the context of a phase 3 randomised clinical trial.

Similarly, our SLR identified no other published studies that could provide adequate data for a treatment comparison between hemin prophylaxis and givosiran.[3]

We briefly outlined some of the reasons for not considering haem arginate prophylaxis as a comparator in Sections 8.1 and 8.2.2, along with a description of associated adverse effects in Section 9.7.2. In real-world UK use as reported by Marsden et al. (2015), hemin prophylaxis has demonstrated only limited effectiveness: 64% of patients still have attacks requiring hospitalization, 50% require regular opioid medications because of chronic pain, and 65% note no improvement in their work capacity since before hemin.[31] In the EXPLORE natural history study, patients receiving hemin prophylaxis still reported impaired HRQoL.[32,33] Frequent use of hemin has also been shown to cause tachyphylaxis (i.e., reduced efficacy with repeated dosing), requiring higher doses and/or more frequent administration over time.[34]

Moreover, recent research by Schmitt et al. (2018), an international team of AHP experts, suggests that long-term use of hemin may even lead to an increased number of attacks by generating chronic hepatic inflammation that maintains a high level of ALAS1, driving attack recurrence.[26] The authors concluded that hemin needs to be restricted to patients with severe attacks, "with the occurrence of progressive signs of a central or peripheral neurological alteration, profound hyponatremia or hyperalgesic acute crisis unresponsive to symptomatic treatment." In other words, Schmitt et al. advocate using haem arginate only for treatment of acute attacks, in line with the SmPC.

Taking all of the above considerations into account, Alnylam maintains that it would be not only unfeasible due to lack of adequate data but also inappropriate to consider haem arginate prophylaxis as a comparator to givosiran for this HST appraisal. The appropriate and approved use of haem arginate is for treatment of acute attacks, representing an important component of BSC, and such use is explicitly included in the CEM.

- **[B5, contd.]** In addition, depending on the response to A1, please outline why GnRH was not modelled as part of the comparator within the analysis

Response: As explained in our response to question A1, it is not feasible to model GnRH analogue prophylaxis as a comparator to givosiran because no comparative data exist.[2] Even were evidence not a limiting factor, this comparison would be of dubious relevance given the

very low utilisation of GnRH analogues in real-world practice for the AHP patient population. In addition, the wide variation in use of GnRH analogues among the few AHP patients in the UK who receive this therapy would preclude any meaningful estimate of resource utilisation parameters for the CEM.

Instead of being modelled as a comparator to givosiran, GnRH analogues are appropriate to consider as a component of BSC. Use of givosiran does not prevent use of GnRH analogues or vice versa, since the two treatments have completely different mechanisms of action: direct reduction of levels of *ALAS1* messenger RNA,[35,36] the first step in the haem synthesis pathway,[6] vs. suppression of gonadotropin secretion,[37] respectively. Indeed, as previously mentioned, a small number of patients in ENVISION did receive GnRH analogues during the trial. Consequently, any contribution of GnRH analogues to the treatment effect observed in ENVISION is already captured in the CEM. It is unnecessary to explicitly model the costs of GnRH analogues since their inclusion in both arms would cancel out and have no net effect.

Utilities

B6. As noted in the CS, the study by Neeleman et al (2018) was used to justify the definition of health states according to attack frequency. However, on p83 of the CS it is also stated that QoL data from the ENVISION study affirms that there is a clinically meaningful separation in how patients experience recurrent and severe disease. As such, please provide further justification for choosing to define health states according to attack frequency given that health states may also have been defined according to disease severity (as per the impact on patients QoL), or biomarkers including ALA or PBG; or alternately by different thresholds for attack rate.

Response: Selection of attack frequency to define model health states is the most appropriate approach because this maps directly to the primary endpoint of ENVISION, namely AAR,[10] which in turn reflects the consensus of regulators and participating clinical experts that attack frequency is the most clinically relevant endpoint to assess in the givosiran pivotal trial. Attack frequency is the fundamental basis on which the patient care pathway is organised by NAPS and NHS England.[28] The European Porphyria Network (EPNET) and the Porphyrias Consortium guidelines stratify AHP disease severity by attack frequency.[5,38] Attack frequency is the most recognised measure for categorising disease severity in AHP in the literature, notably including the EPNET epidemiologic study of porphyrias in Europe.[39] Neeleman et al. (2018) also established that attack frequency is a relevant basis for defining disease severity as this impacts the risk of developing chronic complications.[13]

Acute attacks are undeniably the most patient-relevant basis on which to define CEM health states because they drive the burden of AHP in patients with repeated attacks. We presented patient testimonials of their experience of acute attacks in Table 4 of the CS, and to highlight the severity of these debilitating symptoms—and therefore to further validate reducing attack frequency as the ultimate treatment goal in this patient population—we are providing additional quotes from AHP patients in Table 11 below.

Table 11. AHP patients' descriptions of their experience of acute attacks

Pain
"So, porphyria attacks for me start with pain. Just constant stabbing, whipping, burning pain across my ribs and my abdomen. It will then spread up to my lungs. So, it feels like I can't breathe properly. Spreads down into my lower abdomen, my legs. And the intensity of the pain is anywhere from 8 to 10 out of 10. It doesn't really matter at that stage what pain killers I take, because the pain is just so overwhelming […] it would feel like someone was pouring acid on my intestines and then ripping them open. And then around my ribs and my lungs particularly, it would feel like someone was scraping my ribs with knives. And then in my spine I would feel like a hot poker, pressing into my spinal cord and sending shooting pains up and down my body."[15]
"It's like sharp burning - it's like hot rods digging, that is how I would describe it. In a barbed wire, like wrapped around my back and stomach when it gets really bad down there."[15]
"It's a real hot feeling like it feels like there's hot coals packed in there. And it feels like someone's like poking in more of them, and there's all this pressure, you know, like stretching and burning … And then that like carries on. And then whenever, oh, and then sometimes also I'll feel like hot knives stabbing me."[40]
"… and then the worst days is like being disemboweled, having a hot pan shoved into your intestines or into your abdomen while having your ribs filleted."[40]
"[The abdominal pain] is kind of like […] I could compare it to severe, severe, severe, severe trapped wind at times, then kind of goes on in intense menstrual cramping. The shooting pains, well they are literally that – it will be in my limbs and it will kind of start around the top of my neck and the pain will kind of shoot down to my hands and I'm holding something, my hands will just kind of release. It's almost like an electric shock, actually that's a good way to describe it: an electric shock to the limbs… if it's in my legs – […] it's a similar thing, it will be just like someone stabbing you with an electric current and it can shoot up and down and up and down."[15]
"If you said to me the only way to get rid of this pain is to shoot you, I would do it. I threatened to jump out of a window, I have threatened to do all sorts of things because it hurts so much that it's not worth living through it's so bad."[15]
Nausea
"I have terrible nausea; I can't even keep water down at that point, so I had to be hydrated on a drip in hospital."[15]
Neurological symptoms
"I suffer with hallucinations, confusion, I don't really know what's going on, I don't really know where I am, I'm not safe to be alone."[15]
"… headaches so bad that they've caused me to lose my sight on numerous occasions."[40]
"It's re-occurred several times now. In my 20 attacks, it's happened more recently in my last five, where I've ended up waking up one morning and I can't move my leg or I can't, or I get out of bed to go to the toilet and I fall. And that's just where the nerves have been attacked obviously, during the porphyria attack."[15]
"And then in June I got really poorly again and ended up paralysed, and I could not walk for a year."[15]

Although Alnylam did consider alternate proposals for defining health states in the CEM, all options other than attack frequency suffer from serious limitations. Urinary ALA and PBG are laboratory biomarkers primarily used for diagnostic purposes.[41] Routine monitoring of ALA and PBG provides little clinical value because although spikes in their levels are generally associated with attack occurrence, levels vary at the population level and individual patient level, and may either become normal between attacks or remain elevated and fluctuate widely, hindering establishment of true attack-free baseline values.[42] No clear thresholds exist that would allow prediction of attack occurrence or recurrence from ALA or PBG levels; indeed, a review by NAPS experts notes that plasma and urinary ALA levels do not correlate well with porphyria symptoms.[6]Thus, it would be impossible to use ALA or PBG levels in the CEM to define health states that could capture the clinical and economic consequences of attacks.

Just as urinary ALA and PBG levels cannot be used to predict attacks, there is no predictable relationship between levels of these precursors and chronic symptoms or long-term

complications of porphyria. On the contrary, Neeleman et al. (2018) reported marked overlap in ALA and PBG levels among Recurrent, Symptomatic and Asymptomatic patients.[13]

This information is further confounded by a cohort of patients with AHP known as chronic high excreters who have elevated biomarkers associated with AHP but do not have any acute clinical manifestations of AHP.[13,43] However, studies suggest that these patients may be at increased risk of long-term complications associated porphyria such as HCC and chronic kidney disease.[24,44]

In summary, ALA and PBG cannot predict either acute or chronic consequences of AHP, and as such are unsuitable for defining health states in the model. Attack frequency is the most appropriate basis for defining health states in the CEM, allowing use of ENVISION data for acute attacks and the unique long-term natural history study of Neeleman et al. (2018) for chronic condition prevalence by health state.

Finally, regarding ERG's question about selecting different AAR thresholds for the AHP health states in the CEM, two separate aspects need to be considered. First, the thresholds for Asymptomatic, Symptomatic, and Recurrent were based on those established by Neeleman et al. (2018).[13] Because this natural history study is the only source that provides chronic condition prevalence by health state, selection of different thresholds for these three health states would prevent us from calculating the disutility and costs associated with chronic conditions in the model.

Second, Neeleman et al. did not define the Severe health state, and the senior author on this study has explained to Alnylam that this degree of division (i.e., between Recurrent and Severe) was not possible given the size of the cohort. Although there are no available studies defining thresholds for a Severe health state, expert feedback from clinicians in the UK, France, and Sweden has validated that patients with more than 4 attacks per year cannot be treated as a homogeneous cohort—in other words, patients with 5 attacks and those with 30 or even 50 attacks per year cannot be considered to have the same quality of life, the same costs, and the same experience of their illness. As ERG has noted, we explained on page 83 of the CS that there is a clinically meaningful separation in how patients experience Recurrent (AAR >4 to ≤24) and Severe disease (AAR >24), and this is discussed in more detail in CS Section 10.6.3 (page 79; see especially Figure 26). We acknowledge that we could have chosen a different threshold for the Severe health state (e.g., >23 or >25 instead of >24), but >24 was a logical choice since it corresponds to >2 acute attacks per month. Considering attack frequency on a monthly basis is relevant given that a proportion of patients have attacks tied to the menstrual cycle. Structured interviews with expert clinicians in the UK confirmed that our definitions of the CEM health states were clinically sound.[29]

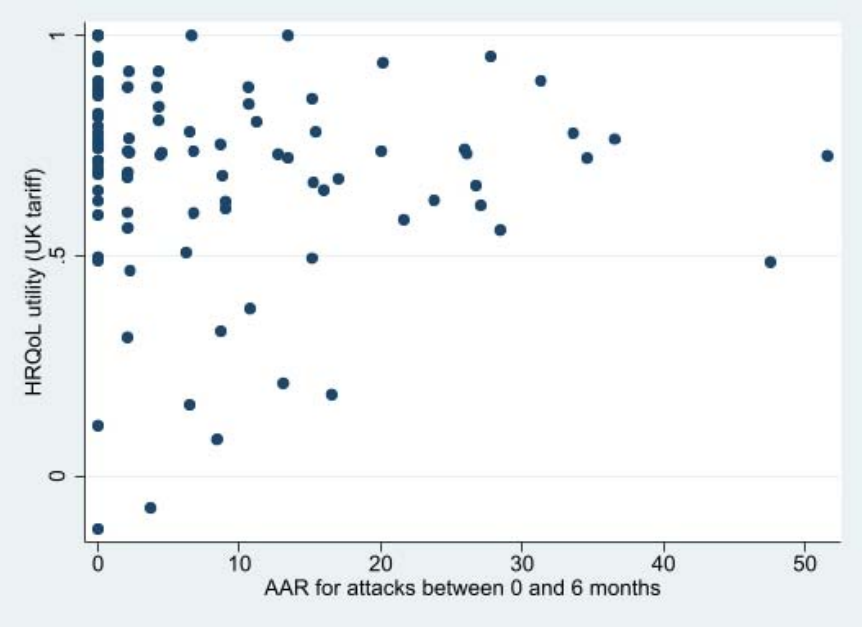
Consequently, we are confident that our thresholds for attack rate in the model health states are justified.

B7. Priority question: From the information provided the ERG understand that the company consider the use of short-term EQ-5D data (from the ENVISION study) to inadequately capture changes in QoL associated with chronic symptoms; however, please provide the following:

- Health state utility values based on EQ-5D data collected within the ENVISION study
- A scenario analysis which uses health state utility values based on EQ-5D data from the ENVISION study

Response: We did not use the EQ-5D data collected in ENVISION to estimate the utility values by health state because, as can be observed in Figure 4, the scatterplot of AAR vs. EQ-5D–derived utility data collected in the double-blind period of ENVISION shows that some patients with very high number of attacks have EQ-5D utility values close to 1 whereas many patients with very few attacks have very low utility values (Pearson correlation coefficient r=-0.0178, p=0.8656). It is possible that the ENVISION study is not of a sufficiently large sample size or long enough duration to reach a "steady state" estimation of the true underlying utility of these patients. In addition, patients in ENVISION had a relatively short average duration of disease, and thus may not yet have accrued the level of HRQoL impairment due to AHP chronic symptoms, comorbidities, and late complications that would be observed in patients with longer disease duration.

Figure 4. AAR vs. EQ-5D collected in the double-blind period of ENVISION



Source: Alnylam, ENVISION data on file
AAR: annualised attack rate; EQ-5D: EuroQol 5-dimensions; HRQoL: health-related quality of life

In addition to the fundamental problem that EQ-5D scores did not correlate with AAR during ENVISION, there are numerous logistical obstacles to using data from this trial to set health-state utilities, including the following critical issues:

1. The EQ-5D assesses instantaneous health status on the day of questionnaire administration[45,46]—i.e., it has no recall period of the past week, month, etc.—whereas health state based on AAR has to be calculated over some longer time period, which creates a mismatch whenever health state is not stable.
2. Health states in ENVISION are not stable for most patients, and indeed this fact underlies the transition probabilities in the CEM. Therefore, EQ-5D measurements averaged from different time points do not correspond cleanly to a given health state and are confounded by treatment.

3. Results in the double-blind period are confounded by treatment, considering that at 6 months 100% of Severe patients were in the placebo arm whereas 80% of Asymptomatic patients were in the givosiran arm.
4. Per the ENVISION eligibility criteria, no patients were in the Asymptomatic state at baseline, so it is impossible to use baseline EQ-5D measurements to populate all four model health states.
5. Considering attacks during the ENVISION OLE, no patients were in the Severe health state by Month 12 or Month 18 (i.e., when AAR was calculated between Month 6 and Month 12 or between Month 12 and Month 18), so it is impossible to use EQ-5D measurements from the OLE to populate all four CEM health states.
6. The relatively low prevalence of chronic conditions among patients in ENVISION, as noted in question A4 above, likely reflects the short disease duration relative to the timeframe over which these conditions accumulate, as seen in the long-term study by Neeleman et al. (2018).[13] Thus, ENVISION does not allow us to appropriately simulate the HRQoL burden of chronic conditions over the model time horizon.

Despite these issues, we attempted to meet the ERG's request for health-state utility values based on EQ-5D values collected within ENVISION by categorising all EQ-5D measurements at 6 months by AAR at 6 months, calculated based on attacks occurring between baseline and Month 6 (i.e., over the double-blind period). As shown in Table 12, this exercise yields utilities that lack face validity, since the mean EQ-5D index value for patients in the Severe health state is higher than for either Recurrent or Symptomatic patients. These results cannot be used to perform a scenario analysis because they imply that a patient with more than 24 acute porphyria attacks per year has better HRQoL than one with >4 to ≤24 attacks or even >0 to ≤4 attacks, which is not only illogical given the high burden of an acute attack but also runs directly contrary to the opinion of clinician experts, who confirmed that their AHP patients with higher AAR have lower HRQoL.[29]

Table 12. Mean EQ-5D index values at Month 6 by health state at Month 6 in the double-blind period of ENVISION

	EQ-5D utility*		
Health state	Mean	SE	95% CI
Asymptomatic	[redacted]	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]

Source: Alnylam, ENVISION data on file
CI: confidence interval; EQ-5D: EuroQol 5-dimensions; SE: standard error
*All EQ-5D data at Month 6; UK tariff; for each patient, the EQ-5D measurement at Month 6 is considered; patients are classified by health state based on AAR at month 6, and the average utility across observations for patients in each health state is then calculated.

As an alternate approach to try to meet the ERG's request, we calculated the average EQ-5D index score for each patient as the mean of their baseline and Month-6 measurements. We then classified patients by health state based on AAR at Month 6, and calculated the average utility across patients in each health state. The rationale for this approach is that by increasing the number of observations for each patient we might obtain a more plausible set of health-state utilities. However, as shown in Table 13, there is an even greater violation of face validity in

these results than with the previous approach (Table 12), because not only does the Severe health state still have a higher utility than the Recurrent and Symptomatic health states, but also the Recurrent health state now has a higher utility than the Symptomatic health state. Therefore, these nonsensical results also cannot be used as the basis for a scenario analysis.

Table 13. Mean EQ-5D index values averaged across baseline and Month 6 by health state at Month 6 in the double-blind period of ENVISION

	EQ-5D utility*		
Health state	Mean	SE	95% CI
Asymptomatic	[redacted]	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]

Source: Alnylam, ENVISION data on file
CI: confidence interval; EQ-5D: EuroQol 5-dimensions; SE: standard error
*All EQ-5D data at baseline and Month 6; UK tariff; for each patient (N=94), the EQ-5D measurements at baseline and Month 6 are averaged; patients are classified by health state based on AAR at month 6, and the average utility across observations for patients in each health state is then calculated.

We have been unable to find a way to use the EQ-5D values from ENVISION to inform a plausible scenario analysis, and would welcome any alternate approaches that the ERG could suggest. Assuming no valid approaches exist that we may have overlooked, we consider the current method in the CS to be the most appropriate. Specifically, we obtained the long-term HRQoL decrements associated with each chronic condition associated with AHP separately from the literature and then applied these disutilities to the proportion of the cohort with each condition in every health state based on prevalence data reported in the long-term, real-world study by Neeleman et al. (2018).[13] Patients in the Neeleman et al. cohort had suffered from AHP for a much longer time than patients in ENVISION, and therefore offer a more accurate representation of the full extent of comorbidities and long-term complications that typically occur in this disease. The 88 patients described by Neeleman et al. had a median age at AHP onset of 30 years, and the reported median age at the end of study follow-up was 54 years.[13] This indicates that the average duration of disease in the Neeleman et al. cohort was approximately 24 years at the end of follow-up. In contrast, the mean duration of AHP in the overall ENVISION trial population was only 9.7 years.[10] Thus, ENVISION data cannot be used to characterise the accumulation of these conditions over the relevant timescale of the CEM, namely a lifetime horizon. Modelling health-state utilities based on the prevalence of AHP chronic symptoms, comorbidities, and late complications reported by Neeleman et al. is appropriate because this long-term study, which reports data on the occurrence of chronic symptoms/comorbidities and long-term complications of AHP over a 50-year period from 1960 to 2016, is more representative of the relevant timescale of HRQoL impact in this incurable, chronic disease than the 6-month ENVISION study.

B8. Priority question: In Table 36 (p78 of the CS), it is assumed that AHP carer disutility for each health state is based on MS stages i.e. a carer disutility associated with a recurrent AHP attack was assumed to be equivalent to MS Stage 4 carer disutility. Please provide details of how each EDSS stage was linked to each AHP health state.

Response: Multiple sclerosis (MS) and AHP share several important similarities. Both diseases:[13,47]

- Predominantly affect women in their reproductive years

- Typically strike people during their productive years
- Impose a HRQoL burden attributable separately to both chronic (i.e., ongoing disease burden) and acute effects (i.e., attack-related) of their respective condition
- Can be staged by disease severity

Furthermore, multiple sclerosis is a chronic, progressive disease, and thus our assumption that caregiver burden is likely to be similar in multiple sclerosis and AHP is consistent with the conclusion of a Swedish Expert Consensus Statement that, "The decreased quality of life of relatives of patients with AHP is not reported in the literature but is likely to be comparable to the quality of life of relatives of patients with other chronic progressive diseases."[48]

NICE has previously considered carer disutility values mapped to disease-specific health states from MS stages in appraisals of therapies for other chronic disease, including elosulfase alfa for mucopolysaccharidosis type IVa,[49,50] velmanase alfa for alpha-mannosidosis,[51] and abatacept, adalimumab, etanercept, and tocilizumab for juvenile idiopathic arthritis.[52] Notably AHP is far more similar to MS than these three diseases, all of which lack an acute-attack component and primarily afflict children.

As in the elosulfase alfa model[50] and velmanase alfa model,[51] our givosiran CEM uses caregiver disutilities by patient MS stage reported by Acaster et al. (2013)[53] on the Patient Determined Disease Steps questionnaire (PDDS), rather than the Expanded Disability Status Scale (EDSS). To obtain caregiver disutilities by AHP patient health state, we mapped from PDDS stage as shown below in Table 14. For the Asymptomatic, Symptomatic, and Recurrent health states it was relatively straightforward to select the matching PDDS stage by considering the frequency of acute attacks and the prevalence of chronic conditions reported in the natural history study by Neeleman et al. (2018).[13] There are no data in the literature on prevalence of chronic conditions in the Severe health state, but it is reasonable to expect an additional caregiver burden relative to the Recurrent health state due to the higher attack rate and presumably a higher rate of chronic conditions. As a conservative assumption, we mapped disutility of caregivers of Severe patients to one PDDS stage higher than for Recurrent patients; i.e., PDDS 5.

Table 14. Caregiver disutility mapping to AHP health state from MS PDDS stage

AHP health state	Mapped to PDDS stage(s)	PDDS stage definition	Disutility: rationale for mapping
Asymptomatic	0–1*	0 Normal: The person that I care for may have some mild symptoms, mostly sensory due to MS but these do not limit his/her activity. If he/she does have an attack, he/she returns to normal when the attack has passed. 1 Mild Disability: The person that I care for has some noticeable symptoms from his/her MS but they are minor and have only a small effect on his/her lifestyle.	**-0.002: At most mild disability of the patient,** resulting in negligible utility difference between caregivers and controls. Asymptomatic AHP patients have no acute attacks, and the low prevalence of other disease manifestations in this health state, as reported by Neeleman et al. (2018),[13] is expected to translate to only minimal impacts on their functioning.

AHP health state	Mapped to PDDS stage(s)	PDDS stage definition	Disutility: rationale for mapping
Symptomatic	2–3*	2 Moderate Disability: The person that I care for doesn't have any limitations in his/her walking ability. However, he/she does have significant problems due to MS that limit daily activities in other ways. 3 Gait Disability: MS does interfere with his/her activities, especially his/her walking. He/she can work a full day, but athletic or physically demanding activities are more difficult than they used to be. He/she usually doesn't need a cane or other assistance to walk, but he/she might need some assistance during an attack.	**-0.045: Moderate disability.** Symptomatic AHP patients experience acute attacks during which they will typically require caregiver assistance. Their disease has not yet progressed to the point at which mobility is impaired substantially between attacks, but chronic conditions such as pain and neurological symptoms are common in this health state,[13] and will impact daily activities.
Recurrent	4	4 Early Cane: The person that I care for uses a cane or a single crutch or some other form of support (such as touching a wall or leaning on someone's arm) for walking all the time or part of the time, especially when walking outside. I think he/she can walk 25 feet in 20 seconds without a cane or crutch. He/she always needs some assistance (cane or crutch) if he/she wants to walk as far as 3 blocks.	**-0.142: Initial walking difficulty.** As reported by Neeleman et al. (2018),[13] the vast majority (82%) of patients in the Recurrent health state have neurological symptoms and nearly half (46%) have motor weakness. This health state can thus be considered to map to initial mobility problems.
Severe	5	5 Late Cane: To be able to walk 25 feet, the person that I care for has to have a cane, crutch or someone to hold onto. He/she can get around the house or other buildings by holding onto furniture or touching the walls for support. He/she may use a scooter or wheelchair if he/she wants to go greater distances.	**-0.160: Significant walking difficulty.** In the absence of chronic-condition data for a separate Severe category,[13] we assumed that the additional impairment associated with the Severe health state relative to the Recurrent would correspond to one incremental step on the PDDS.

Source: Acaster et al. (2013)[53]
AHP: acute hepatic porphyria; MS: multiple sclerosis; PDDS: Patient Determined Disease Steps
*Acaster et al. reported caregiver disutilities pooled for PDDS 0–1 and 2–3, not separately for PDDS 0, 1, 2, and 3.

Resource use

B9. Please advise what source was used to estimate the proportion of patients utilising health care resource use mentioned in model > HCRU sheet (Rows 13:48) i.e. drugs, healthcare visits etc, at home, as an urgent health care visit and in hospital?

Response: The type of healthcare resources (i.e., drugs, healthcare provider services, ambulance transportation, examinations, hospitalisations, etc.) involved in the treatment of attacks, the respective proportion of patients using each resource, and average units were obtained from a survey of clinical experts that estimated healthcare resource use among patients with AHP in the UK.[29] Obtaining utilisation estimates directly relevant to UK clinical practice was a main goal of the survey. The survey was conducted in 2019 for Alnylam Pharmaceuticals by BresMed and involved structured face-to-face or telephone interviews with three UK expert clinicians. The three clinicians interviewed—Dr. Stein, a consultant at King's College Hospital; Professor Rees, a consultant haematologist at King's College London; and Dr. Badminton, a Chemical Pathologist consultant within the Cardiff Porphyria Service based at Cardiff University Medical School—have a combined 48 years of experience in treating 215

patients with AHP. Givosiran will be initiated within the NAPS Highly Specialised Service. The three interviewed clinicians are the lead consultants of the NAPS and have previously been investigators on Alnylam-sponsored studies, speakers at congresses, or advisors to Alnylam. No iteration was used in the collation of the expert clinician opinions. The full report of the survey (BresMed 2020) was included in the submitted reference pack.[29]

B10. The ERG acknowledge that the cost for all severe adverse events in the model were assumed to be the same i.e. £109 based on one physician visit (valued using PSSRU 2020). Please provide further rationale for assuming that each severe adverse event would only require one physician visit.

Response: The severe adverse events (AEs) considered in the model, namely asthenia, lipase increased, iron overload and headache, were obtained from the ENVISION trial (Severe Adverse Events During the 6-month DB Period by System Organ Class and Preferred Term; AHP Patients, Safety Analysis Set). In the safety report of the trial, hospitalisation was not reported for any of these AEs. As a simplifying assumption we therefore assumed that they would involve one visit to a clinician, which we valued using PSSRU. We did not include any drug-related costs as these are expected to be small and given the low incidence of AEs would have extremely small impact on the results of the analysis.

If we were to add a scenario where instead of one we consider three healthcare visits, for a total cost per AE of £327, the ICER would only minimally increase by [redacted]. We would be happy to include any additional scenario on the cost of AEs that ERG may consider appropriate.

Model related clarifications

B11. It would be helpful if you could provide one-way sensitivity analysis (OWSA) results which varies the proportion of patients experiencing chronic symptoms in each health state by +/- 10%.

Response: The prevalence of chronic conditions by health state was not included in sensitivity analyses because the CEM already varies the chronic conditions cost and utility decrements by health state which incorporates them (i.e., both costs and utility decrement by chronic condition are weighted by the respective prevalence in each health state to obtain the overall value by health state). Nevertheless, we addressed this request and we added the prevalence rate of chronic conditions in the OWSA varying base-case inputs by ± 10%. The updated OWSA including these parameters is presented in the model named "CEM Givosiran in AHP in UK_v10".

Table 15 and Figure 5 below present the updated results of the OWSA in terms of changes around base-case results following lower and upper variation in the 15 most influential model parameters. Please note that the updated tornado diagram was run around the new base-case ICER of [redacted], estimated addressing questions B14 (ToT applied for entire time horizon) and B15 (annual cost of opioid addiction divided by two to fit cycle length).

Table 15. Percentage change in base-case results following lower and upper variation in the 15 most influential model parameters

Parameters	Lower value (%)	Upper value (%)
ToT log-logistic parameters - Intercept	[redacted]	[redacted]
Discount rate costs	[redacted]	[redacted]
Discount rate outcomes	[redacted]	[redacted]
Proportion of females	[redacted]	[redacted]

Parameters	Lower value (%)	Upper value (%)
Initial age (years)	[redacted]	[redacted]
One-off cost (£) - Attack treatment	[redacted]	[redacted]
Attacks treated in the hospital (inpatient)	[redacted]	[redacted]
Norm of the general population, Parameters: Fixed	[redacted]	[redacted]
AAR by health state - Severe	[redacted]	[redacted]
Duration of attack (days)	[redacted]	[redacted]
Acute AHP attack disutility	[redacted]	[redacted]
Caregiver utility decrements by health state - Recurrent AHP	[redacted]	[redacted]
Caregiver utility decrements by health state - Asymptomatic AHP	[redacted]	[redacted]
Distribution of the cohort at model start - Symptomatic	[redacted]	[redacted]
Utility decrements by health state - Recurrent AHP	[redacted]	[redacted]

AAR: annualized attack rate; AHP: acute hepatic porphyria; ToT: time on treatment

Figure 5. Tornado diagram around base-case ICUR results for givosiran vs. BSC, presenting the impact of lower and upper variation in the 15 most influential model parameters

[redacted]

AAR: annualized attack rate; AHP: acute hepatic porphyria; BSC: best supportive care; ICUR: incremental cost-utility ratio; QALY: quality-adjusted life year; ToT: time on treatment

B12. The model was hard coded with a lifetime horizon with no option to test alternatives. Please provide the rationale for why shorter time horizons were not considered in the model.

Response: The lifetime horizon was selected in accordance with the NICE *Guide to the methods of technology appraisal*, according to which, "The time horizon for the analysis should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared."[54] The same recommendation was issued by the joint International Society for Pharmacoeconomics and Outcomes Research–Society for Medical Decision Making (ISPOR-SMDM) Modeling Good Research Practices Task Force.[55]

Accordingly, the lifetime horizon is the only relevant time horizon for the current cost-effectiveness analysis because:

1. Costs and health effects of givosiran accrue across a patient's lifespan since AHP is a chronic, hereditary disease—not, for example, an infection that can be cured at one point in time—and patients with repeated attacks also experience chronic symptoms and long-term complications.[5,13]
2. The rapid decrease in acute attack rate upon initiation of givosiran therapy should not be misinterpreted as implying that the cost-effectiveness of this treatment can be captured over a brief timespan. In fact, givosiran is not a short-term cure for AHP; on the contrary, the drug's mechanism of action (RNA interference) provides no basis to expect that attacks will remain suppressed if patients stop taking givosiran, in the absence of underlying changes in a patient's hormonal status unrelated to treatment. Thus, long-term treatment is required to maintain therapeutic effect.
3. Costs associated with treatment of chronic conditions occur immediately, whereas the benefits are likely to appear with some delay. Consequently, analyses with short time horizons would fail to capture important consequences for interventions that incur up-

front treatment costs but accrue a more gradual stream of health benefits (and possibly cost offsets) into the future.[56]

Accordingly, the lifetime horizon is the only relevant time horizon for the CEM according to NICE's own directives and international recommendations for cost-effectiveness modelling. The NICE guidelines explicitly support not considering shorter time horizons in the model: "Analyses that limit the time horizon to periods shorter than the expected impact of treatment do not usually provide the best estimates of benefits and costs."[54]

It should also be noted that the NICE guidelines state, "A lifetime time horizon is required [our emphasis] when alternative technologies lead to differences in survival or benefits that persist for the remainder of a person's life."[54] The ISPOR-SMDM recommendations are consistent on this point.[55] Although as a simplifying assumption our CEM does not assume a mortality difference between givosiran and BSC, it is not unreasonable to suspect some survival advantage for givosiran. Differences in the occurrence of chronic conditions and other complications might lead to differences in the lifetime mortality risk, even though this is not reflected in the current implementation of mortality in the model, which is not based on chronic condition prevalence. However, it is a virtual certainty that the benefits of givosiran will accrue across a patient's life, since not only will patients have a much higher chance of remaining attack free but also they should experience less pain and a lower risk for living the rest of their lives with other chronic conditions, for example by avoiding permanent nerve damage thanks to the suppression of the neurotoxic haem intermediates ALA and PBG. This is supported by the EMA attestation letter from Dr. Eliane Sardh (the head of medical care at Porphyria Centre Sweden and a lead author on the ENVISION study[10]): "My conclusion is that givosiran should be started as soon as you establish recurrent attacks in order to avoid permanent neuronal damage from porphyrin precursors."[57] Therefore, we consider that givosiran for AHP meets the conditions for which NICE requires a lifetime horizon.

Consequently, in order to be able to understand the value of givosiran treatment, yielding ongoing health benefits over a patient's lifespan compared with BSC (which leaves patients with worsening impairment), it is essential to consider the lifetime horizon and shorter time-horizons would not be appropriate.

B13. Section 12.2.1 (AHP mortality) of the CS mentioned that the Baravelli et al. found an overall mortality hazard ratio for AHP cohort versus the general population. However, the original publication only reported a HR for non-primary liver cancer malignancy (Table 3). Please explain this discrepancy.

Response: We believe the ERG is looking at the PDF for Baravelli et al. (2017), an analysis of cancer risk in AHP using 2000–2011 data from the Norwegian Porphyria Centre (NAPOS).[58] This is a different study from the reference used to derive the overall mortality hazard ratio (HR) in the CEM, Baravelli et al. (2020), which is an analysis of sick leave, disability, and mortality in patients with AHP using 1992–2017 data from NAPOS and the Norwegian National Registry.[59] The AHP mortality subsection on p 92 in Section 12.2.1 of the CS correctly cites Baravelli et al. (2020) for the mortality HR. However, it is easy to see how confusion could have occurred because, by pure coincidence, the adjusted HR for primary liver cancer in AHP from Table 3 of Baravelli et al. (2017) happens to be the same as the adjusted HR for AHP mortality reported on p 6 of Baravelli et al. (2020), namely 1.3.

B14. Priority question: Please clarify the following points relating to the extrapolation of time on treatment (ToT):

- ToT has been extrapolated in the model for 30 years. This is inconsistent with the approach taken for efficacy/transition probabilities. Please clarify the rationale for the choice of model horizon (30 years).

Response: The originally submitted model assumed that after 30 years from treatment start, patients who had not discontinued treatment would remain on treatment, since 30 years was considered a long-enough period to demonstrate good compliance and tolerability of treatment. However, we understand ERG's concern that this assumption has no supporting evidence. To address this concern we have changed this in the model so that the ToT is extrapolated over the entire time-horizon and the probability of discontinuation is applied to the cohort for as long as it remains on treatment. This change was made in the newly submitted model named "CEM Givosiran in AHP in UK_v10". The impact on the submitted ICER is a reduction of 0.9%.

- **[B14, contd.]** The ToT KM curve started plateauing from 16 months, which was represented well by the Gompertz function compared to the chosen log-logistic function. Please explain why the Gompertz function was not chosen for ToT extrapolation?

Response: The Gompertz curve is the one which deviates the most from the Kaplan-Meier (KM) curve derived on discontinuation data from the ENVISION (double-blind + OLE) trial. For this reason it was not considered as an adequate option for extrapolation. The Exponential was the best-fitting model based on Akaike Information Criterion and Bayesian Information Criterion values (i.e., lowest value is best fit). However, the exponential model would imply a constant probability of discontinuation in the long term, and this was believed unrealistic since usually discontinuation is highest initially and lower over the long run. For this reason, the log-logistic appeared to be a better option since it shows good visual fit to the observed KM curve and allows us to account for a declining probability of discontinuation over time.

B15. The opioid addiction cost as per Shei et al 2015 was applied per cycle (six months) in the model. However, it was reported as per patient annual incremental health care costs of prescription opioid abuse in the publication. Please comment on this discrepancy.

Response: We thank you for noticing this discrepancy and we apologise for having missed this in the initially submitted version of the model. We have addressed this in the newly submitted version of the model ("CEM Givosiran in AHP in UK_v10") where the annual cost of opioid addiction from Shei et al. (2015)[60] (i.e., £1,381) was divided by two to adjust it for the model cycle length (i.e., 6 months). The updated cycle cost of opioid addiction is therefore £691. The impact on the submitted ICER from this change is an increase of 1.4%.

B16. In the model [redacted] sheet, the probability of attack reported in cells D15:D21 did not match with the [redacted] results in the chart. For example, after six months of stopping treatment the median probability of attack mentioned in the chart was [redacted] whereas [redacted] was used for the calculations. Please comment on this discrepancy.

Response:

[redacted]

B17. Please explain why the following were not included in the OWSA as well as the probabilistic sensitivity analysis (PSA), despite uncertainty existing surrounding these parameters?

- Chronic complications prevalence rate for the health states

Response: As mentioned in the answer to question B11, the prevalence of chronic conditions by health state was not included in sensitivity because the CEM already varies the chronic condition costs and utility decrements by health state which incorporates them (i.e., both costs and utility decrement by chronic condition are weighted by the respective prevalence in each health state to obtain the overall value by health state). Nevertheless, to address the request of question B11 we added the prevalence rate of chronic conditions in the OWSA varying base-case inputs by ±10%. The updated OWSA including these parameters is presented in the model named "CEM Givosiran in AHP in UK_v10", and the results are presented above in our reply to question B11. Chronic condition prevalence has not been added to the PSA where parameters are varied simultaneously because this would result in double-counting of the impact of these components.

- **[B17, contd.]** Givosiran drug costs

Response: The cost of givosiran was not considered relevant to explore as a source of uncertainty since the list price is a known value: £41,884.43 per 189 mg/vial.[61] However, the list price is reduced by [redacted] in the proposed Managed Access Arrangement (MAA), as presented in CS Section 15.

- **[B17, contd.]** Probability of attack for the RDI (start-stop) scenario

Response: The probability of attack for the RDI (start-stop) scenario was not included in sensitivity analysis because it is not included in the reference-case analysis; it applies only to the MAA. Therefore, OWSA and PSA around base-case results would not be sensitive to changes in the probability of attack for the RDI (start-stop).

B18. Please clarify the discrepancy between the starting age in the model (41.6 years) and the average age of diagnosis reported for patients in the ENVISION trial (29/30 years).

Response: The starting age in the model is based on the age of patients at screening in ENVISION. Using age at screening is the appropriate variable on which to base starting age in the CEM because this represents the cross-section of patients who would initiate treatment with

givosiran in clinical practice today. In other words, the model considers prevalent, not only incident patients. Using age of diagnosis as the starting age in the CEM would be applicable if we intended to model only incident patients, but this would not correspond to the characteristics of the patient population that would receive givosiran upon a positive decision from NICE, since most patients in current clinical practice are older and have lived with AHP for many years post-diagnosis.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Givosiran for treating acute hepatic porphyria [ID1549]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

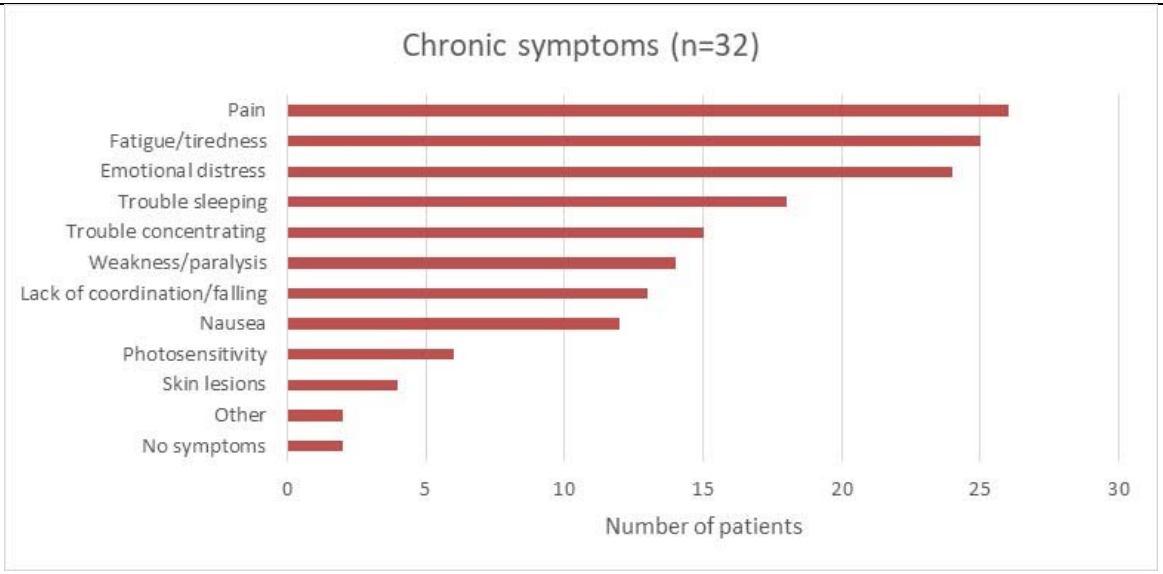
Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	**The British Porphyria Association (BPA)**

3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The BPA is a national charity that supports people with all types of porphyria. BPA funds come from member donations, fundraising efforts and grant-giving organisations. The BPA currently has around 400 UK members and around half of the membership are families affected by one of the acute porphyrias. The remainder are those affected by other porphyrias, plus medical professionals. The BPA's primary aim is to **support** those affected by the porphyrias; **educate** patients, relatives and medical professionals about the porphyrias, so as to improve the lives of those living with its effects; and promote **research** into this group of rare conditions.
4b. Has the organisation received any funding from the manufacturer(s) of the technology (Alnylam [givosiran]) and/or comparator products (Recordati Rare Diseases [haem arginate]) in the last 12 months? If so, please state the name of manufacturer, amount, and purpose of funding.	Yes, the BPA received funding in September 2020 to host an online event (in place of our usual face-to-face AGM which could not happen due to Covid-19) to reduce feelings of isolation in a vulnerable group of people. **Company**: Alnylam **Purpose**: grant for online patient day - Connect 2020 **Amount**: £2,000 **Company**: Recordati Rare Diseases **Purpose**: grant for online patient day - Connect 2020 **Amount**: £2,000
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patients and their families/carers are at the heart of everything that we do. The knowledge shared in this submission is derived from information gained through patient events, helpline conversations/emails with patients and carers and personal experiences of BPA committee members. The BPA's involvement in various surveys and studies relating to porphyria have also provided excellent insight into the patient burden of the

	condition and their experience of treatment. We have been systematic and obsessive about collecting data from members about their experience of living with porphyria and their perspectives on their treatment and care. In 2006, we sent out a postal survey to those with acute porphyria (AIP, HCP, VP) to learn more about the way patients are affected. A similar web-based survey was conducted in 2018 (in conjunction with BresMed and Alnylam Pharmaceuticals) to explore the burden of illness of acute porphyria on patients and their caregivers. The results of the 2018 *Living with Acute Porphyria* study have been formulated into a journal article that was submitted to Orphanet Journal of Rare Diseases on Monday 23 Nov (attached via NICE docs for your information). **NOTE: this article is academic in confidence** until the publication date. Finally, we also include data gathered from qualitative patient testimonials from patients affected by recurrent attacks of porphyria. Seven patients provided information about their experiences and the impact of porphyria on their lives. Three of these took part in the Givosiran trial and provide significant insight into the changes in quality of life that the medication has afforded them.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Acute porphyria patients suffer a high burden of symptoms and high impact on quality of life. **HIGH BURDEN OF SYMPTOMS** The main signs and symptoms of acute attacks are well documented: extreme pain, nausea, vomiting, constipation, hyponatremia, seizures, muscle weakness, paralysis and many stays in hospital. Other symptoms (and long-term complications) are not so well explored: fatigue and extreme tiredness, chronic pain between attacks, insomnia, fear and anxiety, weight loss, appetite loss, weakness, lack of coordination, renal impairment, hypertension, dependence on analgesics, venous access problems and iron overload. The following table notes the chronic symptoms experienced by respondents taking part in the *Living with Acute Porphyria* Survey (2018) (*respondents could choose multiple options*).



Each one of the symptoms is problematic, but the cumulative effect of numerous symptoms (in addition to acute attacks) creates a significant morbidity and immensely impaired quality of life.

ACUTE PORPHYRIA HAS A SIGNIFICANT IMPACT ON QOL FOR PATIENTS, AS WELL AS THEIR FAMILIES AND CARERS

Day-to-day quality of life: Regular hospital in-patient stays, devastating pain, and other chronic symptoms translate into significant debilitating effects on a patient's ability to undertake daily activities, such as personal care, household chores, childcare, personal relationships, work and study. This in turn has an exceptionally negative effect on physical health, family and social relationships, financial stability and psychological and emotional wellbeing.

In the *Living with Acute Porphyria* survey, 30 patients estimated the impact of acute porphyria on different areas of their lives: 60% indicated that the condition severely or extremely impacts on their pain/discomfort, while 70% noted that the condition severely or extremely impacts their psychological wellbeing.

> "*Life is affected in every aspect, it's the little things like losing your independence, but also having to plan life so carefully. It's a relentless managing of everything – accessing portacaths, surgeries, haem, ordering medications, juggling appointments, tracking cycles, booking deliveries, and assessing how much energy I can give to seeing friends or family, versus cleaning the house, or*

	whatever else is going on that day or week, or trying to exercise. I'm constantly thinking ahead and balancing my choices" (Patient Testimonial – R). **Impact on work/study:** acute attacks lead to long or frequent hospital stays or sick leave, while chronic symptoms also impact on working ability. Patients report stopping work entirely, changing from full-time to part-time or self-employment, changing job roles, or reducing hours due to the porphyria. Shift work or demanding careers are often unfeasible, while others are unable to study or fulfil career ambitions. In the 2018 survey, 60% of patients indicated that the condition severely or extremely impacts on their employment ability. Further, 42% of patients were in receipt of state benefits such as DLA, ESA and PIP. **Impact on family, social life and relationships:** when symptoms affect mobility, independent personal care or the ability to work, patients often become dependent on family members or partners for their own personal care, for childcare and for financial stability. This puts an immense physical and emotional pressure on relationships. The unpredictability of attacks, chronic pain, tiredness and anxiety impacts upon the ability to undertake 'normal' day-to-day activities, or even make plans. Forming and maintaining relationships or enjoying hobbies can be an extremely challenging area. **Impact on wellbeing:** The mental and emotional consequences of living with acute porphyria are significant with some patients experiencing suicidal thoughts. As with many long-term health conditions, feelings of anxiety or depression are high, while added to this is the fear of the next attack. Attacks themselves cause immense distress. Furthermore, the reliance on others and inability to take part in usual activities even in between attacks can massively impact self-esteem and feelings of wellbeing. **Impact on carers:** Family members often become full or part-time unpaid carers. The *Living with Acute Porphyria* survey reported dependence on carers and other unpaid family support for emotional support, hospital treatments and appointments, helping with medication, childcare, carrying out household tasks, and assistance with personal care and mobility. Partners of patients with acute porphyria reported the most time caring with an average of 27.7 hours per week, followed by parents who spent an average of 8.3 per week on caring activities. Caregivers indicated that the greatest consequences of providing care to an acute porphyria patient were in the areas of financial situations (with 57% reporting severe or extreme impacts), work (43% severe-extreme) social life (28% severe-extreme), relationship with spouse (28% severe-extreme).

	Respondents also reported challenges related to the emotional burden and the uncertainty associated with the condition, such as anxiety for the health of their loved one. In the survey, 73% of caregivers reported a moderate or severe impact on their psychological wellbeing.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	For patients with recurrent attacks of acute porphyria there are no licensed treatments available on the NHS that prevent acute attacks from occurring. **Haem arginate**: patients note that although haem is an effective treatment for treating an isolated acute attack, it doesn't prevent attacks. Patient-reported side effects of regular haem include venous thrombosis, extravasation injuries, severe venous access problems, numerous venous access devices, iron overload and the treatment becoming ineffective after many years, despite increased dosage. Furthermore, haem doesn't stop the chronic pain that requires opiate-based analgesia, nor does it improve chronic symptoms such as fatigue, insomnia, nausea or the stress of knowing that the next attack will start soon. Patients and carers report that a life on regular haem becomes a relentless cycle centred around infusions. As well as being lengthy, unpredictable and an inexact science requiring constant interaction from porphyria specialists, it requires arduous alterations to life in general and in terms of organising treatments and visits from medical professionals. The physical and emotional stress is compounded by the anxiety of not knowing whether venous access will hold out, whether more will be required over the following days and when/if some relief will finally be felt. **Gonadotrophin analogues (GnRH):** In the majority of patients treated with GnRH, if effective, it is effective for only a short period (a few months) before attacks resume again. It is also not applicable for the few men who suffer recurrent attacks and can only be used for a limited length of time. Even patients treated effectively for a short period with GnRH, note side effects to be 'horrendous' or 'unbearable' and patients report 'not feeling like myself'. Patients consider this to be a short-term option that might be worth a try to get a temporary break from the worst symptoms, rather than an effective treatment. **Liver transplantation**: The considerable risks involved in liver transplantation mean it is considered a last resort option by clinicians and patients. Lack of venous access and other complications can make the procedure risky or impossible. Patients also understand the immense burdens to them and their family/carers (and the NHS) in terms of follow-up care, complications, rejection and life on immunosuppressant medications.

	Acute porphyria patients in the UK are fortunate to have the National Acute Porphyria Service (NAPS) to coordinate their care, but despite the care and attention of NAPS, without an NHS treatment to prevent attacks, patients experiencing recurrent attacks are struggling with the high burden of symptoms and complications, and the consequential impairment to their quality of life, as well as to the quality of life of their families and carers.
8. Is there an unmet need for patients with this condition?	Yes. While the aforementioned treatments have an important place in porphyria care, alone they leave significant unmet need in the current standard of care for those with recurrent attacks of porphyria. None of the currently available treatments prevent recurrent attacks from occurring. Recurrent attacks of porphyria cause significant morbidity and immensely impaired quality of life for both patients and their wider circle of family and carers. We are aware that no one treatment is 100% safe or effective, but we strongly believe the potential magnitude of the benefits of Givosiran are worth investing in for patients, and consequently, for their carers and wider family.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients and carers report the following advantages of Givosiran: • Elimination of acute attacks (no hospital admissions) • Immediate eradication of acute pain • Over time, reduction or complete elimination of chronic pain, thereby leading to reduction or cessation of regular pain relief and dependence on opiates • Decreased fatigue and improved sleep patterns • Reduced or completely eliminated nausea and sickness (although some Givosiran patients have nausea as a side effect in the first few months of treatment it seems to improve over time) • Improvements in strength and general physical ability • Prevention of further decline in venous access, reduced reliance on portacaths and, in some cases, improvements to veins • Prevention of further iron overload and the chance to treat it effectively to bring levels back to normal • Prevention of repeated episodes of paralysis associated with attacks, leading to neurological recovery (not apparent immediately, but has become significant over the extended period on Givosiran) • Patients are less reliant on carers and family members for personal and medical care • Administration is simple and less invasive as compared to intravenous haem arginate (which requires a complex, highly trained procedure)

	• Administration is less time-consuming and requires fewer ancillary and personnel resources (including considerably fewer nursing time/visits) and fewer physical and mental pressures • Vast improvements to general wellness translate into the ability to fully take part in daily activities such as personal care, housework, childcare, work and study. As a consequence of these improvements in physical health, patient testimonials reported significant changes to lifestyle that translate into hugely positive impacts on quality of life for them and their families/carers. Examples quoted include: getting married, being able to work and/or study, the capacity to follow options for career progression and the ability to exercise. The cumulative impact of these changes leads to vast improvements in physical health, family and social relationships, financial stability and psychological and emotional wellbeing for both patients and their carers/family members. The magnitude of improvement to quality of life continues to grow because of the chance to capitalise on reduced morbidity to further improve strength and physical ability. Even modest improvements to nerve damage offer immeasurable, and seemingly disproportionate, enhancements to quality of life.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	• Some patients experience side effects such as an injection site reaction, but this is mild. Some patients also experience nausea, but this appears to alleviate within a few weeks/months of starting treatment • The long-term effects of the medication are not yet known • Anaphylaxis has occurred in one patient on the trial, therefore patients on Givosiran must have an epi-pen and this may impact on the opportunity to self-administer treatment • Some patients on the trial developed abnormal liver and kidney tests for a short period, which means patients will need ongoing monitoring of blood tests • Female patients of childbearing age do not know the potential impact on a pregnancy or unborn child
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than	None known

others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are not aware of any equality issues. However, we believe it is important for porphyria patients to have accessible, affordable and convenient treatment options available to them. With many patients unable to travel due to financial or physical constraints, we are concerned that there could be patients who are disadvantaged by the need to travel to porphyria centres for care. These patients could potentially be those in the greatest need who are very unwell or disabled and/or have limited financial resources. Therefore, we would like to see Givosiran available in a number of ways, including an option to treat at home.
Other issues	
13. Are there any other issues that you would like the committee to consider?	The EQ-5D is unlikely to fully reflect the profound changes that Givosiran can make to quality of life for patients. For example, a patient who has experienced the severe and excruciating pain of attacks, may rate their day-to-day chronic pain as slight or moderate pain as they are managing some level of functionality. Even a change to no pain on the scale, fails to reveal the enormity of the impact that has on all aspects of daily life. The same issue occurs with all of the categories in the EQ-5D where the impact arising from extent of changes in disability and psychological damage is difficult to infer. To try to expand on this gap in the knowledge base, we have collated and summarised a number of qualitative testimonials from patients experiencing recurrent attacks (attached in NICE docs). We would also like to draw NICE's attention to a study undertaken in the Netherlands, which conservatively calculated the basic cost of hospitalised care and haem treatment for acute porphyria patients. With median costs of €24k per recurrent patient per year, the authors acknowledge that their study likely underestimates the true impact on patient's life and costs. We would agree, given that it does not consider the costs of complications, surgeries, other medications, nor costs to wider health resources, social care and the welfare

	state. (Neeleman RA, Wagenmakers MAEM, Koole-Lesuis RH, et al. Medical and financial burden of acute intermittent porphyria *J Inherit Metab Dis*. 2018;41(5):809-817)

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- The devastating impact on QoL for patients with AHP is all encompassing and far reaching; the unpredictability and life-threatening nature of recurrent attacks affects every facet of daily life for patients and those connected to them.
- The side-effects of the existing treatments generate a host of complications and further comorbidities making them unfeasible in the long term, whilst also being traumatic, painful and psychologically damaging for the patient and their families.
- The financial burden is multifactorial, impacting first and foremost on the patient, their family and the wider society, but importantly also on the NHS, the social care system, the welfare system and other government and charitable resources.
- The improvement in symptoms and in physical, emotional and mental health of patients on Givosiran has an exceptional positive benefit on QoL for patients, their families and carers; ultimately alleviating the significant detrimental restrictions that AHP places upon them.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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Experiences from acute porphyria patients (recurrent attacks) presented as a series of patient testimonials

While preparing for the NICE submission, the BPA recognised that the existing literature and data from the trial was unlikely to fully capture the profound impact that AHP has on quality of life, nor demonstrate the immense changes that Givosiran can make to the quality of life for patients. Standard instruments are unable to collect detailed information and may fail to reveal the enormity of the benefit arising from the changes in measures to pain, self-care, usual activities, mobility and mental health. To try to expand on this gap in the knowledge base, we collated seven qualitative testimonials from patients experiencing recurrent attacks. All seven have been treated with regular haem treatment – three of the seven have experience in being treated with Givosiran.

The original design aimed to gather between 10 and 15 cases, however while speaking to volunteer patients, two became quite emotional and distressed at re-living their experiences and it was decided to refrain from collecting any more to protect the psychological wellbeing of this vulnerable cohort of patients.

The information for each case was gathered during a short 30-minute interview using a number of open-ended questions. The responses were written into a concise one-page document and sent to the patient for review and amendment if needed. The following questions were asked:

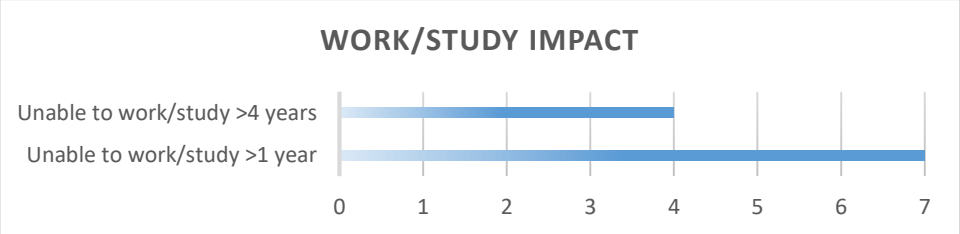
- When/how did symptoms start? What were the main symptoms?
- What kinds of treatment/hospital/interventions have been tried – and how long for?
- What do you do for work or study?
- Please describe the impact on your personal life, including family and relationships
- Has there been any financial impact from the porphyria?
- Is anyone else in the family affected?
- Can you describe how your life has been affected by AHP?

The sample of patients is small, but represents approximately one third of the patients suffering recurrent attacks in the UK at the current time.

Deep insight: The emotive and powerful quotations included within the cases go a small way towards describing the real impact on quality of life. The detailed descriptions provide some context and insight into the daily struggles and all-encompassing nature of living with recurrent attacks of acute porphyria, as well as the dramatic effect on quality of life that Givosiran can afford.

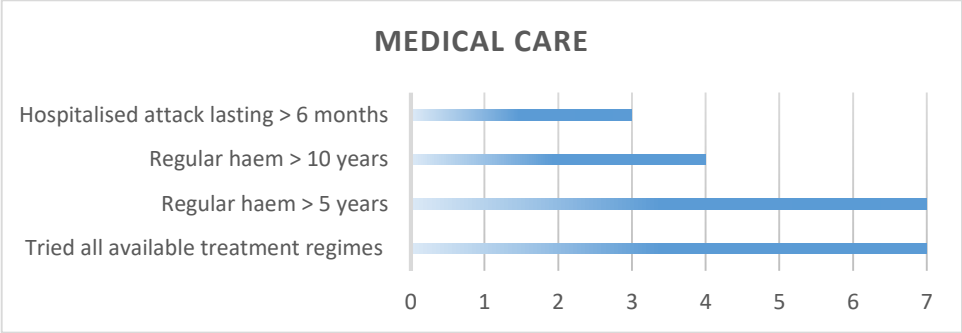
Additionally, the following notable factors have also been extracted from the seven cases.

Impact on work/study: One striking factor relates to the impact on work or study, with all patients reporting that they were unable to work at all for more than a year and many unable to work in any form for more than four years. None of those interviewed were able to work full-time while on haem therapy and some were unable to even commit to part-time hours.

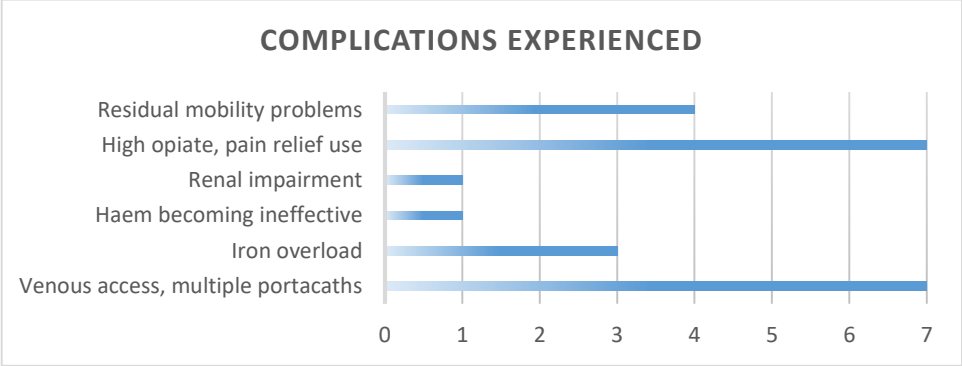


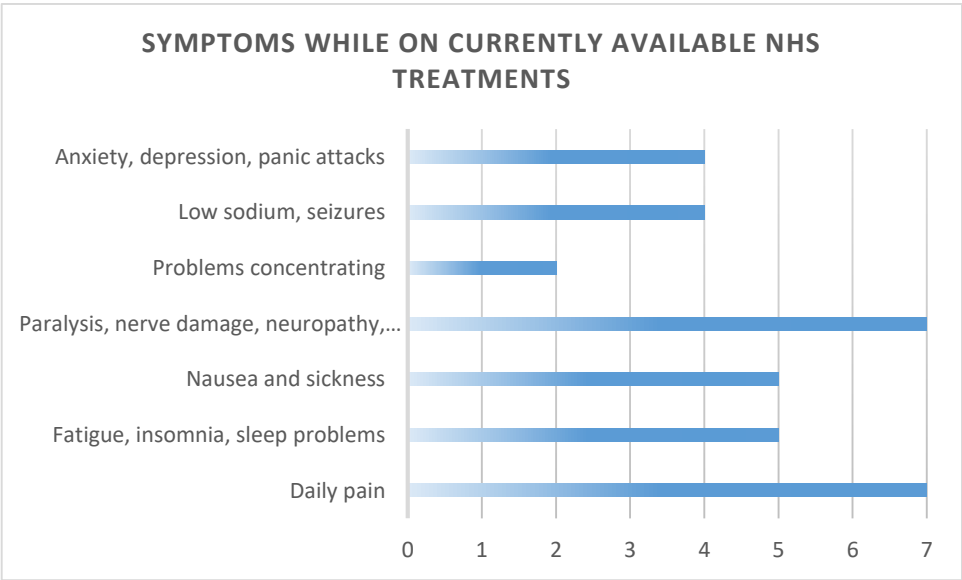
Three out of seven patients interviewed had suffered attacks that had required a hospitalised stay for longer than six months accompanied by long periods of recovery.

Further, all patients noted that it was impossible to calculate the actual number of hospital admissions they had experienced as they were so numerous/had lost count over the prolonged period of their care.



Complications and continuing signs and symptoms: the complications and range of symptoms noted by patients were numerous and provide further evidence of the burden on quality of life, as well as impact on healthcare resources. It is important to note that the factors below were raised during free-flowing conversations of a short, 30-minute duration. This format is unlikely to have identified ALL symptoms and complications experienced by patients, so it is highly probable that this remains an underestimate of the real burden.





Summary: the cases that follow in the subsequent pages provide a powerful insight into the way in which the cohort of patients suffering from recurrent attacks have every element of their lives affected by the condition. The effects permeate through all aspects of their lives, as well as the lives of their families and carers. In addition to the physical symptoms and measurable physical effects, the emotional and mental aspect of living with such a debilitating condition cannot be underestimated.

Patient A

Background and management

Diagnosed aged 19 after a series of severe attacks. Years of recurrent life-threatening paralysing attacks (worst between ages 19 to 26). Hospitalised for at least two weeks out of every month, as well as numerous ICU admissions and an 18-month admission where recovery looked uncertain.

Treatments: Weekly haem arginate for more than 16 years (first as an in-patient, then out-patient, then self-administered at home). Tried GnRH: worked for 6 months before attacks re-started. Started Phase I/II trial of Givosiran in 2016.

Complications: Damaged veins / sixth portacath. Severe nerve damage and muscle wasting. Renal impairment. Assessed for joint liver/kidney transplant 2015-16 due to lack of treatment options.

Impact on day-to-day life

Haem arginate	Givosiran
• Horrific pain on a daily basis – years on pain relief • Constant nausea and lack of appetite • Repeated bouts of paralysis – never got chance to recover from one bout before another added to it • Mobility and ability to self-care severely impaired – wheelchair and sticks used but still had regular falls and injuries • Constant planning, administering and recovering from haem treatments	• No attacks and no pain • Appetite returned • Digestion improved due to not using opiates • After prolonged period with no attacks, improvements in mobility and nerve damage • Improvements to physical strength and fatigue • Givosiran monthly injection easier and less time-consuming to administer and manage, plus no recovery time needed

AIP robbed me of so much: to take part in normal life, the chance to work and develop a career, to have another child, to walk, run and exercise, to travel. Finally, in my mid-40s, Givosiran has given me the chance to start experiencing life as it should be.

Impact on work, study and finance

• Working full time until first bad attacks • Unable to work at all for around 8 years • Eventually became self-employed (a few hours a week) as unable to commit to a regular part-time job due to pain, fatigue, unpredictability of attacks (incl. hospital admissions) and time-consuming treatments • No opportunity to develop a career, buy own home or plan for future financial stability	• Able to plan when treatments are needed • No attacks and no opiate-based pain relief has improved concentration and physical health • Able to increase amount of hours worked and take on regular employment • Now have the potential to plan for a slightly more secure future

Impact on family, social life and relationships

• Periods of complete dependence on partner and family for physical care as well as financial support	• Much valued independence and reduced reliance on others for support

Most of my twenties disappeared in a blurry haze of hospital admissions and all that comes with them – pain, sickness, endless puncturing from needles, total paralysis, breathing assistance, humiliation of being unable to care for personal needs or feed self, haem, more haem, sickness, pain, PAIN, PAIN! And repeat!

Patient B

Background and management

Initially triggered with symptoms aged 21/22

Series of severe attacks and condition deteriorated: pain, paralysis, low sodium, confusion

Currently 'managed' with weekly haem arginate but have still had three hospitalised attacks in last five months

Impact on day-to-day life

- During attacks: intense pain, nerve damage, sickness, weight loss
- After attacks: chronic pain, nerve pain and severe weakness in the months afterwards
- Numbness in legs
- Regular hospitalisation
- Weekly haem arginate for three years
- Damaged veins and third portacath
- Unable to sleep when in pain
- Constant tiredness

I feel like I'm on fire from the inside out, the pain is relentless in my stomach, back and sometimes my legs too. When it's like that I just don't know what to do with myself.

Impact on work, study and finance

- Working full time in the hotel industry until starting with symptoms
- Unable to work for four to five years due to major impact and paralysis from first attacks
- Over last 18 months, able to start working part time on a self-employed basis as a make-up artist
- Recently had a series of three attacks in five months – left very weak and unable to work many hours

Impact on family, social life and relationships

- In a three-year relationship until becoming ill. Break-up was related to the illness and inability to maintain a 'normal' relationship
- Relationships are difficult. 'It's hard to tell people about the porphyria, some people get freaked out about it all. It's difficult to even describe to friends what the condition is and how it affects me.'
- Dependent on family for personal care and financial support

I missed those first few years of establishing a career and doing all the things people in their 20s do – all my friends were developing careers, moving out and starting relationships. I missed out on that phase, and felt stuck in a time warp living with my parents at home!

Other impacts

- Day-to-day mental health significantly affected

I suffer from major anxiety, I'm on edge the whole time and when I'm having more attacks, I feel constantly agitated.

Patient C

Background and management

Diagnosed aged 10, recurrent attacks for many years, and weekly haem arginate from age 13

Life-threatening attacks with pain, sickness, paralysis and severe hypertension (200/140 @ age 10)

Complications: numerous portacaths & PICC lines with extremely poor venous access, iron overload (treated with medication); haem arginate gradually stopping being effective, despite increased dosage

Assessed for liver transplant due to lack of available treatment options

Now age 27, Givosiran for two years as part of ENVISION – completely life-changing effects

Haem arginate	Givosiran

Impact on day-to-day life

Haem arginate	Givosiran
• Constant fatigue • Pain in legs, abdomen, back and chest • Constant nausea and lack of appetite • Extreme weakness and nerve damage • Restrictions on ability to travel due to reliance on haem. No trips abroad • Unable to do any form of physical exercise or sport • Huge amounts of time planning due to constant treatment and recovery making it difficult to juggle any form of normal life	• More energy and active • No longer in pain all the time • Low impact of Givosiran injection in terms of tiredness and strain on body • Able to travel abroad for the first time since starting on the trial • No need to prepare for haem – convenient to administer • Portacath removed after several years • Able to take driving lessons

Impact on work, study and finance

Haem arginate	Givosiran
• Ages 10 to 17, school attendance was only between 9% and 21% due to hospitalised attacks every 6-7 days (4 haem treatments) • Delayed university, graduated later than expected • Missed opportunities and career goals	• Able to make career plans • Time and energy to dedicate to studies • Gained accreditation in a graduate programme since being on the trial • Able to work and earn a salary

Impact on family, social life and relationships

Haem arginate	Givosiran
• Was in a relationship but was reluctant to commit when future was so uncertain • Felt like a burden – disheartened/depressed • Quiet and kept to self without much interaction • Parents constantly worrying	• Able to live a relatively normal life • Recently married and optimistic about future • No longer dependent on others • Able to participate in sports and hobbies • More social and outgoing

Other impacts

Brother started with attacks aged 19/20. Now 30, he is suffering the severe mental impact of regular attacks. He is currently being treated with Haem every 7-10 days. Used to be a very social and outgoing person, but now constantly in pain and unable to work or study. He is depressed and feels trapped at home for the last several years without any sign of improvement.

Givosiran gave me faith that miracles really do happen and that there is hope to live a somewhat normal life, and everyone deserves that chance!

Patient D

Background and management

Diagnosed aged 19 after becoming severely ill receiving antibiotics for a chest infection

Recurrent attacks started quickly afterwards, GnRH used for nine months effectively, then recurrent attacks restarted

Life-threatening attack with paralysis (hospitalised for six months)

Weekly haem arginate

Impact on day-to-day life

- 50% good days, 50% bad days with chronic pain
- Continuing peripheral neuropathy
- Damaged veins and numerous portacaths
- High pain relief use
- Insomnia

I'm in constant pain every day.

Impact on work, study and finance

- Working full time until first bad attacks
- Unable to work at all for a year
- Started volunteer work as couldn't bear to do nothing. Eventually led to a part-time position

Impact on family, social life and relationships

- Highly dependent on partner, family and friends for physical care as well as financial support

The whole family has been hugely affected, but without them I wouldn't be here. They are my voice when I'm unwell as I can't remember much from my attacks at all. They are constantly worried and on edge that I'm going to start with another attack and deteriorate again quickly.

Other impacts

- Day-to-day mental health significantly affected

It took a life threating attack, complete paralysis and 6 months in two hospitals for me to realise that actually I am different, I am really poorly and if I don't listen I could die. This put an emotional strain on my relationship with my partner, my family and my friends. I had to learn to walk again because the porphyria had caused an excessive amount of nerve damage to my legs. Everything I touched was hurting, the sensations felt really weird. I didn't like people touching me. So after this attack I stopped work all together as I wanted to concentrate on my recovery and maintain my relationships with people. I took a whole year out of work but mentally I was struggling. I'm not that sit at home girl. So I made the decision to volunteer

Patient E

Background and management

Age 22 when first became ill with back pain, loss of sensation, weakness, confusion, collapsing, and dangerously low sodium levels, leading to life-threatening seizures

Regular attacks started quickly after the first attack; GNRH used for seven months but side effects too unbearable to live with – didn't feel like self

10 years of repeated attacks, at least 10 major hospitalised attacks where inpatient for around seven days (four or more days of haem) – plus countless attacks every year managed at home

Initially on five preventative haems a month – currently having one every fortnight using homecare – last flare two weeks ago

Ferritin levels very high – venesection likely in future

Impact on day-to-day life

- During attacks: pain, vomiting, nerve damage, altered sensation
- Between attacks: seven years of constant, chronic pain, high doses of pain relief and a cocktail of medications
- Damaged veins and six portacaths – not sure where another one can go due to irreparable tearing

Life is affected in every aspect, it's the little things like losing your independence, but also having to plan life so carefully. It's a relentless managing of everything – accessing portacaths, surgeries, haem, ordering medications, juggling appointments, tracking cycles, booking deliveries, and assessing how much energy I can give to seeing friends or family, versus cleaning the house, or whatever else is going on that day or week, or trying to exercise. I'm constantly thinking ahead and balancing my choices.

Impact on work, study and finance

- Working full time before AIP triggered
- Unable to attend work as a nurse for 18 months out of three years following diagnosis; made the decision to resign as didn't feel able to do the job safely and properly
- Financially lucky to be married to someone with a stable job who could provide financial backing

Impact on family, social life and relationships

- Tough on relationships – partner constantly feels helpless as nothing can do to help
- Delayed having children as too ill to consider being a mother – would have been too brutal on me and would have been incapable of looking after a child; caused a strain as both wanted children while young

Other impacts

I lost my 20s completely, and it takes so much work, time, effort and money every day to try to stay well and have a quality of life that I'm happy with. It's a full-time job. We even paid privately for two portacaths as the waiting lists were so long and PICC lines have a high infection risk, are difficult to manage around day-to-day life.

Patient F

Background and management

Started with symptoms age 27, pain in back, stomach and legs escalated quickly into first attacks.

Rapidly deteriorated to recurrent attacks associated with monthly hormonal fluctuations. Monthly hospital admissions for 6 months with 4 doses of haem each time.

GnRH failed to suppress hormones - attacks continued - but with the addition of 'unbearable' side effects.

Regular haem therapy started monthly, then fortnightly as an out-patient, then weekly via homecare.

Two years on Givosiran (ENVISION trial) – completely life-changing experience.

Haem arginate	Givosiran
Impact on day-to-day life	
• Dependent on a concoction of pain relief medications/approaches to deal with chronic pain • Constantly nauseous • Insomnia and disturbed sleep • Huge anxiety made worse by pain and medications	• No regular pain relief – bowels better as not using opiates • Not sick and nauseous • Sleep pattern has normalised • Reduced anxiety
Impact on work, study, finance and relationships	
• Prior successful career (full time) in training/HR • After attacks started, increased absenteeism from work – functioning <50%, then part-time hours • Made redundant within 7 months of attacks starting • Unable to work for at least a year • Husband took sole financial responsibility as well as helping with personal care • Unable to fully care for daughter when first born	• Able to begin working more hours • Able to plan and adhere to a regular work schedule • Potential to develop a career • Increased independence and the potential for financial input into the relationship • Able to fully contribute to family life and enjoy being a mum

I suffered a progressive deterioration in health with each attack: increased weakness, more pain, more fatigue, disturbed sleep, more haem, more sickness, more use of the wheelchair, escalating levels of medications, anxiety around earnings, lost independence, lost job and company car, downsized home as couldn't afford on one wage, complete dependence on partner for physical care, such as bathing, cooking and cleaning, as well as complete financial dependence on my partner and the benefit system. Administration of the haem was so stressful; none of the nursing staff knew what they were doing – it was terrifying as I didn't know what to do either. One of the hardest things was also having to admit that I couldn't do things that I was previously able to do.

Givosiran has been completely life-changing. I am able to contribute to family life, to my life, to think of the future. I feel able to take on responsibilities as a mother, a wife, and an employee – as everyone should be able to! I don't have to continuously plan. I'm able to live a life that I did before …. and for the first time in a long time … I'm excited for what my future could be again.

Patient G

Background and management

First suffered symptoms aged 18 as a result of hormonal implant: back and stomach pain, collapsing, BP problems, severe weakness and lengthy time to diagnosis

1.5 years of multiple in-patient admissions, plus a hospitalised attack lasting many months and total paralysis during a pregnancy

Weekly haem arginate used for 8 years to try curb attacks; still having a couple of hospitalised attacks per year plus mild attacks dealt with at home and chronic pain in between

Impact on day-to-day life

- 'Indescribable pain that has all types of pain in one'
- Continuing peripheral neuropathy
- Severe weakness
- Damaged veins and numerous portacaths
- High pain relief use during attacks
- Constant chronic pain: can't sit still, constantly moving/fidgeting due to the aches
- Inability to concentrate
- Suffer panic attacks while on medication
- Severe nerve damage – unable to walk fast or run

This past year has been the worst because I began to think that it wasn't worth being alive.

In the years after being diagnosed, I thought that I'd be ill for a little while and then they would fix me, I'd be back to normal again, but after 10 years it has begun to sink in… I'm never going to get over it.

Just living with it continuously is too much and I just couldn't face it.

Impact on work, study and finance

- Not able to work full-time
- Study impaired due to inability to concentrate and poor attendance
- Periods of temporary employment – one role ended after trying to work through attacks which led to vomiting in a customer facing area

Impact on family, social life and relationships

- Negative effect of pain and being unwell on the ability to maintain relationships. 'I sometimes go into my shell and ignore people – cut people off – then it's hard to explain why'.
- Dependent on partner and two young children for personal care, housework and financial support which alters the relationship dynamic

We were just starting to build our family and then it all came crashing down. My partner had to take time off work to look after me, to look after our daughter and then our son too, to do the housework and the shopping, to take me to appointments. I became completely dependent on him. Our finances were hugely impacted, but also our whole relationship changed.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Givosiran for treating acute hepatic porphyria [ID1549]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	**Global Porphyria Advocacy Coalition (GPAC)**
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	GPAC was officially registered in May 2020, but it has been operating as an international group since early 2019. GPAC is an umbrella organisation that provides a unified, collaborative voice for porphyria patients worldwide. It connects, supports and engages national porphyria patient advocacy organisations, through the provision of an integrated international network, in an effort to gain awareness, access to diagnosis, management and treatment of the porphyrias. GPAC inclusively and equally supports all of the porphyrias, promotes knowledge sharing among groups, and is transparent in its working practices. This approach supports patients/caregivers, physicians, researchers and regulatory bodies and ultimately, safeguards the interests of all individuals impacted by the porphyrias. GPAC has 23 country Members including the British Porphyria Association (BPA). GPAC is funded by an annual (advised) Membership Fee from the National Organisation Members and wider donations. GPAC aims to complement and facilitate the existing national patient group's actions. It also promotes the interests of often small national organisations in order to provide more effective support for patients who suffer from this group of rare diseases. GPAC has collaborated on the BPA's submission and is fully in support of all the information provided within it.
4b. Has the organisation received any funding from the manufacturer(s) of the technology (Alnylam [givosiran]) and/or comparator products (Recordati Rare Diseases [haem arginate]) in the last 12 months?	No.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information has been gathered through GPAC's cross-border support of patients and patient organisations. These organisations and their members have decades of experience in supporting patients and carers who suffer from the devastating impact that AHP has on patients, families and carers. These stories have been correlated with the experience of British patients as gathered by the BPA. As president of GPAC, I personally have been a severely affected AHP patient for more than 12 years and have been heavily involved providing direct support to patients via the BPA for over 10 years, also supporting the initiatives detailed in the BPA response. GPAC would like to iterate our support for the Patient Testimonials (presented by the BPA) which MUST be considered as they provide detailed insight (directly from patients) on the impact and high burden that living with AHP has on all facets of life. GPAC strives to share factually accurate information and also recognises the important experiences noted in the academic research papers identified below which provide further insight into AHP and the impact it has on patients, carers and their families: [redacted] Gouya, L., Ventura, P., Balwani, M., et al. (2020) EXPLORE: A Prospective, Multinational, Natural History Study of Patients with Acute Hepatic Porphyria with Recurrent Attacks. *Hepatology*. 71(5):1546-1558. Marsden, J.T., Guppy, S., Stein, P., Cox, T., Badminton, M., Gardiner, T., Barth, J., Stewart, M., Rees, D. (2015) Audit of the use of regular haem arginate infusions in patients with acute porphyria to prevent recurrent symptoms. *JIMD Rep*. 22:57-65.

	Naik, H., Stoecker, M., Sanderson, C., Balwani, M., Desnick, R. (2016) Experiences and concerns of patients with recurrent attacks of acute hepatic porphyria: A qualitative study. *Molecular Genetics Metabolism* 119(3):278-283. Neeleman, R.A., Wagenmakers, M., Koole-Lesuis, R.H., Mijnhout, G.S., Wilson, J.H.P., Friesema, E.C.H., Langendonk, J.G. (2018) Medical and financial burden of acute intermittent porphyria, *J Inherit Metab Dis.* 41: 809-817. Simon, A., Pompilus, F., Querbes, W., Wei, A., Strzok, S., Penz, C., Lyon Howe, D., Hungate, J.R., Kim, J.B., Agarwal, S., Marquis, P. (2018) Patient perspective on acute intermittent porphyria with frequent attacks: A disease with intermittent and chronic manifestations. *Patient.* 11(5): 527-537. Stein, P., Badminton, M., Barth, J., Rees, D., Stewart, F. (2013) Best practice guidelines on clinical management of acute attacks of porphyria and their complications. *Annals of Clinical Biochemistry; International Journal of Laboratory Medicine.* 50(3): 217-223.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	To demonstrate the actual impact of what it is like to live with recurrent attacks of AHP, the BPA has presented some detailed real-life patient perspectives to provide focus on the symptoms and the extent to which these symptoms impact on the patient, their carers and the family. GPAC understands what it is like to live with recurrent attacks of AHP and feels that the patient perspective MUST be considered within NICE's evaluation in order to fully acknowledge the truly devastating impact and high burden that living with recurrent attacks has on every facet of life, including quality of life. This cohort of patients experience a life that is centred around devastatingly frequent attacks of severe pain, sickness, weakness, paralysis and partial paralysis where the outcome is often uncertain. These main symptoms are just the tip of the iceberg, the BPA's submission provides a graph of more detailed symptoms that also need acknowledging, alongside additional comorbidities. The unpredictable and uncontrollable nature of these recurrent attacks of AHP present a significant burden and have a devastating and irreparably damaging impact on the ability of the patient to: • work/study or try to work/study; • form and maintain relationships;

	• contribute to 'normal' family and social life; • earn a living and be financial independent from the state; • contribute: as a parent (or have children), as a partner, as a family member and as a friend. A chaotic and compromised life ensues for these patients and their families which is not only physically but also mentally damaging and traumatic. The physical agony and emotional turmoil is experienced by not only the patient, but also by those supporting and caring for them. It is also important to acknowledge that these patients and their families often find that their whole financial sphere and opportunities in the workplace are compromised, affecting not only the patient but also their partner's ability to work, impeding all parties in their ability to maintain job security, progress in work as well as the potential to have a fulfilling career. Moreover, for many patients, this generates a state of financial hardship, directly leading to dependence on the state and a lack of capacity to obtain financial security from earnings/wages, but also having a knock-on effect on the rest of their financial sphere, such as the inability to secure a mortgage or suitable tenancy agreement. The difficulty of living with recurrent attacks of AHP must not be underestimated. These patients and their families face a life that is wholly and immeasurably compromised. All of which has an exceptionally negative impact on quality of life as well as the psychological wellbeing of the patient, impacting greatly and significantly on feelings of anxiety, depression, failure, inferiority, guilt, loneliness, helplessness and suicidal feelings which must not be overlooked. The journey for family members and carers is equally devastating, scary, traumatic and damaging in the long term; ultimately having a significant and negative effect on the whole household.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	GPAC fully supports the information provided in the BPA's submission.

8. Is there an unmet need for patients with this condition?	Yes. There are no treatments available to NHS patients that STOP recurrent attacks and the subsequent/devastating symptoms and complications that go hand in hand with this awful pattern of disease.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The advantages of this new technology/treatment on the patient and their carers has been described as completely life-changing. Allowing patients to see significant changes in attack occurrence as well as significant improvements in the debilitating symptoms that go hand in hand with recurrent attacks of AHP. The three patient testimonials of patients receiving Givosiran provide a tiny snapshot of what has been observed by GPAC on a worldwide basis for the patients involved in the Phase II and Phase III trials. For the first time ever, for these patients there is a treatment that can end this devastating and unpredictable cycle of recurrent attacks thus allowing the patient time to fully recover from what can only be described as a completely all-encompassing and distressing cycle of chaos for all concerned.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	GPAC agrees with the BPA's response and also notes that as with any new technology the long-term effects of any new medication are still unknown. Thus, follow-up on these patients should be continued in years to come to monitor any long-term effects.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	At this stage, this information is not known to GPAC.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	GPAC fully supports the information provided in the BPA's submission.
Other issues	
13. Are there any other issues that you would like the committee to consider?	GPAC fully supports the information provided in the BPA's submission.
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- There are currently no treatments available to NHS patients that STOP recurrent attacks – Givosiran is a treatment which can STOP this awful pattern of disease and the subsequent/devastating symptoms and complications that go hand in hand with it.
- The devastating impact on QoL for patients with AHP is all encompassing and far reaching; the unpredictability and life-threatening nature of recurrent attacks affects every facet of daily life for patients and those connected to them.
- The side-effects of the existing treatments generate a host of complications and further comorbidities making them unfeasible in the long term, whilst also being traumatic, painful and psychologically damaging for the patient and their families.
- The financial burden is multifactorial, impacting first and foremost on the patient, their family and the wider society, but importantly also on the NHS, the social care system, the welfare system and other government and charitable resources.
- The improvement in symptoms and in physical, emotional and mental health of patients on Givosiran has an exceptional positive benefit on QoL for patients, their families and carers; ultimately alleviating the significant detrimental restrictions that AHP places upon them.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Givosiran for treating acute hepatic porphyria [ID1549]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: National Acute Porphyria Service at Cardiff and Vale University Health Board

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Givosiran for treating acute hepatic porphyria [ID1549]

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Givosiran is a new treatment recently licensed to treat recurrent acute attacks in patients with acute hepatic porphyria (AHP). This subgroup of AHP patients is defined as those who have had four or more admissions to hospital to treat an acute attack over a 12 month period. AHPs include acute intermittent porphyria (AIP), hereditary coproporphyria (HCP) and variegate porphyria (VP), although the majority of those who experience recurrent acute attacks are patients with AIP. AIP is also the most common AHP.

A three year epidemiological survey of porphyria in Europe reported the estimated prevalence of symptomatic (active) acute intermittent porphyria as 5.4 per million, equivalent to about 300 people in England, with about 10% of AIP patients going on to experience recurrent attacks(Elder et al The incidence of inherited porphyrias in Europe. J Inh. Met. Dis. 2013; 36: 849-857). This figure is comparable to the experience of the National Acute Porphyria Service (NAPS) over the past 8 years. The service currently manages 26 AHP patients in England for recurrent attacks, with approximately 2-3 new patients per year and about the same number stopping regular therapy. The majority of patients (>95%) are on regular haem arginate therapy. Patient numbers have therefore remained stable over this period. It is likely that most of these patients would wish to switch to givosiran treatment although this is difficult to predict accurately at present.

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision?

All patients who are diagnosed with an attack of porphyria are cared for by the National Acute Porphyria Service, which also supports the care of patients in Wales and Scotland. Patients are followed up for a minimum period of 2 years, with the main objective being to support local medical teams to treat and manage the condition in the acute setting, supported by regular outpatient care by NAPS. However those patients that develop recurrent attacks are offered life-long follow-up by the NAPS service in order to manage the porphyria and to monitor for the development of long-term complications such as hypertension, progressive renal damage and liver cancers.

Current treatments for recurrent attacks of porphyria include either preventative therapy with regular haem arginate infusions, which is unlicensed, or hormonal therapy with gonadorelin analogues to suppress ovulation in women with pre-menstrual attacks. In patients with severe disease which is no longer responsive to medical therapy liver transplantation may be considered. However to our knowledge there have been no liver transplants performed in the last 2 years, probably due to the recent clinical trial and subsequent licensing of givosiran.

Is there significant geographical variation in current practice?

There is no geographical variation in practice in the United Kingdom to our knowledge.

Are there differences of opinion between professionals as to what current practice should be?

All AHP patients in England, Scotland and Wales are managed by the two NAPS service (Cardiff and King's). We work closely together and are largely in agreement on management of AHP.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Regular intravenous infusions of haem arginate (usually 2-4 doses per month) are used to maintain hepatic haem levels with the objective of preventing acute attacks. As noted this haem arginate use is not licensed and has not been investigated through a clinical trial. However it is the main long-term therapy used to treat severely affected AHP patients, and in most patients reduces the frequency and severity of attacks. However most patients will continue to have occasional attacks requiring hospital admission, and milder symptomatic episodes which they strive to manage at home. Many recurrent patients will experience debilitating symptoms such as pain, nausea, and fatigue in between acute episodes, which have a profound negative impact on all aspects of their lives. Side effects, particularly the difficulty maintaining central venous access, and liver iron overload mean that haem infusions cannot continue indefinitely. Haem is a potentially toxic molecule, which is taken up by the liver following infusion. Regular haem arginate infusion is reported to cause chronic hepatic inflammation, which may contribute to prolonged recurrence of attacks (Schmitt C et al. Recurrent attacks of acute hepatic porphyria: major role of the chronic inflammatory response in the liver J Intern Med. 2018 ;284:78-91)

Some female AHP patients experience frequent acute attacks and symptoms associated with the second half of the menstrual cycle. A proportion of these patients respond to ovulation suppress using gonadorelin analogues to induce a reversible "menopause". The limitations of this therapy include estrogen deficiency side effects, which usually limit the duration of therapy to 2-years (Schulenburg-Brand D et al, An audit of the use of gonadorelin analogues to prevent recurrent acute symptoms in patients with acute porphyria in the United Kingdom. JIMD Rep. 2017;36:99-107.

Liver transplantation has been used to treat recurrent acute attacks where medical therapy is no longer effective, or can no longer be administered due to venous access difficulties. Although generally successful in treating the acute porphyria, it does not improve chronic damage that has occurred as a consequence of the previous attacks or their therapy. Patients require long term immunosuppression, and an association with hepatic artery thrombosis in this subgroup of transplanted patients means that they also require long-term anticoagulation.

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Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

None that we know of.

What is the likely impact of the technology on the delivery of the specialised service?
Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals)?

The current service is commissioned to provide regular haem arginate as Homecare (delivered by a private company), and we would anticipate this facility would continue but deliver givosiran once patients are stable on the therapy. It is therefore unlikely the service requirements would change significantly or require any additional staffing or infrastructure.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Givosiran is very recently been licensed and I have no experience of use at present. It is very specifically designed to target the underlying pathophysiology of acute attacks. In my opinion it is therefore only likely to be used within its licensed indications as directed by one of the NAPS clinicians.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

UK clinical guidelines were developed by the British and Irish Porphyria Network in 2012 and published in 2013 (Stein *et al*. Best practice guidelines on clinical management of acute attacks or porphyria and their complications. Ann Clin Biochem 50:217-23, 2013). These guidelines are based on expert opinion and evidence where available, and were updated in 2017, although not formally published.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The results of the clinical trials strongly suggest that when compared with prophylactic haem arginate infusions or gonadorelin analogue therapy, givosiran is likely to be more effective than these established but unlicensed therapies.

There will be an additional advantage in relation to administration, as givosiran is administered via monthly subcutaneous injections and therefore does not need long-term vascular access via a central venous access device. This frequency and ease of use is also likely to be less intrusive to patient's daily lives.

The requirement for central venous access has also posed additional risks for patients, who often require repeated procedures to replace vascular access devices which block regularly, partly due to the nature of the haem arginate itself. This has been particularly difficult during the COVID pandemic due to reduced access to vascular services. In addition, there is an accumulation of vascular damage to large vessels which has made replacement increasingly difficult in some patients.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Given the natural history of active porphyria in this group of patients it is likely that the frequency and severity of symptoms will diminish with time and patients are unlikely therefore to require lifelong treatment. However at present it is not possible to accurately predict how long treatment should be continued, and because of the variable nature of the disease, this is likely to differ between patients. We have discussed this issue at NAPS meetings, and the consensus view was that patients are likely to require several years of therapy in order to achieve a full remission. It was also suggested that a multi-centre and multidisciplinary team would review patients on an annual basis to make decisions on stopping and starting therapy. The aim would be to ensure consistent, fair and transparent treatment decision making, particularly on initiation and discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

As far as I am aware the clinical use of givosiran reflects current UK practice, certainly in the UK where the patients recruited were amongst the most severely affected patients. Anecdotal information from other porphyria centres in Europe indicates that most countries have a similar proportion of patients with severe recurrent attacks who were recruited to the trial.
The most important outcomes for patients include the attack rate, the effect on pain and quality of life and any ongoing need haem arginate (i.e. because of an attack). All of these clinical outcomes were measured in the trial. It would be expected that

ongoing treatment would continue to provide these benefits, and therefore the long-term outcomes are likely to be maintained. Secondary outcomes included the biochemical markers, porphobilinogen and 5-aminolaevulinic acid which were both suppressed.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

As I understand most reported side effects were mild and self-limiting. However a proportion of patients had changes in liver function, which in most cases settled spontaneously. One case led to a discontinuation of therapy. Some patients were also noted to have a deterioration in renal function, which could have been due to the acute porphyria rather than the treatment as this is a recognised complication. It is likely that these will need to be monitored regularly in AHP patients on treatment.
I am not aware of any other adverse clinical outcomes that have come to light after the trial.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Not that I am aware of.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

In the event of a positive recommendation it is likely that givosiran would replace current treatment for the majority of recurrent patients on regular haem arginate therapy. This treatment and clinical follow-up is in place already as part of the NHS commissioned severe acute porphyria service (i.e. NAPS). Current treatment is administered by qualified nursing staff, and supported by a porphyria specialist nurses employed at each NAPS centre. Additional staff and facilities are therefore very unlikely to be required.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

It is unlikely that severe acute porphyria patients know to the service would be directly affected. However given the novel nature of the treatment and the small number of porphyria centres this could place geographical constraints on some patients, particularly those with physical disability. Patients requiring frequent assessment and monitoring, particularly during the early months of treatment, might need additional support to attend a NAPS centre.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Your privacy

Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Givosiran for treating acute hepatic porphyria [ID1549]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: National Acute Porphyria Service at King's College Hospital

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

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Givosiran for treating acute hepatic porphyria [ID1549]

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

Givosiran is used to treat recurrent attacks of acute hepatic porphyria, which is defined as 4 or more severe attacks requiring hospital admission per year. Virtually all patients with recurrent attacks have acute intermittent porphyria, the most common form of acute hepatic porphyria. It is extremely rare to have recurrent attacks of variegate porphyria or hereditary coproporphyria.

The prevalence of symptomatic acute intermittent porphyria (i.e. with attacks) in Europe is estimated as 5.4 per million people (Elder *et al*., JIMD 36:849-57, 2013) equivalent to about 300 people in England, with about 10% of them experiencing recurrent attacks. This agrees well with the experience of the National Acute Porphyria Service (NAPS) which currently has 26 patients receiving treatment for recurrent attacks all of whom have acute intermittent porphyria. We would expect many, but not all, of these patients to switch to givosiran treatment if it becomes available. This number is fairly stable, with between one and 3 patients starting, and a similar number stopping, treatment each year.

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision?

Patients who experience an attack of porphyria are cared for by NAPS. There are 2 main NAPS centres, one at King's College Hospital, London and one at University Hospital of Wales, Cardiff. The service provides immediate clinical support and management advice to acute care physicians at the patient's local hospital, including provision of haem arginate when necessary. Shared care arrangements are put in place with an appropriate local physician where possible. Outpatient follow up is arranged in specialist NAPS clinics (including a number of outreach clinics) for a minimum period of 2 years to manage ongoing treatment and complications. Patients who go on to develop recurrent attacks are followed up for life as they are at risk of various long-term problems although the majority do not need life-long treatment to prevent attacks.

Current treatments for recurrent attacks of porphyria are:
1. Prophylactic (off label) use of haem arginate
2. Gonadorelin analogues in women with pre-menstrual attacks
3. Liver transplantation

Is there significant geographical variation in current practice?

Current practice is the same in England, Scotland and Wales with care being provided through NAPS.

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Givosiran for treating acute hepatic porphyria [ID1549]

Are there differences of opinion between professionals as to what current practice should be?

There is broad agreement on current practice among porphyria specialists in the UK and Europe (and to some extent world-wide).

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Prophylactic (off label) use of haem arginate is the main treatment to prevent recurrent attacks. The drug is typically administered as an infusion every 1-4 weeks. Patients are required to have a central line (usually a port-a-cath) as the drug is toxic to veins and likely to cause thrombophlebitis if infused peripherally. This treatment usually provides some benefit; 67% of patients had a reduction in pain in an audit of 22 NAPS patients on haem arginate prophylaxis (Marsden *et al*., JIMD Rep 22:57-65, 2015). However the treatment is invasive and time consuming, and almost all patients continue to struggle with debilitating symptoms particularly constant pain, nausea, fatigue, and from time to time, full blown attacks requiring hospital admission. This has a profoundly negative effect on all aspects of their lives including physical and mental health, relationships, family life, social life and ability to work.

A particular problem is that once haem arginate prophylaxis has been started, typically when patients are young adults, it is very difficult to stop, so patients may remain dependent on this treatment for the next 20-25 years. Haem arginate is a potentially toxic molecule which is taken up by the liver following infusion. Recent evidence suggests that long term use of this drug may cause chronic hepatic inflammation, which drives prolonged recurrence of attacks (Schmitt *et al.,* J Int Med 284:78-91, 2018). Liver iron overload due to high haem arginate use may be a contributory factor. Maintaining central venous access over the many years that patients need this treatment is extremely challenging and the main limiting factor.

Gonadorelin analogues to suppress ovulation may be helpful for a short period of up to 2 years in some women with hormonally driven attacks. However oestrogen deficiency side effects are a problem, and efficacy is limited with many patients needing to switch to prophylactic haem arginate instead. Only one NAPS patient with recurrent attacks is currently being managed in this way.

Liver transplantation is a last resort option considered when no other treatments are possible or effective. This is regarded as curative although concerns include the requirement for long term immunosuppression and anticoagulation, and their effect on renal function. Only one patient has received a liver transplant since the start of NAPS in 2012.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

No

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What is the likely impact of the technology on the delivery of the specialised service?
Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals)?

The delivery of NAPS would not change significantly. There should be no requirement for additional staffing or infrastructure. Homecare provision is already part of the service and would continue at a similar level.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

In the UK givosiran is only available through the clinical trial, or the post-trial Expanded Access Program.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The UK clinical guidelines were developed by the British and Irish Porphyria Network (Stein *et al*., Ann Clin Biochem 50:217-23, 2013). These guidelines represent "best practice" and are based on consensus expert opinion and evidence where available.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The results of the clinical trials, including our own experience as a UK trial site, strongly suggest that givosiran is far more effective, better tolerated, and much easier to use in comparison to prophylactic haem arginate.

Five UK patients have been treated with givosiran for periods of between 2.5 and 4 years, and the effect has been transformative. All patients report minimal or no porphyria symptoms, including virtually no pain. They no longer require opiate analgesia and none of them have needed haem arginate for at least 2 years. The drug has been well tolerated by all our patients with only minor side effects.

The practicalities of givosiran treatment are simpler and easier than haem arginate infusions. The administration of givosiran as a quick subcutaneous injection once a month is a huge advantage and far more acceptable to patients compared with prophylactic haem arginate treatment, which involves a complex, 2 hour infusion given through a port-a-cath, typically every 1-2 weeks.

Maintaining central venous access in patients with recurrent attacks is challenging and is usually the limiting factor when trying to continue haem arginate treatment for many years. The fact that givosiran treatment does not require venous access is a big plus.

One problem when managing patients with recurrent attacks of acute intermittent porphyria is that it can be difficult to distinguish between flares of chronic pain and true acute attacks which need to be treated differently. Urine porphobilinogen (PBG) concentration typically remains high in these patients despite prophylactic haem arginate treatment and rarely helps in decision making. An unexpected benefit of givosiran treatment is that in most patients, urine PBG is suppressed to very low levels, so it is much more useful as an attack marker. In particular, the finding of a low urine PBG concentration in a patient with pain can rule out an attack and the need for haem arginate treatment.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

We don't know how long patients will need to be treated with givosiran, or how easy it will be to stop this treatment. Some patients may stop treatment but subsequently need to restart if their attacks recur. There is likely to be quite a lot of individual variation. Factors such as the length of time a patient has been treated with prophylactic haem arginate treatment before switching to givosiran may be relevant. Nevertheless, we expect that for most patients, givosiran treatment would continue for a period of several years, not as a life-long treatment. We plan to review patients once a year in a cross-service MDT to ensure decisions about starting, stopping or restarting treatment are fair and equitable.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The use of givosiran in the clinical trial is consistent with clinical practice in the UK.

The most important outcomes for this group of patients are attack rate, hemin use, effect on pain, quality of life and urine ALA and PBG concentrations, which were all measured in the trial.

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What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The risk of anaphylaxis is significant (1 trial patient out of nearly 100 was affected) and means that patients will need to receive their first few treatments in hospital, and later move to homecare with a visiting nurse administering the injection rather than self-administration.

Abnormal or worsening liver, kidney, or pancreatic function tests were seen in some trial patients, so regular monitoring will be needed in patients being treated with givosiran.

Other side effects (nausea, fatigue, infusion site reactions) are mostly mild, easily managed and improve with time.

Safety in pregnancy has not been determined but is highly relevant given that most patients with recurrent attacks are young women of child-bearing age.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None known

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within
the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

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Givosiran for treating acute hepatic porphyria [ID1549]

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

If NICE made a positive recommendation about givosiran, then patients currently being treated with prophylactic haem arginate would be assessed for their suitability and willingness to switch to givosiran. Minimal staff training would be needed and we anticipate that no additional resources would be required.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

We expect givosiran treatment to be administered mostly at home once treatment is well established. However the risk of anaphylaxis means that patients starting treatment would need to attend a hospital for their monthly injections for an initial period probably of several months. In addition, all patients will require regular monitoring for side effects which may be best carried out in a hospital environment.

We would need to make sure that patients living anywhere in the England could access treatment, and that they would not be disadvantaged if they were unable to travel to a NAPS centre to receive treatment or for monitoring, because of long travel times, cost, availability of transport or disability.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Givosiran for treating acute hepatic porphyria [ID1549]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England and Improvement**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? **x**☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no national NHSE clinical commissioning policies for acute hepatic porphyria
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There has been a commissioned service from two providers as part of the National Acute Porphyria Service (NAPS) since 2012/13. Patients are seen in outpatient clinics across the country. The service provides acute care support and clinical advice for two groups of patients with active acute porphyria suffering neurovisceral symptoms: • patients suffering isolated acute attacks requiring haem arginate treatment; • patients with recurrent acute attacks. The aim of the service is to provide immediate clinical support and advice to acute care physicians in the patient's local hospital on management and treatment of all acute attacks of porphyria. Outpatient follow-up to manage ongoing treatment and complications will then be arranged at one of the regular clinics. Wherever possible NAPS put shared care agreements in place with an appropriate local clinician and will support these arrangements with outreach support where necessary.
8. What impact would the technology have on the current pathway of care?	The technology will not alter the current pathway of care.
The use of the technology	
9. To what extent and in which population(s) is the technology	Patients have received treatment through clinical trials but the treatment is not routinely commissioned by NHS England.

being used in your local health economy?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is anticipated the technology would be administered through the HSS under existing arrangements
• How does healthcare resource use differ between the technology and current care?	The technology would provide an important alternative treatment option for this cohort. The mechanism of administration via monthly subcutaneous injection is different to haem arginate which is administered via an infusion but both can be delivered by homecare. There may be an overall reduction in healthcare resource use due to reduction in complications.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Initially the technology would be delivered within the HSS using shared care protocols. In the longer term the technology could be delivered via homecare
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment

• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	No evaluations/audits known to NHS England.
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Severe acute porphyria disproportionately affects women, particularly young women.
12b. Consider whether these issues are different from issues with current care and why.	Access to the technology would significantly improve the quality of life of all patients with severe recurrent acute porphyria.

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Givosiran for treating acute hepatic porphyria [ID1549]

Highly Specialised Technologies Evaluation Programme

Produced by

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Abbreviations

AE(s)	adverse event(s)
AAR	annualised attack rate
ADP	ALA dehydratase deficient porphyria
AHP	acute hepatic porphyria
AIC	Akaike information criterion
AIP	acute intermittent porphyria
ALA	delta aminolevulinic acid
ALAD	delta-aminolevulinic acid (ALA) dehydratase
ALAS1	delta aminolevulinic acid synthase 1
ALT	alanine aminotransferase
AR	attack rate
AUC	area under the curve
BIC	Bayesian information criterion
BMI	body mass index
BPI-SF	Brief Pain Inventory (Short Form)
BSC	best supportive care
CASP	Critical Appraisal Skills Programme
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CKD	chronic kidney disease
CRD	Centre for Reviews and Dissemination
CS	company submission
CSR	clinical study report
DB	double blind
EDSS	Expanded Disability Status Scale
eMIT	electronic market information tool
EPNET	European Porphyria Network
EQ-5D	EuroQol 5-dimensions questionnaire
ERG	Evidence Review Group
GnRH	gonadotropin-releasing hormone
HCC	hepatocellular carcinoma
HCP	hereditary coproporphyria
HCRU	healthcare resource use

hepB	hepatitis B
hepC	hepatitis C
HIV	human immunodeficiency virus
HMBS	hydroxymethylbilane synthase
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology appraisal
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IQR	interquartile range
IRS	interactive response system
ITC	indirect treatment comparison
ITT	intention to treat
IV	Intravenous
KM	Kaplan-Meier
LS	least squares
M	Month
MAA	managed access agreement
MAD	multiple-ascending dose
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimal important difference
MIMS	Monthly Index of Medical Specialties
mRNA	messenger ribose nucleic acid
MS	multiple sclerosis
N	number
N/A	not applicable
NAPS	National Acute Porphyria Service
NCT	National Clinical Trial
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	not reported
NRS	numeric rating scale
OLE	open-label extension
OWSA	one-way sensitivity analysis

PAS	patient access scheme
PBG	Porphobilinogen
PCS	physical component summary
PDSS	Patient-determined Disease Steps Scale
PGIC	Patient Global Impression of Change (questionnaire)
PRISMA	Preferred Reporting Items for Systematic Review and Meta-analysis
PRO	patient reported outcomes
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
QM	every morning
QoL	quality of life
RCT	randomised controlled trial
RDI	relative dose intensity
RR	rate ratio
RRMS	relapsing-remitting multiple sclerosis
SAD	single-ascending dose
SAE	serious adverse event
SC	Subcutaneous
SD	standard deviation
SE	standard error
SF-12	Short Form- 12 Health Survey
SF-36	Short Form- 36 Health Survey
SLR	systematic literature review
SmPC	summary of product characteristics
TBC	to be confirmed
ToT	time on treatment
TWSA	two-way sensitivity analyses
UK	United Kingdom
VAS	visual analogue scale
VP	variegate porphyria

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1. Overview of the ERG's key issues

Table 1: Summary of key issues

ID1549	Summary of issues	Report sections
The ERG reviewed the approach of the company to addressing the NICE decision problem for this appraisal and identified the following key issue for the committee's consideration. Key Issue 1	The lack of a comparison versus off label prophylactic treatment options	2.2; 2.3; 3.3; 4.2.4
The ERG reviewed the clinical effectiveness and safety evidence presented in the	Generalisability of the ENVISION trial to NHS practice	2.3; 3.2.2.2; 3.2.2.3; 3.2.2.4; 3.2.3.1

ID1549	Summary of issues	Report sections
CS and identified the following key issue for consideration by the committee. Key Issue 2		
Key Issue 3	Uncertainty surrounding long-term clinical effectiveness of givosiran and BSC	4.2.6 and 6.2.3
Key Issue 4	: Uncertainty surrounding quality of life data and utility values used within the model	4.2.8 and 6.2.1.4
Key Issue 5	: Uncertainty surrounding treatment discontinuation and time on treatment	4.2.9.3
Key Issue 6	Uncertainty surrounding patient baseline characteristics and other model assumptions	1.7, 4.2.3 and 4.2.7

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are as follows:

- The ERG considered long term treatment efficacy for givosiran should be based on 18-month data from the ENVISION open-label extension (OLE) i.e., transition probabilities from month 12 to 18 should be frozen after 18 months. In the company's base case, it was assumed that patients treated with givosiran would continue to transition through health states based on transition probabilities observed within ENVISION OLE (up to year 5). See Section 4.2.6.1 and 6.2.

- The ERG considered that Health state utility values should be based on RRMS utilities as reported in Hawton et al.[1] In the company's base case, health state utilities (incorporating the impact of chronic symptoms on health-related quality of life, HRQoL), were captured via utility decrements, which were identified in published literature and applied to a baseline utility. See Section 4.2.8 and 6.2.

- The ERG considered that time on treatment (ToT) is more appropriately assessed via a piece-wise approach i.e. Kaplan-Meier (KM) curve from ENVISION used until 18 months,

and the log-normal curve used for extrapolating to the remaining duration of the model. In the company's base case analysis ToT extrapolation was based on a fully parametric curve (Log-logistic). See Section 4.2.9.3 and 6.2.

- The ERG considered that the per-cycle probability of menopause onset should be based on mean age from UK Women's cohort study[2] (fitting a normal distribution). In the company's base case analysis a published study was used to estimate mean age of menopause and per cycle probability of onset. See Section 4.2.7 and 6.2.

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Reducing the frequency of acute attacks, thereby keeping patients in 'better', less severe health states for longer. The model predicts that a higher proportion of patients in the givosiran treatment arm (compared to the BSC treatment arm) transition to the asymptomatic health state early in the model and remain in this health state.

- Improving patient quality of life. Due to the improved efficacy of givosiran, a higher proportion of patients in the BSC treatment arm experience disutility associated with an acute attack [redacted]. In addition, a higher proportion of patients in the BSC arm treatment arm experience chronic symptoms such as chronic pain, neurologic and psychiatric disorders, compared to those in the givosiran treatment arm. As such, patients treated with givosiran have a higher quality of life due to experiencing fewer acute attacks and chronic symptoms. Disutility assumptions used within the model are considered to be a key driver of the givosiran incremental QALY gain.

- Improving carer quality of life. Carer disutility has been included in the company's base case.

Overall, the technology is modelled to affect costs by:

- Preventing acute attack hospitalisations. As givosiran keeps patients in better health states for longer most patients experience less acute attacks and therefore have fewer hospitalisations (associated with a high unit cost).
- Treatment discontinuation assumptions, including both the extrapolation method used to estimate long-term treatment patterns and discontinuation after the menopause.
- Resulting in fewer patients experiencing opioid addiction. Patients receiving BSC are assumed to have a higher rate of opioid addiction compared to those receiving givosiran.

The modelling assumptions that have the greatest effect on the ICER are:

- Long term efficacy assumptions used within the model for both givosiran and BSC.
- Time on treatment (ToT) and treatment discontinuation extrapolation assumptions.
- Assumptions related to the health state utilities (utility decrements by health state applied on general population baseline utilities, health state utilities from similar conditions or ENVISION trial EuroQol 5-dimensions questionnaire, EQ-5D).
- Assumptions surrounding healthcare resource use i.e., the proportion of patients hospitalised for an acute attack.
- Menopause onset distribution and the assumption that 100% of patients who are asymptomatic at the age of menopause will stop treatment with givosiran.
- Assumptions regarding modelled patient baseline characteristics (particularly starting cohort age and proportion of females).
- Time horizon of the model.

1.3. The decision problem: summary of the ERG's key issues

The ERG reviewed the approach of the company to addressing the NICE decision problem for this appraisal and identified the following key issue for the committee's consideration.

Key Issue 1: The lack of a comparison versus off label prophylactic treatment options

Report sections	**2.2; 2.3; 3.3; 4.2.4**
Description of issue and why the ERG has identified it as important	Based on clinician advice to the ERG, off-label use of IV heme and gonadatrophin analogues are currently being used by UK patients as prophylaxis for reducing the frequency of acute attacks in AHP. However, the company did not provide a comparison versus these treatments (see Section 4.2.4). Based on NICE methods guidance (2013)[3], the committee can consider treatments that do not have a marketing authorisation for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS. Thus, the ERG noted that the cost utility analysis presented by the company may not fully reflect the cost effectiveness of givosiran compared to prophylactic use of these treatments. Liver transplant has also been identified as a possible treatment option, however the ERG noted that this is not routinely provided to patients and therefore is appropriate to exclude from the analysis.
What alternative approach has the ERG suggested?	Overall, the ERG recognised the paucity of data surrounding the clinical effectiveness of off label use of prophylactic IV heme and gonadatrophin analogues, and the lack of direct studies comparing givosiran to these treatments (as prophylaxis). A cost-utility analysis comparing givosiran to these comparators would therefore likely need to utilise relatively weak clinical data and/or assumptions within the economic model. This would introduce further uncertainty into the analysis. The ERG therefore considered the company's base case approach to be reasonable (albeit not fully reflecting clinical practice).
What is the expected effect on the cost-effectiveness estimates?	Currently, the cost utility analysis submitted by the company does not include prophylactic IV heme and gonadatrophin analogues as comparators. Hence, the impact of including the same on the cost-effectiveness estimate is unknown.
What additional evidence or analyses might help to resolve this key issue?	Robust clinical data comparing prophylactic use of givosiran to prophylactic use of IV heme and gonadatrophin analogues would be helpful in addressing uncertainty. More robust clinical evidence from published analyses or individual patient data e.g. from a registry could be used within an indirect treatment comparison to support inference on comparative effectiveness.

Abbreviations: AHP, acute hepatic porphyria; ERG, Evidence Review Group; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; UK, United Kingdom

1.4. The clinical effectiveness evidence: summary of the ERG's key issues

The ERG reviewed the clinical effectiveness and safety evidence presented in the CS and identified the following key issue for consideration by the committee.

Key Issue 2: Generalisability of the ENVISION trial to NHS practice

Report sections	**2.3; 3.2.2.2; 3.2.2.3; 3.2.2.4; 3.2.3.1**
Description of issue and why the ERG has identified it as important	The clinical effectiveness evidence for givosiran is primarily drawn from the ENVISION trial; which is a well conducted, placebo-controlled RCT with 98 patients. The company identified that the prevalence of rarer subtypes of AHP was underrepresented in the trial, and patients were older, had fewer chronic symptoms, and could be considered to have 'less severe' symptoms of AHP than the target population. There is also uncertainty of the extent to which BSC received in either arm represents the care that would be received in the NHS. The ERG noted that the dose of givosiran evaluated varied between other trials (the ENVISION OLE and Phase I/II trial) and the intended use of givosiran in practice. Clinical advisors to the ERG were unable to comment on how the above differences could affect the generalisability of the evidence to NHS practice There is poor understanding of the factors that affect disease prognosis, and could affect the efficacy of givosiran. The ERG was also aware that AHP has a heterogeneous impact on patients, and that only larger trial samples would provide a better representation of the target patient population. Due to the small sample size of the included trials, limited investigation of a differential effect in outcome across patient characteristics was possible, and there is uncertainty about the potential magnitude of treatment effects in the target patient population in England and Wales.
What alternative approach has the ERG suggested?	The ERG was satisfied that the company have presented all available evidence. The ERG accepted that as this is a rare and heterogeneous disease area, and that limitations in the generalisability of the available trial data are inevitable.
What is the expected effect on the cost-effectiveness estimates?	Variation in the magnitude of treatment effects would have implications for cost-effectiveness estimates; for example, the ERG identified that small variations in patient demographic information have implications for the ICER (e.g. Key Issue 6Key Issue 6). However, at this stage the ERG was unable to quantify the impact of a lack of generalisability.
What additional evidence or analyses might help to resolve this key issue?	Evidence within the target UK population would be most informative for reducing uncertainty. In the absence of this, further data that characterise the UK population, and guidance from clinical experts about the expected difference in treatment outcomes according to patient characteristics, would reduce some of this uncertainty. This may result in a reweighted analysis of trial data to generate comparisons that are more meaningful in the UK context.

Abbreviations: AHP, acute hepatic porphyria; BSC, best supportive care; ERG, Evidence Review Group; RCT, randomised controlled trial; UK, United Kingdom

1.5. The cost effectiveness evidence: summary of the ERG's key issues

The ERG reviewed the company health economic evidence and economic evaluation presented in the CS, and identified the following key issues for consideration by the committee.

Key Issue 3: Uncertainty surrounding long-term clinical effectiveness of givosiran and BSC

Report sections	**4.2.6 and 6.2.3**
Description of issue and why the ERG has identified it as important	The transition probabilities used to estimate treatment effectiveness in the model were informed by clinical data from ENVISION (which was used to estimate transition probabilities for both givosiran and BSC in the first six month model cycle) and ENVISION OLE (which was used to estimate transition probabilities for givosiran after Month 6). However, due to the lack of long-term clinical data, the company made the following assumptions relating to the long term effectiveness of both givosiran and BSC • For givosiran, patients were assumed to transition through health states from Years 3 to 5 based on clinical data from ENVISION OLE (Months 12 to 18). After Year 5 patients remained in their respective health states for the duration of the model. • For BSC, the company assumed that transition probabilities were 'frozen' after Month 6 in the model i.e. patients remained in their health states for the duration of the model. The ERG noted that the company's long-term effectiveness assumptions were a source of considerable uncertainty. Furthermore, no sensitivity analyses were provided by the company to test the impact of alternative effectiveness assumptions on the ICER. The ERG considered the base case transition probabilities and associated assumptions to be a key driver of the incremental QALY gain and the ICER.
What alternative approach has the ERG suggested?	The ERG conducted scenario analyses using alternative long-term efficacy assumptions for both the givosiran and BSC treatment arms. See Sections 4.2.6 and 6.2.3 for description and results.
What is the expected effect on the cost-effectiveness estimates?	The ERG scenario analyses had varying impact on the base case ICER. See Sections 6.2.1 and 6.2.3
What additional evidence or analyses might help to resolve this key issue?	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.

Abbreviations: BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OLE, open-label extension

Key Issue 4: Uncertainty surrounding quality of life data and utility values used within the model

Report sections	**4.2.8 and 6.2.1.4**
Description of issue and why the ERG has identified it as important	The ERG noted the following uncertainties surrounding the company's estimation of utilities/disutilities within the model. • Quality of life data were collected in the ENVISION study using the EQ-5D instrument; however, the company did not use these data

Report sections	4.2.8 and 6.2.1.4
	within the base case analysis. The ERG considered the omission of direct and relevant quality of life data to be a source of uncertainty. • The approach to estimating health state utilities lacked robustness. The company estimated disutilities associated with chronic symptoms using published literature. The ERG noted that the studies, which reported HRQoL data for non AHP conditions, were used as a proxy for AHP, due to the lack of long-term chronic symptom HRQoL data in these patients (see Section 4.2.8). The ERG acknowledged that modelled utility/disutility in the company's base case was a source of uncertainty.
What alternative approach has the ERG suggested?	In order to address uncertainty surrounding modelled utilities, the ERG conducted the following scenario analyses; • Used utilities based on EQ-5D data from ENVISION. Although considered useful, the ERG acknowledged that this scenario may lack plausibility as the utility associated with being in the severe health state was higher than the utility associated with being in the recurrent health state. See Section 6.2.1.4. • Assumed ENVISION utility values for symptomatic, recurrent and severe health states were identical in order to address the implausibility of ENVISION values. The ERG acknowledged that this scenario may lack clinical plausibility as it assumed that severe patients have the same QoL arising from chronic symptoms as those who are symptomatic. See Section 6.2.1.4 • Assumed that AHP health state utilities correspond to RRMS stages (based on a published study by Hawton et al[1]). Due to the paucity of robust QoL data, the ERG considered RRMS utility values to be a reasonable proxy for AHP health states. See Section 6.2.1.4.
What is the expected effect on the cost-effectiveness estimates?	The additional scenario analyses indicated a moderate impact on the ICER. See Section 6.2.36.2.1.4 for results.
What additional evidence or analyses might help to resolve this key issue?	Robust long-term HRQoL data (elicited directly from AHP patients) would address uncertainty surrounding AHP utility values. Proxy values elicited from clinical experts would also assist with validation. The ERG also noted that further evidence validating specific HRQoL measures used within AHP, would have been useful.

Abbreviations: AHP, acute hepatic porphyria; EQ-5D EuroQol 5-dimensions questionnaire; ERG, Evidence Review Group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QoL, quality of life; RRMS, relapsing-remitting multiple sclerosis

Key Issue 5: Uncertainty surrounding treatment discontinuation and time on treatment

Report sections	4.2.9.3
Description of issue and why the ERG has identified it as important	The ERG noted that treatment discontinuation is likely to have a considerable impact on the ICER, given the high treatment acquisition cost of givosiran.

Report sections	4.2.9.3
	The proportion of patients continuing givosiran treatment was estimated via a ToT curve (log logistic) which was fitted over KM curves from ENVISION and ENVISION OLE (up to 18 months) and extrapolated the proportion of patients remaining on treatment over 30 years. The ERG noted the following concerns surrounding the company's approach to extrapolating treatment discontinuation • A fully parametric approach does not appear to fit the ENVISION KM curves and therefore may not adequately represent discontinuation during the trial period or beyond. The ERG considered that a piecewise approach may be more robust. • The company did not provide sensitivity analysis using alternative curve fits which introduces further uncertainty. Furthermore, the ERG acknowledged that there is uncertainty surrounding how givosiran will be used in clinical practice and therefore how long patients will remain on treatment. Clinical responses received by the ERG have been mixed and somewhat conflicted. Input from NAPS clinicians indicated that there is likely to be substantial individual variation. For instance, it may be the case that some patients stop after achieving several years of clinical benefit but restart treatment if attacks reoccur. It was suggested that lifelong treatment with givosiran is unlikely. Additional expert opinion to the ERG noted that it may be unlikely that patients experiencing clinical benefit would cease treatment. As such, lifelong treatment may be plausible. [redacted]This approach is described further in Section 4.3. The ERG considered this analysis to be highly exploratory and subject to major limitations.[redacted]
What alternative approach has the ERG suggested?	The ERG conducted the following scenario analyses • Used a piecewise approach (KM curve used until 18 months and then the log normal curve fitted). The ERG considered the log normal to be the second best fit (after the exponential curve), based on AIC/BIC scores and visual fit. See Section 6.2.1.3. • Extrapolated treatment discontinuation using alternative parametric curves including the Gompertz curve. See Section 6.2.1.3.
What is the expected effect on the cost-effectiveness estimates?	Use of alternative curves, such as the Gompertz curve resulted in an increased ICER as a higher proportion of patients are assumed to remain on treatment.
What additional evidence or analyses might help to resolve this key issue?	Long-term real world data outlining givosiran use in clinical practice would help reduce uncertainty surrounding this issue.

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ERG, Evidence Review Group; KM, Kaplan-Meier; MAA, managed access agreement; NAPS, National Acute Porphyria Service; OLE, open-label extension

1.6. Other key issues: summary of the ERG's views

The ERG also identified the following key issue, concerning uncertainty in model parameters. However, the ERG did not consider this to be pivotal for decision-making as the impact on the ICER was minimal.

Key Issue 6: Uncertainty surrounding patient baseline characteristics and other model assumptions

Report sections	**1.4, 4.2.7 and 4.2.3**
Description of issue and why the ERG has identified it as important	The ERG noted uncertainty surrounding the following modelled parameters, which had an upward impact on the ICER when varied. • Starting age of cohort; the company used a starting age of 41.64 years. However, based on clinical opinion to the ERG, the most plausible starting age may be younger. • The company included opioid addiction costs in the model based on published literature, which were associated with considerable uncertainty. Due to the lack of robust opioid addiction data, the ERG considered that the exclusion of these costs may be more appropriate. • The ERG noted that the proportion of patients experiencing chronic symptoms was based on a single study by Neeleman et al. (2018)[4]. Furthermore, unit costs for these conditions were largely dated and derived from unconventional sources. • The distribution used to estimate the per cycle probability of menopause onset was taken from on a published study by Greer et al[5]. The ERG noted that the study used data from a Finnish cohort and therefore may not be generalisable to women in the UK. • Assumption that 100% of patients who are asymptomatic at menopause stop treatment. The ERG acknowledged that the majority of patients were likely to discontinue at menopause onset, however based on clinical opinion to the ERG, it may be plausible that a small proportion of patients would continue treatment.
What alternative approach has the ERG suggested?	The ERG conducted a number of scenario analyses to address uncertainty surrounding modelled assumptions • Reduced the starting age of the cohort to 30 years. • Removed opioid addiction costs. • The per cycle probability of menopause onset based on mean age from UK Women's cohort study (fitting a normal distribution). • Assumed 10% of patients continue givosiran treatment after menopause onset.
What is the expected effect on the cost-effectiveness estimates?	All scenarios had an upward impact on the ICER. See Section 6.2.3 for results.

Report sections	1.4, 4.2.7 and 4.2.3
What additional evidence or analyses might help to resolve this key issue?	The company largely used clinical expert opinion to validate base case assumptions, which was helpful. However, additional data outlining long term opioid use in UK AHP patients would further reduce uncertainty.

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis

1.7. Summary of ERG's preferred assumptions and resulting ICER

The preferred ERG base case results are presented below. Results have been presented both with and without the managed access agreement (MAA) assumptions included by the company. Due to the limitations surrounding the proposed MAA, highlighted within Section 4.3, the ERG considered the base case results (including MAA assumptions) to be subject to considerable uncertainty.

Table 2: Summary of ERG's preferred assumptions and ICER (excluding MAA assumptions)

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
Company base-case	*5.1.1*	[redacted]
Givosiran transition probabilities based on OLE data (frozen at 18 months)	*4.2.6 and 6.2.3*	[redacted]
AHP utilities based on RRMS values in Hawton et al[1]	*4.2.8 and 6.2.3*	[redacted]
ToT extrapolated using piecewise approach (KM curve + log Normal cure)	*4.2.9.3 and 6.2.3*	[redacted]
The per cycle probability of menopause onset based on mean age from UK Women's cohort study (fitting a normal distribution).	*4.2.7 and 6.2.3*	[redacted]
Opioid addiction costs removed	*4.2.9.6 and 4.2.9.64.2.9.64.2.9.6*	[redacted]

Abbreviations: AHP, acute hepatic porphyria; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; MAA, managed access agreement; OLE, open label extension; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; ToT, time on treatment; UK, United Kingdom

Table 3: Summary of ERG's preferred assumptions and ICER (including MAA assumptions)

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
Company base-case	*5.1.1*	[redacted]

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
Givosiran transition probabilities based on OLE data (frozen at 18 months)	*4.2.6 and 6.2.3*	[redacted]
AHP utilities based on RRMS values in Hawton et al[1]	*4.2.8 and 6.2.3*	[redacted]
ToT extrapolated using piecewise approach (KM curve + Log Normal cure)	*4.2.9.3 and 6.2.3*	[redacted]
The per cycle probability of menopause onset based on mean age from UK Women's cohort study (fitting a normal distribution).	*4.2.7 and 6.2.3*	[redacted]
Opioid addiction costs removed	*4.2.9.6 and 4.2.9.64.2.9.64.2.9.6*	[redacted]

Abbreviations: AHP, acute hepatic porphyria; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; MAA, managed access agreement; OLE, open label extension; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; ToT, time on treatment; UK, United Kingdom

Modelling errors identified and subsequently corrected are described in Section 6.1. For further details on the exploratory and sensitivity analyses done by the ERG, see Section 6.2.

2. INTRODUCTION AND BACKGROUND

2.1. Critique of underlying health problem

The company provided an overview of the burden of acute hepatic porphyrias (AHP) in the target population in Sections 6 and 7 of the CS (Document B).

Acute hepatic porphyrias (AHP) are a group of rare conditions caused by defects in the haem biosynthesis pathway within the liver and characterised by chronic symptoms interspersed with acute episodes ('attacks'). The defective enzymes lead to an accumulation of delta-aminolevulinic acid and porphobilinogen intermediate precursors in the liver. There are several sub-types of porphyria, each caused by a defect in a different enzyme in the eight-step haem pathway. The target population for givosiran are those with acute intermitted porphyria (AIP), delta-aminolevulinic acid (ALA) dehydratase (ALAD) deficiency porphyria (ADP), hereditary coproporphyria (HCP) and variegate porphyria (VP) subtypes.

The first step in the haem biosynthesis pathway is the activation of delta aminolevulinic acid synthase 1 (ALAS1), which can be upregulated by many triggers including menstrual hormones, alcohol and stress. These triggers increase ALAS1 activity in the liver, which can lead to acute 'attacks'. These are characterised by extreme pain, neurological symptoms, constipation, nausea, vomiting, seizures and skin damage, according to the type of porphyria. The most severe attacks may be life-threatening, or result in long-term health complications. The impact of AHP on the lives of patients varies considerably, depending on the frequency and severity of acute attacks, and any medical complications arising from past attacks. One of the most severe complications that may occur following an attack is neurological impairment, which can lead to mobility and cognitive difficulties, as well as mental health disorders. Many patients' lives are further impacted by the presence of chronic symptoms between attacks, which can include fatigue, pain and emotional distress. In addition, there are a number of long-term complications associated with AHP, including hepatocellular carcinoma (HCC), chronic kidney disease (CKD) and hypertension.

A minority of AHP patients suffer from recurrent acute attack; frequently defined as four attacks in a 12-month period.[6] The company estimates that 35 patients in the UK suffer from recurrent attacks, six of whom have receive givosiran in clinical trials. The vast majority of patients with AHP and recurrent attacks are female. Onset is rarely before puberty and usually occurs in the early 20s, although diagnosis is often delayed due to the complex, non-specific symptom profile

and the rarity of the disease. Prognosis varies, though many patients with acute attacks will continue to experience attacks until menopause, at which point most women will experience a reduction or cessation in attacks. Attack severity is not clearly associated with attack frequency, and those with fewer attacks can nevertheless experience severe attacks.

Overall, the ERG considered that the company provided an accurate summary of the best available evidence for the epidemiology and burden of acute attacks in patients with AHP. The ERG considered that the greatest risk of acute attacks is associated with the most severe attacks, as these may carry a greater risk of death and ongoing health complications; however the ERG considered that a reduction in all types of attack may nevertheless reduce the impact of the condition on patients' lives. The ERG also considered that a reduction in acute attacks may have a beneficial effect for mental wellbeing, if it were to reduce patients' anxiety towards attacks, and also reduce opioid use and dependence. Clinical advice to the ERG was that acute attacks lead to burden for the carers of patients with AHP where they are needed to support patient recovery, and the impact on carers may be particularly profound when patients experience mental health difficulties, opioid dependence, and when they experience neurological complications following an attack. However, the ERG also understood that a significant cause of burden for patients with AHP and their carers is related to chronic symptoms, such as chronic pain, and therefore treatments to reduce the frequency of acute attack may not resolve the full burden of AHP on patients' lives.

The diagnostic criteria for AHP and the presence of recurrent attacks appear to be established, though diagnosis may be delayed some years after onset, particularly when patients' attacks are mild and/or less frequent, or if they are not identified by a specialist AHP centre. Clinical advisors noted that the diagnosis of acute attacks may be challenging, as symptoms may resemble chronic symptoms or other health conditions. Disease presentation and prognosis appear to vary widely between patients, and clinical advice to the ERG was that a patient's condition may fluctuate naturally over their lives (though very few patients with recurrent attacks will experience spontaneous, permanent remission). The company argued that, if left untreated, patients would not experience an improvement in symptoms (CS Document B, p. 72); however, this was at odds with a submission from a NAPS clinician, who stated that symptoms are likely to diminish with time (see Section 8.1).

The ERG noted that as this is a rare disease area, there is a limited evidence base for patients with AHP who experience recurrent attacks. The ERG also considered that the heterogeneous

nature of the condition, where medical complications and the symptoms of AHP vary widely, provides additional complications for evidence generation.

2.2. Current and proposed treatment pathway

The company provide an overview of current treatment options for recurrent attacks in patients with AHP, and the proposed treatment pathway with givosiran, in Section 8 of the CS (Document B).

There are limited treatment options available for the treatment of acute attacks in patients with AHP. Broadly speaking, treatment for AHP generally involves management of chronic symptoms and support to self-manage triggers of acute attacks. There are two treatments currently used as prophylactic treatment to reduce the frequency of acute attacks, both of which are used off-label. The most common of these is intravenous (IV) heme, which is used as a prophylactic treatment in addition to its licensed use to acutely treat attacks of AHP. Clinical advisors to the ERG confirmed that IV heme is widely used as a prophylactic treatment in the NHS, and is generally considered to be effective, though there is a paucity of high-quality evidence for its efficacy. Clinical advisors also echo the risks of using IV heme long-term as described by the company (including risks of iron overload and liver damage). Clinical advisors also agree that it can be difficult to withdraw prophylactic IV heme, as patients may choose to continue with treatment despite the risks because they fear acute attacks. IV heme is available in various forms, and includes hemin, heme/haem arginate and hematin (brand names include Panhematin® [lyophilised hematin], Recordati Rare Chemicals] in the United States and Normosang® [heme arginate, also from Recordati] in the European Union).

Patients who experience acute attacks associated with their menstrual cycle may also be offered gonadotropin-releasing hormone (GnRH) analogues. This treatment suppresses oestrogen production, which reduces the frequency of attacks. However, clinical advice to the ERG concurred that few patients may use GnRH analogues, and that treatment is rarely used for more than two years due to the side effects of GnRH.

As a final resort, patients may be considered for a liver transplant; however clinical advice to the ERG was that these are rarely performed, due to the lack of donor livers and the long-term complications and healthcare needs associated with transplant.

Acute attacks of AHP mostly require hospital admission, although some patients may be treated at home or in outpatient centres. The principal treatment for acute attacks is IV heme, along with

analgesia and treatments to manage the symptoms (e.g. anti-emetics). Treatment for the chronic symptoms of AHP may include analgesia, including opioids, for patients who experience chronic pain.

The CS provides an overview of the mechanism of givosiran (Givlaari®) in Section 2 (Document B). The marketing authorisation for givosiran is for patients aged ≥12 years with AHP; however, the scope for this appraisal is directed towards a sub-population of AHP patients who experience recurrent acute attacks. Givosiran is administered as a monthly subcutaneous injection at a dose of 2.5mg/kg body weight. According to the CS, patients are expected to be treated with givosiran for the duration of their lives, subject to clinical judgement, though patients who experience a cessation in acute attacks at menopause are expected to discontinue treatment. The CS states that no dose adjustments are required, though the ERG understood that a reduction in dose to 1.25mg/kg may be expected according to adverse events. [redacted] clinical experts to the ERG stated that this may be reasonable, as the frequency of acute attacks may fluctuate over the life course, and so treatment may be stopped and started according to need. However, the ERG noted that this proposed use of givosiran was not evaluated in the relevant clinical trials and the cost-effectiveness of this strategy was only included as a scenario analysis in Section F of the CS (p. 122). Furthermore, clinical advisors to the ERG also advised that patients with AHP are frequently reluctant to stop prophylactic treatment, due to a fear of recurrent attacks and the potential for severe consequences (such as neurological impairment) that these may cause. [redacted] Further discussion of the appropriateness of a treatment discontinuation rule in givosiran is provided in Section 4.3.

In the UK, there are two National Acute Porphyria Services (NAPS) and two associate centres, which are designated centres of excellence in treating AHP. These are based in London, Cardiff, Salford and Leeds. The CS states that givosiran would initially be administered only in these centres, though in time treatment may be delivered at home using local providers (CS, Document B, p. 33). The company did not state the rationale for limiting treatment initially to the specialist centres, though the ERG considered that this may be due to the need to reduce uncertainty in procedures for the treatment and follow-up of patients. Clinical advisors to the ERG agreed that treatment may ultimately be delivered at home, though noted that while treatment is restricted to specialist centres, this will lead to inequality in access. Furthermore,

clinical advisors considered that initial doses of givosiran treatment should always be administered in hospital or in a specialist centre, due to the risk of analphylaxis.

Overall, the ERG agreed with the company's description of the current treatment pathway for patients with AHP who experience recurrent acute attacks [redacted]. The ERG also noted that patient populations in the evidence for givosiran included patients with less frequent attacks than are generally considered to be 'recurrent'. The ERG has discussed the uncertainty associated with the use of givosiran and the generalisability of the evidence base in Key Issue 5 and The ERG reviewed the clinical effectiveness and safety evidence presented in the CS and identified the following key issue for consideration by the committee.

Key Issue 2.

2.3. Critique of company's definition of decision problem

The company statement regarding the decision problem is presented in Section 1 of the CS (Document B). The company position and the ERG response is provided in Table 4 below.

The ERG considered that the evidence presented by the company was broadly consistent with the decision problem, although noted that some patients in the included trials experienced fewer attacks in the previous 12-months than the threshold for recurrence used in current guidelines.[6] The intervention was consistent, though the ERG clarified that givosiran is expected to be delivered alongside best supportive care (BSC), which is how it was evaluated in the included trials.

A notable gap in the evidence presented by the company was evidence for the efficacy of current comparators to givosiran (see The ERG reviewed the approach of the company to addressing the NICE decision problem for this appraisal and identified the following key issue for the committee's consideration.

Key Issue 1), including prophylactic heme and GnRH analogues. The ERG accepted that the latter is used infrequently, though noted that prophylactic IV heme is used widely in the NHS and is considered by clinical advisors to the ERG to be effective at reducing the frequency of acute attacks. The company rationale for the exclusion of evidence related to prophylactic IV heme from the CS was in regard to its off-label use. The ERG noted that off-label treatments that are widely used in common practice may be considered within a NICE appraisal. However,

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. The lack of evidence for the effectiveness of comparators to givosiran nevertheless remain an area of uncertainty for this appraisal.

The company was unable to conduct subgroup analyses related to disease subtype due to the low recruitment of patients with less common subtypes of AHP (ADP, HCP, VP) in the company's pivotal trial, and the exclusion of these subtypes from earlier trials. The ERG was unclear to what extent the evidence in AIP patients is generalisable to other subtypes, and this remains an area of uncertainty in the evidence base.

The ERG considered that the outcomes reported in the CS were consistent with the NICE scope, though the omission of neurological outcome data is a significant limitation of the evidence base. Clinical advisors to the ERG did not consider the omission of evidence related to autonomic function to be significant. The ERG agreed that the economic model appeared to capture the key HRQoL impact of AHP by incorporating disutility associated with acute attacks and chronic symptoms. However, the base case values, particularly the disutilities associated long term complications, were subject to uncertainty as these were derived from published literature (using other conditions as proxy for AHP). The ERG was unclear whether carer disutilities included in the model were appropriate. The model did not incorporate treatment specific disutilities and costs associated with AE's, though the ERG did not consider that this would have material impact on the ICER.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults and young people aged 12 years or older with recurrent severe attacks of AHP	Consistent with NICE scope	N/A	The ERG agreed that the evidence submitted by the company was consistent with the NICE decision problem and the licence for givosiran.
Intervention	Givosiran	Consistent with NICE scope	N/A	The intervention evaluated in the evidence presented by the company was consistent with the NICE scope and the marketing authorisation
Comparator(s)	Established clinical management without givosiran, which may include: • prophylactic IV heme • gonadotrophin analogues • liver transplantation	Liver transplantation has not been included as a comparator in the economic model.	Due to its extreme rarity, liver transplantation is not considered a relevant comparator.	The ERG agreed with the company that liver transplantation is rarely used in England and Wales, and therefore agreed with the decision to not include liver transplantation as a comparator in the economic model. No evidence for the clinical effectiveness of liver transplantation was included in the CS; however, for the same reasons the ERG did not consider this to be an important omission for this appraisal. No evidence was presented in the CS comparing givosiran with either prophylactic IV heme (haem arginate) or gonadotrophin analogues. The ERG disagreed with the company's rationale for not presenting the evidence for prophylactic IV heme (that it is used off-label), because of its widespread use in practice. However, the ERG identified serious flaws with all studies evaluating prophylactic IV heme, and therefore considered the evidence base to be of too poor quality to contribute meaningfully to this appraisal. The absence of evidence for the efficacy and safety of prophylactic IV heme is a major uncertainty in this appraisal, and is discussed further in Key Issue 1.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				The ERG considered the omission of evidence for GnRH analogues to be inconsistent with the NICE scope, though the ERG understood that the side effects of using GnRH analogues limit their utility in practice, and mean they may not be a strong comparator to givosiran. The ERG also did not consider the omission to have major implications for estimating the efficacy of BSC. In the CS the company presented some evidence for the efficacy of IV heme therapy when used acutely to treat attacks of AHP. The ERG did not consider this to be a comparator for givosiran, as it would continue to be used to treat acute attacks alongside givosiran as part of BSC. BSC is the main comparator to givosiran in the company's economic model, as mentioned in Section 12.1.2 of the CS.
Outcomes	• numbers of acute attacks • porphyrin precursor concentrations in urine • neurological impairment • autonomic function • mortality • AE of treatment • HRQoL (for patients and carers).	Consistent with NICE scope	N/A	The company presented evidence towards most of the outcomes in the NICE scope, though no evidence was presented for neurological impairment or autonomic function. The lack of evidence for neurological function was considered by the ERG to be a facet of the short follow-up of the included trials, and was considered to be a major omission from the current evidence base for givosiran. This is due to the potential impact of neurological impairment following acute attacks on patient and carer HRQoL and on healthcare resource. Clinical advisors could not suggest any outcomes related to autonomic function that they considered to be a major omission from the CS. In addition to the outcomes in the NICE scope, the company presented evidence for

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				several other outcomes from their ENVISION trial. The ERG considered these to be useful for understanding the efficacy of givosiran. The ERG agreed that the economic model appeared to capture the key HRQoL impact of AHP by incorporating disutility associated with acute attacks and chronic symptoms. However, the base case values, particularly the disutilities associated long term complications, were subject to uncertainty as these were derived from published literature (using other conditions as proxy for AHP). See Section **Error! Reference source not found.**. Carer disutility was included in the base case and the company assumed that carer disutility from those caring for patients with MS (as reported by Acaster et al 2013)[7], would be generalisable to AHP patients. The ERG noted that the appropriateness of this assumption was unclear, however overall agreed that there may be similarities between AHP and MS with respect to and need for carers. The model did not incorporate treatment specific disutilities associated with AE's. The ERG noted that due to the small patient numbers within the ENVISION study (and short duration of follow up), the proportion of AE's attributable to treatment with givosiran was not clear. Overall, the ERG was of the opinion that including AE disutilities would not have a material impact on the ICER. Mortality was included but not considered a key driver of the ICER. Givosiran did not result in an incremental life year gain compared to BSC.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Subgroups to be considered	If the evidence allows, subgroups based on the subtype of acute hepatic porphyria (i.e., AIP, ADP, HCP, VP) will be considered.	Consistent with NICE scope	N/A	The evidence base for givosiran is primarily derived from samples of patients with AIP, which is the most common subtype of AHP within this indication. Very few patients recruited to the trials were diagnosed with VP, ADP, and HCP subtypes of AHP, and therefore it was not possible for the company to conduct meaningful comparison of outcomes between subtypes. The company stated that the efficacy of givosiran is likely to be effective across the subtypes of AHP; however, the ERG was unable to validate the rationale provided by the company, and the potential clinical and cost effectiveness of givosiran is therefore more uncertain in VP, ADP, and HCP subtypes of AHP.
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	Consistent with NICE scope	N/A	The ERG agreed that the evidence submitted by the company is consistent with the NICE decision problem
Cost to the NHS and PSS, and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life-year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	Consistent with NICE scope	N/A	The company submitted a cost utility analysis which reported ICERs and QALYs as appropriate. The ERG noted that a formal PAS was not submitted. The company has included a PAS within the scenario analysis summarised in Section 4.3. However, this has not been approved for implementation. Givosiran is not anticipated to result in changes to AHP service provision.
Impact of the technology beyond direct health benefits,	• Whether there are significant benefits other than health	Consistent with NICE scope	N/A	The model includes direct health benefits (patient utility) and indirect health benefits

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
and on the delivery of the specialised service	• Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise.			(carer disutilities). The ERG considered the inclusion of carer disutilities to be reasonable. The analysis has been conducted from an NHS perspective. Costs included therefore reflect those incurred by the NHS. Indirect costs such as productivity losses have not been considered, as appropriate.
Special considerations, including issues related to equality	• Guidance will only be issued in accordance with the marketing authorisation • Guidance will consider any Managed Access Arrangements	Consistent with NICE scope	N/A	No equity concerns were noted.

Abbreviations ADP, ALA dehydratase deficient porphyria; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; BSC, best supportive care; CS, company submission; ERG, Evidence Review Group; GnRH, gonadotropin-releasing hormone ; HCP, hereditary coproporphyria; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; QALY, quality-adjusted life year; VP, variegate porphyria

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify evidence for the clinical effectiveness of givosiran and prophylactic IV heme for the treatment of acute attacks in patients with AHP who experience recurrent attacks. The inclusion criteria were sufficient to capture all relevant evidence for this appraisal, and the methods used to conduct the review were of a high standard.

The company's SLR also identified evidence for the efficacy of IV heme therapy when used acutely to treat attacks. The ERG did not consider this to be a direct comparator of givosiran, since the treatment is intended to be used alongside givosiran as a component of BSC.

Table 5: Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Section C.9.1; Appendix 1.	The searches 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	Section C.9.2	The inclusion criteria specified in Table 10 (Document B, p. 35) for the clinical effectiveness review are appropriate to the decision problem.
Screening	SLR report[8]	Screening was conducted to appropriate standards
Data extraction	SLR report[8]	Data extraction was conducted to appropriate standards
Tool for quality assessment of included study or studies	Section C.9.5; Appendix E	Quality appraisal for the included trials was conducted using an appropriate tool (adapted CRD[9] tool for RCTs, and CASP[10] for the OLEs) and using two reviewers, with a third to resolve discrepancies. Quality appraisal was conducted at the study-level, and did not take into consideration the potential for variation in the risk of bias across outcomes. The quality appraisal of the ENVISION OLE was missing from the CS.
Evidence synthesis	N/A; Alnylam feasibility assessment[11]	The findings of the included trials were presented without meta-analysis or evidence synthesis. The company submitted the report of a feasibility assessment for conducting an ITC between givosiran and prophylactic IV heme, which concluded that ITC was not feasible. This is due to concerns about the quality of studies evaluating prophylactic IV heme, and heterogeneity between the study methods and populations. The ERG agreed with the company decision to not conduct an ITC with these studies and

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		the trials of givosiran. The ERG also agreed with the decision to not provide a narrative comparison of efficacy data from the studies of prophylactic IV heme, due to these being of very poor evidence quality.

Abbreviations: CASP, Critical Appraisal Skills Programme; CRD, Centre for Reviews and Dissemination; CS, company submission; ERG, Evidence Review Group; ITC, indirect treatment comparison; N/A, not applicable; OLE, open-label extension; RCT, randomised controlled trial; SLR, systematic literature review

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The company's clinical effectiveness review identified seven studies reported across ten publications evaluating treatment with either givosiran or prophylactic IV heme in patients with AHP. These included two trials of givosiran (reported across five publications): a double-blind randomised controlled, placebo controlled trial with an open-label extension (OLE[12]; 'ENVISION'[13] and 'ENVISION OLE'[14]), and an open-label, dose finding Phase I/II trial with an OLE[15,16] ('Phase I/II trial'). Of the latter, only a sub-sample from the trial ('Part C') was considered relevant for consideration by the ERG, as this sample included patients from the target population (i.e. patients who experience recurrent acute attacks). These studies are summarised in Table 6.

The five observational studies[4,17-20] evaluating prophylactic IV heme were considered to be low quality evidence by the ERG. These studies and their limitations are briefly summarised for the committee in Section 3.3, but the ERG did not use evidence from these studies to draw comparison with evidence from the included trials of givosiran.

Table 6: Clinical evidence included in the CS

Study name and acronym	Study design	Phase	Intervention / Comparator	Study Objectives	Population
ENVISION RCT NCT03338816 (Balwani et al, 2020[12])	Randomised, Double blind, placebo-control.	III	Givosiran 2.5 mg/kg / Placebo. Sodium Chloride 0.9%	Efficacy and safety.	N = 94 Men and women (≥12 years), diagnosis of AHP. At least 2 attacks in the last 6 months prior to screening requiring hospitalisation urgent healthcare visit or prophylactic IV heme at home.
ENVISION OLE [as ENVISION: NCT03338816][13,14]	OLE of 6 month trial. Median duration; 26 months.	III	Givosiran 2.5 mg/kg/none	Long term efficacy and safety	N=46
Phase I NCT02452372 (Sardh et al, 2019[16])	Randomised, single ascending dose (single blind), multiple-ascending dose (single blind) and multi-dose (double-blind) Part A: 42 days Part B: 70 days Part C 168 days	I	Givosiran Part A (single injection): (n=3 for each dose) 0.035 mg/kg, 0.10 mg/kg, 0.35 mg/kg, 1.0 mh/kg, 2.5 mg/kg Part B (1 month for 2 injections): (n=4 for each dose) 0.35 mg/kg, 1 mg/kg Part C: 2.5 mg/kg 1 x QM 4 injections (n=3), 2.5 mg/kg 1 x Q3M 2 injections (n=3) 5 mh/kg 1 x QM	Safety (efficacy as an exploratory outcome).	N = 40 Men and women diagnosed with AIP (18-65 years) Part A&B: N=23 Patients with urine PBG level >4 mmol/mol Cr for at least two measurements during the screening period. Part C: N=13 (givosiran) N = 4 (placebo).

Study name and acronym	Study design	Phase	Intervention / Comparator	Study Objectives	Population
			4 injections (n=3), 5.0 mh/kg 1 x Q3M 2 injections (n=4) / placebo (n=4)		Patients who have had at least 2 attacks in the 6 months before the trial.
Phase I/II OLE NCT02949830 (Bonkovsky el al, 2019[15])	OLE from NCT NCT02452372. Maximum Median time in OLE – 19 months. Maximum OLE duration – 42 months.	I/II	Givosiran. 5.0mg/kg 1 x Q3M (n=4), then 2.5 mg/kg. 2.5 mg/kg QM (n=9) 5.0 mg/kg QM, then 2.5 mg/kg QM (n=3)	Safety and tolerability.	N=16 All eligible patients from Part C of Phase I trial enrolled in the OLE.

Abbreviations: AE(s), adverse event(s); AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, delta aminolevulinic acid; NCT, National Clinical Trial; NR, not reported; OLE, open-label extension study; PBG, porphobilinogen; QM, every morning; QoL, quality of life; RCT, randomised controlled trial

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

The study designs of the trials of givosiran are summarised in the CS (Document B, Section 9.3.1, Table 11), and summarised above in Table 6.

ENVISION and ENVISION OLE

The company's pivotal trial ENVISION[12] is a blinded, placebo-controlled randomised controlled trial (RCT; up to six months), with a subsequent single-arm open label extension (OLE; up to 24 months follow-up). ENVISION was an international multi-center trial, conducted in 36 sites in 18 countries across North America, Europe, Australasia, Asia and Central America. Of the 94 included patients, 42 (44.6%) were from Europe, including 4 (4.3%) from Britain. Clinical sites were centres of excellence for the diagnosis and treatment of patients with AHP (ENVISION CSR, p.78). The ERG considered that the availability of an RCT in such a rare disease area is notable, and adds significant strength to the interpretation of the clinical efficacy and safety data in this appraisal. However, the ERG considered that the short follow-up of ENVISION may limit the detection of outcomes that may be slow to change, and cannot demonstrate the clinical efficacy and safety implications of givosiran in the medium- and long-term. Interim data from the OLE of ENVISION provides further data for givosiran, though this evidence is without a control, and is still relatively short-term for detecting change in an outcome where there is heterogeneity between patients, and natural fluctuations in event rate over time. The ERG also noted that evidence in the CS beyond the 18-month follow-up showed significant missing data (this may be due to ongoing data collection at this time point).

Clinical advisors to the ERG believed that patient outcomes may be improved where patients are treated within specialist centres, such as those within the trial. Treatment provision also varies between countries, including use of comparator treatments, and the provision of analgesia. Subgroup analyses presented by the company suggest similar findings between North American and European patients for the primary trial outcome (annualised attack rate, AAR; CS Figure 10, p.50-51), which is reassuring. However, the generalisability of ENVISION to the target NHS population remains uncertain, and is a Key Issue identified in this appraisal (The ERG reviewed the clinical effectiveness and safety evidence presented in the CS and identified the following key issue for consideration by the committee.

Key Issue 2)

Phase I/II trial

The Phase I/II trial[15] of givosiran was a small, dose finding, safety and tolerability trial comprised of three parts in which patients were randomised 3:1 to either givosiran or placebo. Only one part (Part C) was considered relevant to this appraisal, as it was the only part of the trial to only recruit patients with AHP and recurrent acute attacks. This part of the trial was a double-blind evaluation of four different doses of givosiran (n=13) as compared to placebo (n=4). Follow-up was 168 days (subsequently referred to as 6 months, for ease of comparability between trials).

As the sample size of this trial is so small, the ERG considered it highly unlikely that randomisation would have been successful in balancing the trial arms for potential confounders. The ERG therefore considered the data to ultimately be observational in nature. Furthermore, the trial was not powered to evaluate efficacy outcomes for givosiran. Nevertheless, the ERG considered that evidence from the trial could be used to support evidence from the main ENVISION trial, even if the data should be interpreted with caution.

3.2.2.2. Population

The inclusion criteria for the trials evaluating givosiran are summarised in Table 7Table 7. The ERG considered the inclusion and exclusion criteria for both trials to be relevant to the appraisal and the intended use of givosiran. However, the ERG identified two issues with the population inclusion criteria used in both ENVISION and the Phase I/II trial that may affect the generalisability of the evidence. Firstly, both trials defined recurrence of acute attack as having experienced two or more acute attacks in the six months prior to trial entry. While this appears consistent with the intended population for givosiran (four or more attacks per year), the CS reported that ENVISION recruited a sizeable minority (25/92, 27.2%) of patients who experienced fewer than four attacks over the previous 12-month period (CS Table 42, p.88). This suggests that the trial populations included a number of patients who experienced fewer acute attacks at baseline than the target population.

Furthermore, the ERG considered whether the requirement for patients to discontinue treatment with prophylactic IV heme to participate in either trial may discourage those patients with more severe and/or frequent acute attacks from participating in the trial. Clinical advice to the ERG was that the fear of further attacks and the risk of complications that can be caused by an attack, such as neurological impairment, can dissuade patients from stopping treatment. The ERG therefore considered whether those patients who experience severe attacks, or have high

anxiety over attacks, may be excluded from the sample. The company did not conduct analyses to explore whether the efficacy of givosiran may vary according to different baseline risk in the frequency or severity of attack, due to the small sample sizes involved. However, this issue contributed to the uncertainty about the generalisability of the trial populations to the target patient population.

Table 7: Inclusion and exclusion criteria of givosiran studies

Study	Inclusion criteria	Exclusion criteria
Balwani et al. (2020)[12] ENVISION (Phase 3 and OLE)	≥12 years of age AHP (AIP, HCP, VP or ALAD) Elevated urinary PBG or ALA in last year ≥2 attacks in last 6 months Willing to discontinue/stop prophylactic IV heme Women of child-bearing age must have negative serum pregnancy test, not be nursing and using acceptable contraception	Clinically significant abnormal lab results Anticipated liver transplant History of multiple drug allergies or intolerance to subcutaneous injections Active HIV, hep B or hep C infections
Sardh et al. (2019)[16] Part C (NCT02452372)	Aged 18-65 Confirmed HMBS mutation Diagnosis of AIP Recurrent attacks (≥2 in 6 months before run-in) or taking prophylactic medication Women of child-bearing age must have negative serum pregnancy test, not be nursing and using acceptable contraception Willing to provide written informed consent and willing to comply with study requirements Willing to discontinue/not start prophylactic IV heme during the run-in and study periods	Clinically significant health concerns Started new prescription medication within 3 months of screening Clinically significant abnormal lab results Received investigational agent within 90 days before the first dose of the study drug or are in follow-up of another clinical study History of multiple drug allergies or intolerance to subcutaneous injection
Bonkovsky et al. (2019)[15] Phase 1/2 OLE (ongoing) (NCT02949830)	Completed participation in Part C of ALN-AS1-001 Not on scheduled prophylactic IV heme regimen Women of child bearing potential must have a negative serum pregnancy test, not be nursing, and use acceptable contraception Willing and able to comply with the study requirements and to provide written informed consent	Clinically significant abnormal lab results Received an investigational agent (other than in ALN-AS1) within 90 days before the first dose of study drug or are in follow-up of another clinical study History of multiple drug allergies or intolerance to subcutaneous injection

Abbreviations: AIP, acute intermittent porphyria; ALA, delta aminolevulinic acid; HCP, hereditary coproporphyria; hep B, hepatitis B; hep C, hepatitis C; HIV, human immunodeficiency virus; HMBS, hydroxymethylbilane synthase; OLE, open-label extension; PBG, porphonilinogen; VP, variegate porphyria

3.2.2.3. Intervention

The intervention evaluated in both trials was givosiran plus BSC.

Givosiran

Dosing is summarised in Table 8. In ENVISION and ENVISION OLE, patients were treated with givosiran according to its licensed dose. This was a standard dose of 2.5mg reductions to 1.25mg/kg permitted for participants with elevated liver transaminase levels. This occurred in 1 patient in ENVISION, who stopped treatment and continued ENVISION OLE at the lower dose. No stopping rules were used, though treatment could be stopped if patients exhibited unacceptable AEs. Almost all patients completed the treatment, with very few missing doses. Those missing doses reported were due to a transient AE or difficulties in scheduling doses within the dose window.

In the ENVISION OLE, the trial protocol was amended ahead of the trial to permit evaluation of two monthly doses: 1.25 mg/kg (n = 37) and 2.5 mg/kg (n = 56). Clinicians were permitted to move patients between doses, either to address AEs or else to increase dose efficacy. The number of patients moving to either dose was not reported in the CS, and efficacy data were reported for all patients irrespective of starting dose. It is unclear to what extent the dose of givosiran used in the ENVISION OLE would therefore generalise to the dose that would be received by the target population, who are intended to begin treatment at a dose of 2.5 mg/kg, unless a dose reduction is indicated because of baseline risk of AEs.

In the Phase I/II trial, patients in Part C were randomised to receive one of four different doses of givosiran: 2.5mg/kg monthly for 4 injections; 5.0mg/kg monthly for 4 injections; 2.5mg/kg every three months for 2 injections; and 5.0mg/kg every 3 months for 2 injections. In the Phase II OLE, two different doses of givosiran were evaluated: 9/16 patients started with 2.5 mg/kg givosiran once monthly and 7/16 patients started with either 5.0 mg/kg once monthly or 5.0 mg/kg once every 3 months[21]. However, during the OLE, a protocol change led to all patients transitioning to the 2.5mg/kg dose. At the cut-off date in October 2019, 2/16 (12.5%) had discontinued treatment (one due to lack of response, one due to SAE).

Table 8: Givosiran dosing in the included trials

	ENVISION (6 months) N=48	**ENVISION OLE (30 months) N=93**	**Phase I (12 weeks) Part C N=13**	**Phase I/II OLE (42 months) N=16**
Time on treatment	Mean 5.51 months (SD 0.15; range 5.3, 6.0)	Givosiran/givosiran (n=47):Mean 8.05 months (SD 2.23; 2.7, 13.8) Placebo/givosiran (n=46): Mean 2.68 months (SD 1.9; range 0.1, 7.9)	12 weeks	42 months
Protocol dose	2.5 mg/kg monthly. Dose reduction to 1.25 mg/kg permitted following AE.	2.5 mg/kg (n=56) or 1.25 mg/kg (n=37) monthly. Dose reduction to 1.25 mg/kg permitted following AE; dose increase to 2.5 mg/kg permitted due to poor efficacy.	2.5mg/kg monthly 2.5mg/kg every 3months 5 mg/kg monthly 5 mg/kg every 3 months	2.5 mg/kg monthly (see below)
Dose increases/decreases	1 patient had dose reduced to 1.25 mg/kg	NR	None	A protocol change during the OLE led to 7 patients who started on other doses being switched to 2.5 mg/kg. Original doses as follows: 5.0 mg/kg every 3 months (n=4) 5.0 mg/kg monthly (n=3)
Missed Doses	5/48 patients missed 1 or more dose (1 dose n=4; 2 doses n=1)	2/93 (2.2%) patients missed 1 or more dose	NR	NR
Discontinuation (AEs)	1/48 (2.1%) One additional patient withdrew after ENVISION but before the OLE.	3/93 (3.2%)	None	3/16 (18.8%) 1 patient with anaphylactic reaction

	ENVISION (6 months) **N=48**	**ENVISION OLE (30 months)** **N=93**	**Phase I (12 weeks)** **Part C N=13**	**Phase I/II OLE (42 months)** **N=16**
				1 patient discontinued and withdrew due to lack of response to givosiran 1 death determined to be unrelated to study drug

Abbreviations: AEs, adverse events; OLE, open label extension

Source: ENVISION CSR[22] p.85; Company clarification response (A1).

Best supportive care (BSC)

BSC was defined by local treating clinicians and protocols, and included management of both chronic symptoms and acute attacks. Treatment with prophylactic IV heme was prohibited during both trials, though IV heme was permitted to treat acute attacks. The proportion of patients receiving IV heme and analgesia (opioid and non-opioid) was a trial outcome of ENVISION (data reviewed in Section 3.2.3.2). During ENVISION, just under half of participants receiving givosiran (22/48, 45.8%) received IV heme at least once; this proportion decreased to 29.8% (14/47) in the OLE (Clarification response A3). In ENVISION, by six months the vast majority (43/48, 89.6%) of patients were receiving analgesia, including 32/48 (66.7%) of patients receiving opioid medication (Clarification response A3). A small minority of patients were also using GnRH analogues during the trial; the proportion in the givosiran arm was not reported in the CS, though at clarification the company reports that 4.3% of patients across both arms were using GnRH analogues (Clarification A1). Based on clinical advice, the ERG anticipated that BSC may vary between centres in the number of healthcare visits/appointments, frequency of patient follow-up, and delivery of psychological and wellbeing support. The latter may include support for patients' self-management of the triggers of acute attacks, which the ERG understood can help to reduce attack frequency.

3.2.2.4. Comparators

The primary comparator used in ENVISION and the Phase I trial was placebo plus BSC; there was no comparator in either of the OLEs. The placebo used in ENVISION was IV sodium chloride 0.9% administered subcutaneously; the placebo in the phase I/II trial was not reported. BSC in both trials was the same as described in Section 3.2.2.3. The CS reported that 73.9% of patients in the comparator arm of ENVISION used acute IV heme, and almost all (45/46, 97.8%) patients used analgesia, including 38/46 (82.6%) patients who received opioid medication.

3.2.2.5. Outcomes

The outcomes reported in the trials of givosiran are summarised in Table 9 below. The Phase I trial was primarily intended to capture safety outcomes and surrogate outcomes of efficacy (urinary delta aminolevulinic acid, ALA and porphobilinogen, PBG); however, a composite outcome of annualised attack rate (AAR composite) was included as a secondary outcome. In the ENVISION trial, the company measured a wide range of outcomes, including clinical efficacy (AAR, acute hemin administration, analgesic use), surrogate outcomes of clinical efficacy (urinary ALA and PBG), and patient-reported outcomes. Not all scoped outcomes were

measured in the trials, as no data were available for rates of neurological impairment and impairments in autonomic function. The ERG considered that rates of neurological impairment, which can occur following an acute attack, are important for understanding the efficacy of a reduction in acute attacks, as rates of neurological impairment have a significant impact on the lives of patients and on healthcare needs. However, the ERG considered that the follow-up of the trials (up to 24 months in the ENVISION OLE and Phase I/II OLE) were likely too short to capture meaningful differences in this outcome, and longer follow-up data would be needed. The ERG considered that the length of trial follow-up was likely to capture a meaningful change in AAR in the trial population, but that the follow-on benefits of a change in AAR may take longer to emerge (e.g. a knock-on effect of a reduction in attacks on opioid use). Clinical advisors to the ERG could not suggest any outcomes related to autonomic function that they considered would be pivotal to decision-making.

Frequency of acute attack

The primary outcome evaluated by the company for determining the clinical efficacy of givosiran is the annualised attack rate (AAR), which is a composite outcome of acute attacks that result in either hospitalisation, acute IV hemin use, or urgent care. The ERG considered the measurement of attack according to the need for resource to be appropriate, as there is no clear clinical criteria for when an acute attack occurs, and clinical advice to the ERG was that it can sometimes be difficult for clinicians to distinguish between an exacerbation of chronic symptoms and an acute attack. This may be most relevant for milder attacks where treatment is not required. As a significant number of attacks require treatment, and these attacks are those most likely to affect patients' health and healthcare needs, the ERG considered that the company's approach would be the most appropriate for measuring acute attacks. At clarification (in response to question A3), the company also provided the AAR separately for each type of resource use, which the ERG considered to be informative for the impact of a change of AAR on healthcare needs, and also to evaluate whether givosiran has a differential impact on attacks of different severity (i.e. between attacks requiring hospital vs. non-hospital care).

Surrogate outcomes for clinical efficacy

Both trials evaluated urinary ALA and PBG as surrogate outcomes for clinical efficacy, though the company and the ERG considered that the utility of these outcomes for evaluating the clinical efficacy of givosiran is limited. While reductions in these levels following treatment may provide evidence for the mechanism of givosiran, there is known to be natural fluctuations in

these rates independent from the presence of attack, and there are no stablished thresholds for determining whether an attack is more or less likely. The company also noted that there is no established relationship between urinary ALA or PBG and the frequency at which patients experience attacks, chronic symptoms or long-term complications of porphyria. The ERG therefore considered that these outcomes may have limited bearing for decision-making.

Analgesic use

While not a scoped outcome, the ERG considered that rates of analgesic use in the trial populations were nevertheless an important clinical outcome. Clinical advisors to the ERG advised that use of analgesia is high in patients with AHP, and patients are at an increased risk of opioid dependence as compared with the general population. A clinically meaningful reduction in opioid use may therefore have broad benefits for the patient population. Analgesic use was measured using medical records and daily diary entries throughout the ENVISION trial; however, to explain unexpected findings in this outcome in the ENVISION OLE, the company stated that the measurement of this outcome was challenging, due to the aggregation of data from the two sources.

HRQoL and patient-reported outcomes

HRQoL data were measured in ENVISION at baseline, and at 3- and 6-month follow-up, using the EQ-5D visual analogue scale (VAS) and subscales of the Short Form-12 Health Survey (SF-12). Both measures provide a valid and reliable measure of change in generic HRQoL that can be interpreted alongside thresholds for minimally important differences (MIDs). MIDs used by the ERG to interpret data for the SF-12 and EQ-5D VAS were consistent with those specified for the Short Form-36 Health Survey (SF-36, user's manual v2, third edition)[23].

The company argued that these generic measures of HRQoL may be unable to adequately capture a change in HRQoL following a reduction in the frequency of acute attacks in patients with AHP. The company argued that this was partly due to the high prevalence of crhonic conditions in patients with AHP. The ERG considered that this rationale not clearly explained, although reflected that the prevalence of some chronic conditions that are irreversible or slow to change may not be evidence in short-term follow-up (e.g. neurological impairment, or addiction). The ERG considered that HRQoL at later follow-up in the ENVISION OLE may have been more informative, although while the data were measured in the trial, the results were not provided in

the CS. The ERG identified partial data for these timepoints in the trial CSR[22] provided by the company, however the full data were in the appendices of the report, which were not provided.

The company further suggested that the EQ-5D may be insensitive to change as it requires patients to respond on the basis of their wellbeing that day (as opposed to over a broader period of time, e.g. one month). The company further suggested that as very few assessments were administered during an attack (0.4%; CS p.75), the measure would be unable to capture the impact of acute attacks on HRQoL. The ERG was unsure about this argument; on the one hand, the ERG considered that more HRQoL data measured during an acute attack would inform on the impacts of acute attacks on the lives of patients. However, on the other hand, the ERG considered that the EQ-5D may nevertheless be appropriate for capturing the broader impact of acute attacks on the lives of patients.

The ERG considered that HRQoL is a crucial outcome for understanding the impact of AHP on the lives of patients; however the ERG accepted that the measurement and interpretation of HRQoL data may be challenging, due to the prevalence of chronic conditions, the lack of HRQoL data during an acute attack of AHP, and the short-term trial follow-up. Clinical advice to the ERG was that HRQoL also varies widely between patients, and is affected by many factors other than the frequency of acute attack.

A range of other patient-reported outcomes were measured in the ENVISION trial, including scales evaluating daily worst pain, daily worst fatigue, nausea, and two questionnaires: the porphyria patient experience questionnaire (a new measure developed by the company, which has been used in several patient groups) and the patient global impression of change (PGIC; an adaptation of a subscale of the clinical global impressions scale). None of these measures have been subjected to psychometric appraisal and validation in any publication that the ERG could identify, and therefore the ERG was unable to verify the reliability and validity of these measures for understanding the experience of patients, and for measuring the efficacy of treatments. The ERG also considered that data from these measures would be difficult to interpret, due to the lack of any validated thresholds for meaningful change. In addition, the ERG was advised that the symptoms of AHP vary widely between patients, and therefore variation in levels of daily pain, nausea and fatigue may be misleading, particularly in small trial samples.

Overall, the ERG considered that the measurement of HRQoL and patient reported outcomes (PROs) is relevant for understanding the impact of a change in the frequency of acute attacks on the lives of patients. However, the ERG considered that HRQoL measures were a stronger

source of evidence than the PRO measures, but that the validity of these measures in this population is uncertain.

Table 9: Clinical efficacy outcomes reported across the included trials

Outcome	ENVISION	ENVISION OLE	Phase I	Phase I/II OLE
Composite AAR	✓	✓	✓	✓
Breakdown of AAR across resource use	✓	✓	X	X
ALA	✓	✓(graph)	✓(no variance data)	X
PBG	✓	✓(graph)	✓(no variance data)	X
Neurological impairment	X	X	X	X
Autonomic function	X	X	X	X
HRQoL	✓	✓	X	X
Acute IV heme use	✓	✓	✓	?
Daily worst pain	✓	✓	X	X
Daily worst nausea	✓	✓(graph)	X	X
Daily worst fatigue	✓	✓(graph)	X	X
PGIC	✓	✓	X	X
PPEQ	✓	✓ (no overall score)	X	X
Additional post-hoc analyses				
Attacks with pain score ≥7	✓	X	X	X
Pain during attacks	✓	X	X	X
Analgesic use	✓	✓	X	X

Abbreviations: AAR, annualised attack rate; ALA, delta aminolevulinic acid; ALAS1, delta aminolevulinic acid synthase 1; HRQoL, health-related quality of life; IV, intravenous; mRNA, messenger ribose nucleic acid; OLE, open label extension; PBG, porphobilinogen; PCS, physical component summary; PGIC, patient global impression of change questionnaire; PRO, patient reported outcome

Safety

Adverse events (AEs), serious adverse events (SAEs), discontinuation, withdrawals and fatal events were collected across all included trials.

3.2.2.6. Critical appraisal of the design of the studies

The company's critical appraisal of ENVISION and the Phase I trial were reported in the CS (Document B, p. 46-47), and the critical appraisal of the Phase I/II OLE was reported in the company's internal SLR report,[8] provided by the company at clarification. The company's critical appraisal of the ENVISION OLE was missing from the CS, and has been completed by the ERG below.

ENVISION and ENVISION OLE

Generally speaking, the ERG considered that ENVISION appears to be a well conducted, high quality trial. Despite the relatively small sample, baseline characteristics appeared similar between trial arms; although the ERG noted that this is a heterogeneous population, and there is likely to be unknown confounders. The ERG noted that there is potential risk to unblinding caused by injection site reactions, though this was expected to only be a risk to PROs. The company critical appraisal did provide separate ratings across outcomes, and the ERG further noted risks of bias associated with post-hoc analyses of ENVISION, and PRO measures (other than HRQoL) as these measures have not be psychometrically tested. The company also noted that measurement of analgesia use is at a high risk of bias due to potential measurement error, though this was not noted in the company's critical appraisal. For the ENVISION OLE, additional concerns included a lack of variance data for some outcomes, and missing data at the final timepoint (24-months for givosiran/givosiran and 18-months for placebo/givosiran). The ERG assumed that the cause of the missing data is because data collection for this timepoint is ongoing, but the ERG considered that data reported at the 18-/12-month' follow-up was nevertheless more robust.

Phase I/II trial

Baseline characteristics for Part C of the Phase I trial were remarkably similar, though there was a difference in gender, and few baseline characteristics were reported. Given the very small sample size of this trial, the ERG considered that randomisation would have been unlikely to balance across potential confounding factors. The Phase I/II trial and OLE were not powered to

detect efficacy outcomes, and safety data were generally reported across all parts of the trial, and so included some patients outside of the target population.

Table 10: Critical appraisal of ENVISION

Item	Company response	Company detail	ERG comment
Was randomisation carried out appropriately?	Yes	Patients were stratified according to AHP type and use of prophylactic IV heme.	The ERG agreed with the company's assessment.
Was the concealment of treatment allocation adequate?	Yes	Patients were assigned study identification numbers via an interactive response system (IRS) and once inclusion criteria were confirmed, the IRS assigned a blinded treatment.	The ERG agreed with the company's assessment.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Groups were comparable with respect to baseline characteristics including chronic symptoms, previous treatments, and indicators of disease severity.	The ERG agreed with the company's assessment.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Participants and outcome assessors were blinded to the allocation of treatment. Treatment assignments were maintained by the IRS and members of the study team did not have access to the 6-month treatment period unblinded data until the final analysis.	Yes/partial – in general the ERG agreed with the company's assessment, although note that 25% of patients experience injection-site reactions with givosiran, which may therefore have posed a risk to blinding. If unblinding did occur, this would be unlikely to affect AAR and other clinical outcomes, but may be associated with an increased risk of bias for patient-reported outcomes.
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No	All but one of the 94 patients went on to participate in the OLE phase of this study.	The ERG agreed with the company's assessment.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes were clearly stated a priori and reported accordingly.	The ERG agreed with the company's assessment.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Full analysis set included all randomised patients who received at least 1 dose of study drug. All but one patient that discontinued treatment went on to participate in the OLE phase of the study.	The ERG agreed with the company's assessment.

Abbreviations: AAR, annualised attack rate; AHP, acute hepatic porphyria; ERG, Evidence Review Group; IRS, interactive response system; OLE, open-label extension

Table 11: Critical appraisal of ENVISION OLE

Item	ERG comment
Was the cohort recruited in an acceptable way?	Yes – all eligible patients from ENVISION enrolled
Was the exposure accurately measured to minimise bias?	Yes
Was the outcome accurately measured to minimise bias?	Yes – AAR, acute hemin doses, laboratory markers, HRQoL Unclear: Analgesic use, and patient-reported outcomes. As discussed in Section 3.2.2.5, there are concerns about the accuracy of analgesic use data, due to the complexity of analysing data from daily diary entries and medical records. Patient reported outcomes were assessed using non-validated measures, and are therefore at a higher risk of bias. The company used a daily measure of pain, which was a single scale from the BPI-SF NRS. The accuracy of this outcome, and the ability of this outcome to detect change in pain in this population, is unknown.
Have the authors identified all important confounding factors?	Yes. The ERG considered that the company reported all known confounding factors. However, the ERG also noted that this is highly heterogeneous population captured in a relatively small sample, and that very little is known about the factors that may contribute to poor prognosis and may affect treatment efficacy of givosiran.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes
Was the follow-up of patients complete?	Partial: at 12-month follow-up (18-months for givosiran/givosiran patients) data were available for most patients. However, by the final follow-up at 18-months (24-months for givosiran/givosiran patients) data were available for very few patients (e.g. for AAR, data were available for 18/94 (19.1%) patients).
How precise (for example, in terms of confidence interval and p values) are the results?	Variable: there are no MIDs available for the reported outcomes, and therefore the ERG could not determine the level of imprecision that would be clinically meaningful. Differences in AAR outcomes were all statistically significant, and all bounds of the confidence intervals were interpreted as consistent with a clinical benefit for givosiran. However, in the case of acute attacks requiring IV heme, the ERG noted that the confidence intervals came close to the line of null effect, suggesting uncertainty in clinical benefit. A statistical comparison was not reported for other outcomes.

Abbreviations: AAR, annualised attack rate; BPI-SF, brief pain inventory (short form); ERG, Evidence Review Group; HRQoL, Health-related quality of life; MID, minimal important difference; NRS, numeric rating scale

Table 12: Critical appraisal of Phase I trial

Item	Company response	Company detail	ERG comment
Was randomisation carried out appropriately?	Yes	Randomisation and treatment allocation ratios were clearly described in each part of the study	While the trial was conducted as a RCT, the number of patients randomised (13 to givosiran and 4 to placebo) mean that it's unlikely that randomisation was able to create a sample balanced for all confounders.
Was the concealment of treatment allocation adequate?	Yes	Randomisation lists generated by biostatistician and maintained by dispensing pharmacist.	The ERG agreed with the company's assessment
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Group sizes in Parts A and B were too small to assess and not presented. The two treatment groups in Part C of the study appear comparable although sample sizes small.	The ERG agreed that the samples in Part C appear similar on a limited number of factors, though there was a difference in gender. However, as stated above, due to the small samples and the limited number of confounders reported at baseline, it's unlikely that the two arms were balanced for all confounders.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Partially for Parts A and B Yes, for Part C	Part A and Part B were single-blind only by design (MAD/SAD study in patients that did not experience acute attacks). The risk of bias is low because it was a SAD/MAD study of the same intervention. The study was double-blind in Part C (recurrent attack patients).	The ERG agreed with the company's assessment.
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No	All patients were accounted for.	The ERG agreed with the company's assessment.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Outcomes were stated a priori and reported accordingly. Exploratory endpoints were clearly identified.	The ERG agreed with the company's assessment.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	All randomised patients were included in the analysis and all patients were accounted for. Investigators had stated methodology for handling missing data a priori.	The ERG agreed with the company's assessment.

Abbreviations: ERG, Evidence Review Group; MAD, multiple-ascending dose; RCT, randomised controlled trial; SAD, single-ascending dose

Table 13: Critical appraisal of Phase I/II OLE

Item	Company response	Company detail	ERG comment
Was the cohort recruited in an acceptable way?	Yes	This study included all eligible patients who were previously enrolled in a Phase 1 study (i.e., Part C of givosiran Phase 1 randomised trial).	The ERG agreed with the company's assessment.
Was the exposure accurately measured to minimise bias?	Yes	Exposure is very clear, specified measured dose via injection.	The ERG agreed with the company's assessment.
Was the outcome accurately measured to minimise bias?	Yes	Acute attacks, acute hemin doses, and laboratory values are likely to be accurately measured.	The ERG agreed with the company's assessment.
Have the authors identified all important confounding factors?	Yes	The baseline characteristics from the original Phase 1 trial from which these patients originated were reported here and included age, gender, weight, race, prior therapy, previous attacks, and laboratory parameters.	Unclear – as stated for the earlier phase of the trial, fewer baseline characteristics were measured for this trial than in the subsequent ENVISION trial, and due to this being a rare disease area, little is known about important confounding factors.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Patient population was based on a randomised study.	Unclear – the sample size was too small to allow for adjustment for confounders
Was the follow-up of patients complete?	Partially	There was complete follow-up for most outcomes (i.e., annualised attack rate, acute hemin doses). There is a variable n over time for some outcomes (e.g., ALA), however is [sic] may be due to patients moving through the cohort in the long-term follow-up which is not yet completed.	Missing data were not reported in the CS
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	N was small, no p-values	Any relative effect estimates are likely to be highly imprecise.

Abbreviations: CS, company submission; ERG, Evidence Review Group; OLE, open label extension

3.2.3. Description and critique of the results of the studies

3.2.3.1. Baseline characteristics

Baseline characteristics for ENVISION and the Phase I/II trial were provided by the company separate from the CS, in an internal report of the company's clinical effectiveness review.[8] The baseline characteristics for ENVISION OLE were not provided. A summary of key baseline characteristics are provided in 14.

Comparability of trial arms

Generally speaking, both trials reported that arms were well balanced in baseline patient characteristics. A notable exception in ENVISION was that patients in the givosiran arm included a higher proportion of patients with elevated liver transaminase, and this confounded analyses related to liver complications in the trial. It's unclear whether this difference would have impacted on the comparability of the arms for other adverse events, though clinical advice to the ERG was that there is no clear mechanism through which this difference would affect the clinical efficacy of givosiran.

Aside from a difference in the proportion of female patients in each arm, the treatment arms in the Phase I/II trial were surprisingly similar given the small sample size used in randomisation. This may be due to the methods for identifying trial patients selecting a reasonably homogenous group; however due to the few characteristics reported and the potential for unknown confounders in this patient group, the ERG considered the comparability of the trial arms in the Phase I/II trials to have some uncertainty.

Generalisability of the evidence to NHS patients

The ERG were unclear to what extent the characteristics of the patients included in the two trials represent the target NHS population. There are some indications that the trial populations may vary from the target NHS population in some factors, though the importance of these factors for determining the generalisability of the evidence is unclear. This issue is discussed in The ERG reviewed the clinical effectiveness and safety evidence presented in the CS and identified the following key issue for consideration by the committee.

Key Issue 2.

Firstly, the company's clinical experts proposed that the ENVISION trial population (mean = 41.6 years) was likely to be older than the target population[24]: the typical age of AHP patients with recurrent symptoms is reported to be between 20 and 40 years' old[25]. This was at odds with the company assertion that the ENVISION population may have had the disease for less time than the target population (in response to clarification question B7). Clinical experts were unable to comment on whether treatment efficacy was likely to vary according to patient age.

It is also unclear whether treatment efficacy may vary according to baseline risk, and this was not explored within the trials, due to small patient samples. Several data suggest that the ENVISION patient population may be at a lower baseline risk than the target population. A sizeable minority (27.2%) of patients did not meet the standard threshold for 'recurrence' of acute attack at baseline (i.e. four attacks in a 12-month period). The company also noted that fewer patients in ENVISION reported chronic symptoms at baseline than is reported in other studies, although they noted that the methods used to evaluate chronic symptoms at baseline may not have been comprehensive (in response to clarification query A4). In comparison with the EXPLORE study,[18] a natural history study of patients with AHP, patients in the ENVISION trial reported a lower attack rate, reduced use of prophylactic IV heme, and lower rates of opioid use.

Very few patients (n=5/94, 5.3%) included in ENVISION were diagnosed with the less common subtypes of AHP (VP, HCP and ADP) and only AIP patients were eligible for inclusion in the Phase I/II trial. The proportion of non-AIP patients in ENVISION is lower than population estimates (e.g. AIP is eight times more common than VP, and twice as common as HCP [CS, Document B, Table 8, p. 26]). The company stated that givosiran will have the same impact on outcomes for all subtypes of AHP due to the common ALAS1 induction across the subtypes, however no evidence was presented to support this. The generalisability of evidence to the subtypes of AHP is therefore uncertain.

Fewer baseline characteristics were reported for patients in the Phase I/II trial. Patients were of a similar age to those in ENVISION, and with a similar history of prophylactic heme. However, patients' attack rate at baseline was slightly greater (despite the inclusion criteria permitting the inclusion of patients with <2 attacks in the past 6 months if they were receiving prophylactic IV heme). The proportion of patients with chronic symptoms was not reported, though a higher proportion of patients were receiving opioid analgesia between attacks, suggesting chronic pain.

Table 14: Baseline characteristics

	ENVISION		PHASE I/II	
Population (n)	Givosiran n=48	Placebo n=46	Part C Givosiran n=13	Part C Placebo n=4
Age, median (range)	42 (19–65)	36 (20–60)	36 (21–-59)	42 (27–60)
Female, n (%)	43 (90)	41 (89)	13 (100)	2 (50)
Years since diagnosis, median (range)	6.98 (0.2–43.3)	6.11 (0.1–38.5)	—	—
AHP type, n(%)				
AIP (HMBS)	46 (96)	43 (94)	13 (100)	4 (100)
AIP (unidentified)	0	2 (4)	0	0
HCP	1 (2)	0	0	0
VP	1 (2)	1 (2)	0	0
Attacks in last 6 months, median (range)	4.0 (2–17)	3.5 (0–23)	–	–
Attacks in last 12 months, median (range)	–	–	9.0 (0–36)	10.0 (5–50)
Daily chronic symptoms between attacks, n (%)	23 (48)	26 (57)	–	–
Ever diagnosed with neuropathy, n (%)	20 (42)	16 (35)	–	–
Iron overload (ever diagnosed), n (%)	16 (33)	15 (33)	–	–
Liver transaminase elevation >ULN, n (%)	13 (27)	3 (6.5)	–	–
Prior hemin prophylaxis, n (%)	20 (42)	18 (39)	6 (46)	2 (50)
Opioids between attacks, n (%)	14 (29)	13 (28)	7 (54)	2 (50)
GnRH analogue use, n (%)	4.3% across both arms		4 (31)	0

Source: adapted from company's SLR report, provided at clarification

Abbreviations: AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; GnRH, gonadotrophin releasing hormones; HCP, hereditary coproporphyria; HMBS, hydroxymethylbilane synthase; ULN, upper limit of normal; VP, variegate porphyria

3.2.3.2. Clinical effectiveness results

An overview of the clinical effectiveness results presented by the company for givosiran as relevant to the outcomes specified in the NICE scope are summarised below. In addition to the

outcomes in the NICE scope, the company presented evidence for pain incidence and severity, use of analgesia, and a series of additional PRO outcomes.

Frequency of acute attack

Efficacy data for the effect of givosiran on composite AAR in patients with AIP in ENVISION and the Phase I/II trial are summarised in Table 15 and Table 16.

Across the trials, the relative reduction of acute attacks in patients treated with givosiran compared with placebo was consistently large (between 74% in ENVISION to 95% in Phase I/II OLE), and was statistically significant. The AAR was not reported for patients in ENVISION OLE who received givosiran during ENVISION, though a graph provided by the company showed that AAR was comparable with the placebo/givosiran arm (CS Figure 20, p. 57).

While the ERG did not identify a threshold for the reduction in AAR that would be clinically meaningful to patients, clinical advice to the ERG was that the effect size reported in both trials would represent a clinically meaningful benefit for the lives of patients with AIP. Confidence intervals around the reported effects show some uncertainty in the magnitude of effect that would be seen in the target patient population, which may be due to the limited sample sizes of the included trials, or else may reflect some variation in effect across patients in such a naturally heterogeneous patient population. However, the ERG considered that the most conservative interpretation of the data would nevertheless have clinically meaningful benefits for the patient group as a whole. Clinical experts further noted that where each acute attack could potentially lead to life-changing consequences (such as neurological damage), any reduction in the frequency of acute attacks may be seen as clinically meaningful.

Table 15: Efficacy of givosiran for composite AAR in patients with AIP

	ENVISION	**ENVISION OLE**	**Phase I**	**Phase I/II OLE**
Final follow-up	6 months	18 months	6 months (168 days)	
Placebo	12.5 (95% CI 9.35, 16.76)* n=43	N/A	16.7 (SE 5.0)*	N/A
Givosiran (2.5 mg/kg monthly)	3.2 (95% CI 2.25, 4.59)* n=46	Givosiran/givosiran: NR Placebo/givosiran: 2.56 n=43	2.9 (SE 1.9)*	Treated with givosiran in Phase I: 0.8 (95% CI NR) Crossed over from placebo in

	ENVISION	ENVISION OLE	Phase I	Phase I/II OLE
				Phase I: 0.6 (95% CI NR)
Relative reduction	74% (95% CI 59% - 84%)*	Givosiran/givosiran: NR Placebo/Givosiran: 82% (75% - 87%)≠	82.8% (95% CI 44.5% - 94.7%)*	95% (95% CI NR)^

Abbreviations: AAR, annualised attack rate; AIP, acute intermittent porphyria; CI, confidence interval; DB, double blind; N/A, not applicable; NR, not reported; OLE, open-label extension; SE, standard error; SLR, systematic literature review

Notes: *based on annualised rate ratio. ^as compared with AAR of patients receiving placebo in phase I. ≠Placebo/givosiran arm only, as compared with DB period (placebo)

Source: Company clarification response (question A3); Alnylam givosiran SLR report (p.33); CS p.49, 60

In response to clarification, the company provided a breakdown of the composite AAR effect in ENVISION (shown in Table 16 below). These analyses show a reduction in AAR as compared to placebo across all types of acute attack, though in ENVISION the effect for attacks requiring hospitalisation was smaller and not statistically significant. At 6-months, the proportion of total attacks experienced by patients that resulted in hospitalisation was greater in the givosiran arm (51.8%) than the placebo arm (23.9%). These data suggest that in ENVISION, givosiran had a greater impact in reducing those attacks that do not require hospitalisation. The breakdown in AAR for patients who received givosiran in ENVISION was not reported at later timepoints in ENVISION OLE, and so it is unclear if this effect persisted over time. However, in patients who crossed over from placebo to givosiran in ENVISION OLE, the data also showed a smaller relative reduction in attacks requiring hospitalisation than for other types of attacks (though in this case, the effect was statistically significant, and was larger than the effect reported in ENVISION). Overall, the data suggest that givosiran results in a reduction in all types of attack measured in ENVISION and ENVISION OLE, though there is evidence that the effect may be greater for those attacks that are currently treated without hospitalisation.

Findings were consistent with findings in the full AHP population, though this is to be expected given the small difference in sample size (see Section 3.2.3.1).

Table 16: Efficacy of givosiran for AAR according to resource need

	ENVISION		ENVISION OLE (18 months)
	Placebo (n=43)	**Givosiran (n=46)**	**Placebo/givosiran** (n=43)
Attacks requiring hospitalisation	3.21 (95% CI 1.98, 5.20)	1.65 (95% CI 0.98, 2.78)	0.94 (NR)

	ENVISION		ENVISION OLE (18 months)
	RR: 49% (95% CI-4% - 75%)		RR: 73% (95% CI 57% - 84%)
Attacks requiring urgent healthcare visit	7.53 (95% CI 5.13, 11.05)	1.22 (95% CI 0.73, 2.05)	1.56 (NR)
	RR: 84% (95% CI 69% - 91%)		83% (95% CI 75% - 89%)
Attacks requiring acute IV hemin administration	NR Total attacks: 32	NR Total attacks: 3	0.06
	NR		RR: 96% (95% CI 81% - 99%)

Abbreviations: AAR, annualised attack rate; CI, confidence interval; IV, intraveneous; NR, not reported; OLE, open label extension; RR, relative reduction

Subgroup analyses in the ENVISION trial (CS p.51) showed the relative reduction in AAR was relatively stable across subgroups analysed, with no apparent differences in effect between most subgroup categories (age, race, region, body mass index (BMI), and prior he prophylactic IV heme use). There was a trend for the reduction in AAR to be smaller in patients who experienced chronic symptoms, and for those who use opioids to manage chronic symptoms, though the ERG did not consider it possible to conclude on the potential for subgroup differences on the amount of data available. As a post-hoc analysis, the company further evaluated the effect of givosiran for acute attacks associated with increased pain; these findings are discussed under additional outcomes reported by the company.

Porphyrin precursor concentrations in urine

Evidence from ENVISION demonstrated statistically significant reductions in urinary ALA and PBG at 3- and 6-months for patients treated with givosiran as compared to placebo. At three months the treatment difference was -18 mmol/mol Cr (95% confidence interval (CI): -22.3,-14.2; p=8.74x10 14), and at six months the least squares (LS) mean treatment difference was -19 mmol/mol Cr (95% CI: -26.0, 12.2; p=6.24x10-7; Alnylam SLR report[8]). Median ALA and PBG levels in patients treated with givosiran were reduced by 86% and 91% compared to baseline, respectively, as shown in Figure 11 in the CS (Document B, p. 52). These graphs further showed that such reductions in ALA and PBG in patients treated with givosiran occurred within the first month of treatment, and that the reduction was sustained across the six-month follow-up. No ALA and PBG data were reported for the ENVISION OLE, though graphs reported in the CS (p.58) showed that mean reductions in ALA and PBG shown at 6-months were

maintained. Without variance data for these differences, it's unclear how much variation was seen across the patient sample.

Reductions in ALA and PBG were replicated in the Phase I trial, and data from the Phase I/II OLE further showed that the reduction in ALA was maintained up to 18 months (91%, n=14). Between Month 21 and 24 of the OLE, mean ALA appeared to increase; however, sample size at this stage of the trial was very small, with only four and two patients with data at each timepoint. Mean reductions in PBG was stated by the company to remain consistent until 24 months, though these data were not reported in the CS. Reductions of 84% and 86% from baseline were reported at 12 and 18 months in the cited publication[15], though without variance data, and no further outcome data were presented in the publication beyond these timepoints.

Reductions in ALAS1 mRNA were reported for patients receiving givosiran in the Phase 1 OLE only, where patients in the target population demonstrated a 67% (95% CI 61.1, 72.9) reduction from baseline at six months (168 days). No data for the placebo arm was reported, and there were no other comparative data for this outcome presented by the company.

The ERG considered that the large reductions in ALA, PBG, and ALAS1 are consistent with the biological mechanism of givosiran as presented by the company. As stated in Section 3.2.2.5, clinical experts to the ERG advised that the relationship between these surrogate outcomes and clinical efficacy outcomes such as AAR and the severity of chronic and acute symptoms is unclear. The company further stated that these outcomes cannot be used to predict the risk of acute attack. The relevance of these outcomes for understanding the clinical efficacy of givosiran is therefore uncertain.

However, the ERG noted that one of the stakeholder submissions for this appraisal (NAPS Kings College University statement) suggested that a reduction in PBG levels following treatment with givosiran may offer an unexpected clinical benefit for patients with chronic symptoms. In practice, testing of PBG levels can be used to diagnose an acute attack, however this test can be insensitive in patients with chronic symptoms, in whom levels of PBG are frequently high. The stakeholder suggested that persistent lower levels of PBG in patients with chronic symptoms may allow for more accurate testing for acute attack, although the ERG did not believe that this strategy has been evaluated in practice.

Neurological impairment

The company did not present evidence for the rate of neurological impairment experienced by patients in trials of givosiran. As discussed in Section 3.2.2.5, the ERG considered this to be a major omission from the clinical evidence base for givosiran.

Health-related quality of life and PROs

Evidence for HRQoL and PRO outcomes in this section is derived from the ENVISION trial only, as these outcomes were not measured in the Phase I/II trial.

Data from ENVISION showed that EQ-5D VAS scores were higher in the givosiran arm at 6-months as compared to placebo; however while the difference in scores was above the MID, the difference was not statistically significant. The lack of a statistically significant difference in EQ-5D effect is surprising, given the large reduction in the frequency of acute attacks in the givosiran arm. However, this finding is consistent with evidence presented by the company at clarification [question B7] showing that there was no correlation between AAR and EQ-5D scores (pearson's r = -0.02) in ENVISION. An accompanying scatterplot of individual patient data further showed that a number of patients reported high HRQoL despite a high rate of attack, and vice versa.

SF-12 data from ENVISION also showed a mixed picture: givosiran was associated with a trend towards improved HRQoL across all subscales as compared to placebo, but these effects were only above the MID for subscales related to physical wellbeing (physical component summary (PCS), physical role, and bodily pain) and social functioning. Effects across subscales evaluating mental wellbeing (mental component summary (MCS), vitality, emotional role, and mental health) were all lower than the MID and were not statistically significant.

Overall, the ERG considered that mixed data for the EQ-5D and SF-12 are consistent with statements by clinical experts that the relationship between attack frequency and HRQoL can be complex. Clinical advisors state that patients' HRQoL is heavily influenced by the presence of chronic symptoms, such as chronic pain, as well as comorbid health conditions, and the presence of neurological impairment. This may mean that reductions in AAR may not alone lead to significant change in patients' HRQoL. However, the ERG also considered that HRQoL may be slow to change following reductions in AAR, particularly outcomes related to mental wellbeing. For example, the ERG considered that anxiety about the risk of attacks, and addictions such as to opioid medications, may take time to change, and so may not be easy to

measure within the follow-up of a clinical trial. Based on clinical advice, the ERG also considered that the high prevalence of mental health conditions in patients with AHP may be in part driven by the number of previous acute attacks they have experienced. Therefore, the availability of givosiran earlier in the treatment pathway for new patients may have a beneficial effect on the risk of mental health conditions over the course of the disease. However, no evidence as to the potential impact of this was available.

Only limited data for HRQoL from the ENVISION OLE were reported in the CS. The ERG identified partial 12- and 18-month follow-up data for the PCS and MCS subscales from the trial CSR[22] (full data were reported in the clinical study report (CSR) appendix, though these were not supplied). These data showed further improvements in median PCS scores between six- and 12-months (placebo/givosiran patients) and six- and 18-months (givosiran/givosiran patients) as compared to baseline. [redacted]

Overall, the evidence from the ENVISION trial and ENVISION OLE does not show a reliable improvement in overall HRQoL in patients treatment with givosiran. However, there are positive trends towards meaningful change in HRQoL, and data from the SF-12 shows meaningful improvements in physical wellbeing and social functioning. It may be that longer follow-up data would provide further evidence of improvements in HRQoL, although the ERG considered that there is evidence that the impact of chronic symptoms and comorbid health conditions may restrict the extent to which reductions in AAR alone may improve HRQoL. The ERG also noted that the measurement of HRQoL in AHP patients may be complicated, and demonstrating change in HRQoL may require validation of measures of HRQoL.

Table 17: Change from baseline in PCS and MCS in ENVISION OLE

	Placebo/givosiran	Givosiran/givosiran
	Median (IQR)	Median (IQR)
PCS		
Baseline	[redacted]	[redacted]
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
MCS		
Baseline	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]

Abbreviations: CSR, clinical study report; IQR, interquartile range; MCS, mental component summary; N/A, not applicable; NR, not reported; OLE, open-label extension; PCS, physical component summary

Source: ENVISION OLE CSR p. 105

As stated in Section 3.2.2.5, the ERG did not consider that the other PRO outcomes measured in the ENVISION trial were psychometrically robust and therefore are a lower source of evidence quality than HRQoL measures. However broadly speaking, patients receiving givosiran were more likely to say that their condition had improved (89.1% minimally, much, or very much improved) and that they were satisfied with treatment (72.2%) compared to those receiving placebo (36.8% and 13.5%). The ERG considered it interesting that a third of patients receiving placebo reported that their symptoms had improved ("minimally" or "much") during follow-up, and speculated that this may either reflect a placebo effect and/or demonstrate the known natural fluctuation in symptoms for patients. The ERG also noted that 10.8% of patients receiving givosiran noticed either no change in their condition (2.7%) or thought their condition has worsened (8.1%).

Additional outcomes provided by the company

In addition to the scoped outcomes for this appraisal, the ERG considered that evidence presented by the company for the potential efficacy of givosiran for pain (frequency of attacks associated with the most pain, the use of pain medication, and self-reported pain during and between attacks) from ENVISION and ENVISION OLE were also useful for understanding the

potential efficacy of givosiran in patients with AHP. Analyses related to the frequency of attacks associated with most pain, and self-reported pain during and between attacks, were reported by the company to be post-hoc analyses, and as noted in Section 3.2.2.6, these analyses should be considered exploratory and at a higher risk of bias.

The company evaluated whether the reduction in AAR associated with givosiran as compared to placebo was replicated in those attacks associated with a higher degree of pain. This analysis suggested that this was the case; with an 80% relative reduction in attacks with a median pain score ≥7 at six-months (on a 0 to 10 NRS; higher scores indicating more pain; rate ratio 0.19, 95% CI 0.12, 0.33; calculated by the ERG). More patients in ENVISION who received givosiran also did not experience one or more acute attacks with a median pain score ≥7 (Table 18).

Table 18: Composite porphyria attacks with median pain score ≥7, ENVISION trial, AHP patients

	Placebo (N=46)	Givosiran (N=48)
Total number of attacks	297	90
Total number of attacks with median pain scores ≥7*, n (%)	95 (32.0)	19 (21.1)
Number of patients with at least one attack, n	38	24
Number of patients with at least one attack with median pain score≥7*; n/N (%)	24/38 (63.2)	10/24 (41.7)

Abbreviations: AHP, acute hepatic porphyria

Source: CS p.54

*The BPI-SF NRS is an 11-point scale: 0=no pain; 10=pain as bad as you can imagine. Median pain scores of attacks were calculated based on pain scores collected during each composite attack. AHP: acute hepatic porphyria; BPI-SF NRS: Brief Pain Inventory-short form numeric rating scales. Source: ENVISION Clinical Study Report (2020)119; Kauppinen (2020)12026

However, findings on the effect of givosiran for use of analgesia was mixed. In ENVISION, treatment with givosiran was associated with an 11% (95% CI 9% - 19%) reduction in pain relief compared to placebo at six-months (Table 19). The largest reduction in pain relief was in the use of opioids, where the effect was an overall 24% reduction (95% CI 5% - 40%). Pain relief may be used to control pain from both acute and chronic symptoms of AHP, though the ERG considered that these findings were consistent with the reduction in AAR. However, while the reduction in AAR was maintained in ENVISION OLE, findings from ENVISION OLE showed an increase in overall use of pain relief between 12- and 18-months in both the placebo/givosiran and givosiran/givosiran arms. As shown in Table 20, at the 12- and 18-month follow-ups, there was no consistent difference in pain relief to that used by the placebo arm in the double-blind

phase. It is difficult to compare the data between ENVISION and ENVISION OLE, as the data are reported differently and are not separated by opioid vs. non-opioid use. However, the lack of a demonstrable effect of pain relief in ENVISION OLE casts doubt on the reliability of the effect in ENVISION, and at this stage the ERG regarded that it is not possible to conclude that givosiran is associated with a meaningful reduction in pain relief.

The company stated in its clarification response that the measurement of pain relief was highly complex to calculate, and was based on a combination of daily diaries and medical notes. The ERG acknowledged that these data are indeed complex and can be difficult to interpret. Furthermore, it may be that use of pain relief, particularly opioid pain relief, may be slow to change due to psychological and physiological dependence. However, the ERG also considered the possibility that the use of pain relief in patients with AHP may be more closely related to the experience of chronic pain, which has not been shown to change following treatment with givosiran (see discussion below).

Table 19: Analgesic use at six-months in ENVISION: AIP

	Placebo (n=43)	**Givosiran (n=46)**
Either opioid or non-opioid		
Patients with use, n (%)	43 (100.0)	41 (89.1)
Rate ratio (95% CI); relative reduction		0.89 (0.81, 0.91) 11% (9% - 19%)
Opioid		
Patients with use, n (%)	38 (88.4)	31 (67.4)
Rate ratio (95% CI); relative reduction		0.76 (0.60, 0.95) 24% (5% - 40%)
Non-opioid		
Patients with use, n (%)	32 (74.4)	30 (65.2)
Rate ratio (95% CI); relative reduction		0.87 (0.66, 1.16) 13% (-16% - 34%)

Abbreviations: AIP, acute intermittent porphyria; CI, confidence interval

Table 20: Days using pain relief in ENVISION and ENVISION OLE

	Placebo/Givosiran (n=46)	Givosiran/Givosiran (n=48)
Mean (SD)		
DB period	44.97 (39.79)	32.08 (37.28)
OLE period		
Month 12	43.47 (40.47)	34.75 (35.11)
Month 18	55.46 (39.33)	51.69 (35.14)
Median (IQR)		
DB period	7.64 (0.58, 25.44)	2.42 (0, 16.00)
OLE period		
Month 12	19.01 (6.06, 86.73)	23.32 (2.65, 66.83)
Month 18	33.33 (2.18, 64.82)	44.93 (1.13, 63.80)

Abbreviations: DB, double blind; CI, confidence interval; IQR, interquartile range; OLE, open-label extension; SD, standard deviation

At clarification [question A3], the company provided further data for self-reported pain, as assessed between and during attacks in ENVISION and ENVISION OLE (to 12-months). These data are replicated below (Table 21), and show no obvious change in pain during attacks between those treated with givosiran and placebo.

Table 21: Change in daily worst pain during and between acute attacks in ENVISION and ENVISION OLE: AIP

Month 6 (DB period)				
	Placebo (n=43)		**Givosiran (n=46)**	
	During attacks	**Not during attacks**	**During attacks**	**Not during attacks**
n	38	43	28	46
Mean (SD)	1.63 (1.905)	-0.49 (1.514)	1.89 (2.072)	-0.66 (1.192)
Median (IQR)	1.75 (0.49, 2.67)	-0.41 (-1.30, 0.25)	1.37 (0.79, 3.02)	-0.59 (-1.46, 0.02)
Month 12 (OLE)				
	Placebo DB/Givosiran OLE		Givosiran DB/Givosiran OLE	
	During attacks	Not during attacks	During attacks	Not during attacks
n	28	43	23	46
Mean (SD)	0.86 (2.350)	-0.73 (1.845)	1.86 (2.484)	-0.86 (1.605)
Median (IQR)	0.27 (-0.97, 2.41)	-0.75 (-1.73, 0.01)	0.47 (0.18, 2.71)	-0.90 (-1.77, 0.24)

Abbreviations: AIP, acute intermittent porphyria; DB, double blind; IQR, interquartile range; OLE, open label extension; SD, standard deviation

3.2.3.3. Safety results

Adverse effects

The company summarised data for AEs in the CS (Document B, Section 12): Table 24 [ENVISION], Table 27 [ENVISION OLE], Table 28 [Phase I], and Table 29 [Phase I/II]).

Data from ENVISION showed that almost all participants in both arms experienced at least one AE at six-months (43/48, 89.6% in the givosiran arm and 37/46, 80.4% in the placebo arm). AEs common to patients taking givosiran in ENVISION were generally mild or moderate in nature and transient, and included nausea (27.1%), injection site reactions (16.7%), and fatigue (10.4%), and chronic kidney disease (CKD; 10.4%). The company stated that nearly half of all participants receiving givosiran (22/48; 45.8%) experienced an AE related to the study drug. The nature of drug-related AEs experienced by participants was not reported in the CS, though it was stated by the company that only three of these events were considered to be SAEs (chronic kidney disease, abnormal liver function, elevated transaminase). Overall, SAEs were

twice as common in the givosiran arm as compared to placebo (10/48, 20.8% vs 5/46, 10.9%). A variety of SAEs was reported (CS Table 25, p.62), most of which were experienced by one participant only. AE data from ENVISION OLE were generally consistent in the rates of AEs from ENVISION, though the company stated that they did not identify any further cases of CKD, renal or hepatic AEs.

Findings from the Phase I/II trial were also considered to be consistent with the rates of AEs reported in ENVISION. Notable events associated with givosiran included one SAE of pancreatitis in Part C of the Phase I trial, which was fatal, and one SAE of anaphylaxis, which occurred in one patient (1/16, 6.3%) in the Phase I/II OLE after their third dose of givosiran.

Clinical advice to the ERG was that the complex and heterogeneous medical history of patients with AHP make it difficult to interpret the risks associated with givosiran, and each patient will have their own risk profile. The ERG was aware that the product licence for givosiran included a warning for the risk of pancreatitis, CKD and elevated transaminase, particularly in patients with a history of hepatic or renal disorders. While the risk of anaphylaxis appears low, one of the stakeholder submissions for this appraisal (Section 8.1) received from NAPS suggested that treatment with givosiran should initially be delivered in hospital or in specialist centres, rather than at home, in case of the risk of anaphylaxis.

Mortality

As noted above, one fatal event (haemorrhagic pancreatitis) during givosiran treatment occurred in the Phase I/II trial in a patient receiving a 5 mg/kg monthly dose. The patient had a complex medical history and the death was judged by the Investigator to be unrelated to study treatment.

3.3. Critique of trials identified that evaluate the effectiveness of prophylactic IV heme

The company's clinical effectiveness SLR identified five studies that evaluated the efficacy of prophylactic IV heme in patients with AHP: these comprised two prospective[17,27] and three retrospective observational[4,19,20] studies (Table 22). However, the ERG considered all of these studies to be flawed as evidence to evaluate the efficacy and safety of prophylactic IV heme in patients with AHP and recurrent attacks. The ERG identified a small Phase II, placebo-controlled trial of prophylactic IV heme is currently underway (NCT02922413), and is expected to complete by September 2022.

Table 22: Studies evaluating prophylactic IV heme in patients with AHP

Author (date)	Location	Population	Intervention	Study design	Outcomes	Limitations
Anderson et al. (2006)[17]	United States	AHP and recurring acute attacks (N=40)	Prophylactic IV heme, given at variable dose, frequency and length of time, according to clinician discretion. Prophylactic IV heme was made available to patients for up to 8 months	Case series (prospective)	Rate of acute attack AEs	Acute attack data reported in the publication suggesting that prophylactic IV heme may have prevented attacks in 21/31 patients (68%) was at an unclear timepoint and without a meaningful control. AE data were not reported separately for those patients treated with prophylactic IV heme. There is very little data reported about the patient population to determine the generalisability of the evidence.
Sardh et al. (2019)[27] EXPLORE (NCT02240784)	International	AHP patients with recurrent acute attacks (≥3 attacks/year) (N=112)	N=112 Prior prophylactic IV heme (n=52) No prior prophylactic IV heme (n=60)	Observational, prospective Up to 12 months	Attack rate	The abstract for this study reports a comparison in attack frequency between those patients receiving and not receiving prophylactic IV heme. As attack frequency is an indication for treatment with prophylactic IV heme, this comparison is flawed.
Marsden et al. (2015)[20]	United Kingdom	AHP patients receiving prophylactic IV heme	Prophylactic IV heme: 3 mg/kg, (N=22) Median doses (range): 150 (2–1000) Duration of prophylaxis, median (range) months: 50 (1–150)	Observational, retrospective study	AEs Number of hospital admissions Pain frequency Physical function Work capacity	Attack rate was measured but not reported. The follow-up of other outcomes is unclear. Before/after study with small sample.

Author (date)	Location	Population	Intervention	Study design	Outcomes	Limitations
Neeleman et al. (2018)[4]	Netherlands	AIP patients with recurrent attacks (n=11)	Prophylactic IV heme given every other week, weekly, or biweekly Duration of prophylaxis, range: 1–14 years	Observational, retrospective	Attack rate Resource use Treatment costs AEs	Before and after comparison in small sample, with incomplete data for acute rate (no variance data reported). Generalisability of population is unclear.
Schmitt et al. (2018)[19]	France	AIP patients with recurrent attacks (n=46, of which 18 patients were treated with prophylactic IV heme)	N=602 Prophylactic IV heme	Observational, retrospective	AEs Attack rate	This publication reports a comparison of the rate of attacks in the population between 1985-2008 and 2008 onwards, which is when treatment with prophylactic IV heme became available. This is a flawed comparison for evaluating the efficacy of prophylactic IV heme.

Abbreviations: AE, adverse event; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria

3.4. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect treatment comparison was possible for this appraisal.

3.5. Additional work on clinical effectiveness undertaken by the ERG

None.

3.6. Conclusions of the clinical effectiveness section

The company considered that the company presented the best available evidence for the efficacy of givosiran for reducing the frequency of acute attacks in patients with AHP. The availability of an RCT is notable in such a rare disease area, though while the ERG considered that data for the efficacy of treatment for AAR was of high quality, other outcomes were at a higher risk of bias. Further risk of bias was identified for the ENVISION OLE and for the Phase I/II trial.

Overall, the clinical evidence suggested that givosiran was associated with a significant and clinically meaningful reduction in the frequency of acute attacks. The breakdown in AAR across resource type showed that all types of attack were reduced, thought the evidence suggested that the largest reductions were in attacks that did not require hospitalisation. Clinical advisors to the ERG suggested that such reductions in the risk of acute attack would have widespread benefits for patients and carers, including benefits for HRQoL, mental wellbeing, pain (and use of analgesia), and for the risk of complications arising from acute attacks. However, the ERG considered that the current evidence base has not demonstrated these benefits, and so the potential impact and magnitude of a reduction in AAR remains uncertain. To a large extent, this uncertainty is driven by the relatively short follow-up of the ENVISION trial, and uncertainty surrounding the validity of generic HRQoL measures in the target population.

In addition, the ERG considered that the generalisability of the evidence base for givosiran was uncertain, noting variations between the trial populations and the target population for givosiran, and the heterogeneous nature of the disease.

4. COST-EFFECTIVENESS

4.1. ERG comment on company's review of cost-effectiveness evidence

The company undertook a SLR to identify evidence for outcomes relevant to the cost-effectiveness, HRQoL, healthcare resource use (HCRU) and cost of givosiran for the preventative treatment of acute attacks in patients with AHP who experience recurrent attacks. The inclusion criteria were appropriately comprehensive, and the methods used to conduct the review were of a high standard. A few reporting discrepancies were identified and although these could not be resolved, scrutiny of the company's SLR report and the CS indicated no cause for concern.

Table 23. Summary of ERG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Section C.9.1; Appendix 1.	The searches 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	CS Document B, Table 10	The inclusion criteria specified in Table 10 (Document B, p. 35) for the review of economic evaluations (cost-effectiveness analyses or cost-utility analyses) were appropriate to the decision problem.
Screening	SLR report[8]	Screening was conducted to appropriate standards
Data extraction	SLR report[8]	No economic evaluations (cost-effectiveness analyses or cost-utility analyses) were identified by the SLR. Data extraction was therefore not completed.
QA of included studies	SLR report[8] and CS, Document B, Section 11.2.2	No economic evaluations (cost-effectiveness analyses or cost-utility analyses) were 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.
Studies identified	CS, Document B, Sn 11.2	No economic evaluations (cost-effectiveness analyses or cost-utility analyses) were identified by the SLR.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; QA, quality assessment; SLR, systematic literature review

Table 24. Summary of ERG's critique of the methods implemented by the company to identify health related quality of life evidence

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Section C.9.1; Appendix 1	The searches 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	CS Document B, Table 10	The inclusion criteria specified in Table 10 (Document B, p. 35) for the HRQoL review were appropriate to the decision problem. The inclusion criteria for HRQoL outcomes specified: "*from (HR)QoL studies, PROs, caregiver burden, utility values*"
Screening	SLR report[8]	Screening was conducted to appropriate standards.
Studies identified	SLR report;[8] CS Document B, Figure 5 and Section 10.4	In the CS (Document B, Section 10.4), the company indicated that of the evidence included: • One study reported HRQoL associated with givosiran (ENVISION) • Two studies reported HRQoL associated with hemin. Neither reported utility values compatible with the economic model. • The majority of non-interventional studies quantified the frequency of attack symptoms affecting HRQoL (e.g. pain fatigue and nausea), two reported the impact on HRQoL qualitatively and only five described the measurement of HRQoL in AHP. Of those only one study was considered to report values compatible with the structure of the economic model (EXPLORE). The ERG noted what it considered were minor reporting discrepancies; e.g. between the PRISMA reported in the CS (Document B, Figure 5) (n=25 articles), and the total studies referred to in Section 10.4 of the CS (Document B) (n=21: "*The search results for QoL evidence included one givosiran study, two hemin studies, and 18 non-interventional studies*"). Scrutiny of the 29 articles documented in the SLR report versus the studies referenced in the CS indicated that no evidence had been omitted that would have provided additional relevant information for the economic model.

Abbreviations: AHP, acute hepatic porphyria; CS, Company Submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis; PROs, patient reported outcomes; QA, quality assessment; QoL, quality of life; SLR, systematic literature review

Table 25. Summary of ERG's critique of the methods implemented by the company to identify healthcare resource use and costs evidence

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Section C.9.1; Appendix 1.	The searches 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	CS Document B, Table 10	The inclusion criteria specified in Table 10 (Document B, p. 35) for the HCRU and costs review were appropriate to the decision problem. The inclusion criteria for economics studies specified: "*from economic studies: costs, cost effectiveness, utility values, resource use, lost productivity*"
Screening	SLR report[8]	Screening was conducted to appropriate standards
Studies identified	SLR report;[8] CS Document B, Figure 5 and Section 12.3.1	The PRISMA in the CS (Document B, Figure 5) indicated that a total of 19 economic studies were identified in the review. In Section 12.3.1 (CS, Document B), resource identification, measurement and valuation studies, the company stated "*…was designed with broad search terms to capture any relevant resource data for the NHS in England"* No discussion was provided as to the potential relevance of the studies to inform model parameters. The studies identified in the review were, however, described in the SLR report provided. Despite what the ERG considered to be minor reporting discrepancies between the CS and the SLR report, scrutiny of the two reports and of the identified studies indicated that no evidence had been omitted that would have provided additional relevant information for the economic model.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; HCRU, healthcare resource use; PRISMA Preferred Reporting Items for Systematic Review and Meta-analysis; QA, quality assessment; SLR, systematic literature review

4.2. Summary and critique of company's submitted economic evaluation by the ERG

4.2.1. NICE reference case checklist

Table 26: NICE reference case checklist

Attribute	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALYs were estimated for patients and carer disutilities

Attribute	Reference case	ERG comment on company's submission
		were included in the company's base case.
Perspective on costs	NHS and PSS	NHS and PSS as appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company submitted a cost utility analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A life time horizon was used in the base case analysis (60 years). The ERG considered the base case time horizon to be appropriate, however shorter time horizons were not explored by the company.
Synthesis of evidence on health effects	Based on systematic review	The clinical data used to estimate the effectiveness of givosiran and BSC in the economic model were based on transition probabilities from the pivotal studies ENVISION and ENVISION OLE.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	QALYs were used as appropriate. Base case utility values were derived via the application of health state disutilities to a baseline utility value. The ERG noted considerable uncertainty surrounding the company's approach. Direct EQ-5D data were available from ENVISION, however the company did not use this in the base analysis or provide this as part of a scenario analysis.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The company used published literature to derive disutilities in the base case analysis. See Section 4.2.8.2.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Published literature, see Section **Error! Reference source not found.**.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	There were no equity concerns.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be	Costs were mostly valued using PSSRU. However, several costs relating to the management of

Attribute	Reference case	ERG comment on company's submission
	valued using the prices relevant to the NHS and PSS	chronic symptoms were not valued using appropriate sources, due to a paucity of data.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and outcomes were discounted at 3.5% as appropriate.

Abbreviations: EQ-5D, EuroQol 5-dimensions questionnaire; HRQoL: health-related quality of life; NHS, National Health Service; OLE, open label extension; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALY: quality-adjusted life year; TA: technology appraisal; UK, United Kingdom

4.2.2. Model structure

The company submitted a Markov model (Figure 1, below), which simulated a cohort of AHP patients through a series of mutually exclusive health states using transition probabilities. The ERG noted that a key feature of the model was the categorisation of disease severity based on four health states, which the company defined according to annualised attack rate (AAR) (Table 25). In the CS (Document B, p.92), the company stated that there is no widely accepted, standardised system for classifying patients' disease severity of AHP. Instead, a published study by Neeleman et al (2018)[4] was used to support the company's decision to adopt an 'attack frequency approach' with respect to the classification of AHP disease severity and selection of health states. The company further justified the use of AAR (CS, Document B, p.83), stating that *'AAR is relevant in the context of a disease that is characterised by recurrent acute attacks, each of which have a debilitating impact on patient wellbeing and Qol.'*

Table 27: Health state definition

Disease severity	Model health state definition/number of attacks per year
Asymptomatic	0
Symptomatic	>0 ≤ 4
Recurrent	>4 ≤ 24
Severe	>24

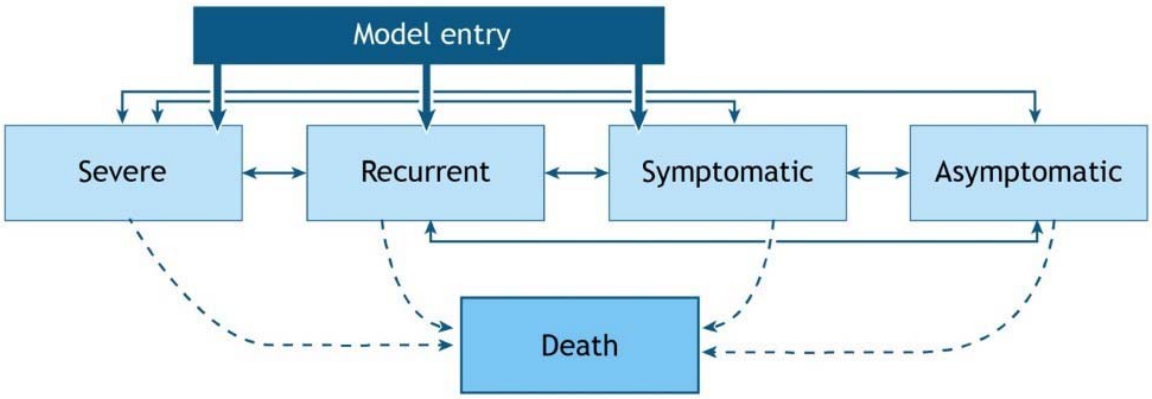
The ERG acknowledged there is limited published evidence available with respect to the classification of AHP disease severity. However, the decision to rely upon a single study may not be considered robust, particularly as Neeleman et al[4] was a non UK based study (The

Netherlands), which aimed to determine the burden of illness of AIP. During the clarification process (question B6), the company was asked to comment on why alternative means of categorising disease severity such as change in quality of life and/or elevated biomarker levels; i.e. ALA and PBG, were not considered. The company responded noting the following:

- The UK NAPS patient pathway is organised according to attack frequency.
- The European Porphyria Network (EPNET) and the Porphyrias Consortium guidelines stratify AHP disease severity by attack frequency.
- No clear thresholds exist that would allow prediction of attack occurrence or recurrence from ALA or PBG levels.

To further validate the model structure, clinical opinion was sought by the ERG. Responses noted that it may be reasonable to use frequency of attack as a proxy for disease severity; however, as AHP is a heterogeneous condition, it is plausible that patients may have frequent attacks that have a limited impact on patients' physical and mental wellbeing, or they could experience relatively few attacks that can have a major impact. Overall, the ERG recognised the challenges surrounding the classification of disease severity and considered that the company's decision to use attack frequency to define health states was reasonable.

Figure 1: Model structure



With respect to the appropriateness of the model structure, the ERG identified uncertainty surrounding the inclusion of a severe health state. In the CS (Document B, p.86), the company stated that the inclusion of a severe health state allowed for a more granular estimation of the

severity of AHP, and that HRQoL data from ENVISION identified a clinically meaningful separation in how patients experienced 'recurrent' and severe' disease. The ERG noted that exploratory HRQoL data from ENVISION as outlined in the CS (Document B, p.79), appeared to support the link between attack frequency and disease severity; however, these data were derived from small patient numbers over six months and are therefore subject to uncertainty.

To explore uncertainty, the ERG conducted a scenario analysis whereby the model was altered to 'switch off' the severe health state. The ERG noted; however, that carer disutility differed between the recurrent and severe health states (see Section 6.2.3).

4.2.3. Population

The patients included in the economic model were based on those within ENVISION (Table 28). The starting distribution of patients across health states was based on pooled data from ENVISION i.e. 27% symptomatic, 63% recurrent and 10% severe. The ERG noted that several characteristics including starting age and weight were not based on the ENVISION intention to treat (ITT) population i.e. the starting age used in the model was 41.64 years in the model, whereas the average age of diagnosis in ENVISION was approximately 30 years. During the clarification stage (question B18), the ERG asked the company to comment on the reason for the discrepancy in patient starting age. The company noted that the starting age of the cohort was based on the age at screening (representing a cross-section of patients who would initiate treatment with givosiran in clinical practice today). The ERG was aware that leading NAPS clinicians interviewed by the company were asked to comment on the generalisability of patient baseline characteristics in the ENVISION study. Based on feedback, all clinicians noted that the starting age of UK patients is likely to be younger than the company's modelled age of 41.64 years.

Starting age was considered to be a key model parameter (as highlighted by the one way sensitivity analysis [OWSA] provided by the company, which varied the starting age of the cohort using 95% confidence intervals). Reducing the starting age to 37.9 years caused the base case incremental cost-effectiveness ratio (ICER) to increase by approximately 33%. Therefore, given the uncertainty surrounding the most appropriate starting age of patients, the ERG conducted a scenario analysis which reduced the starting age to 30 years (Sections 6.2.1 and 6.2.3).

The mean modelled patient weight was [redacted] kg, which appeared to reflect EU patient weight only i.e. US patients were excluded. The ERG agreed that the average adult weight of US patients is likely to differ to UK patients due to fundamental differences in diet and lifestyle. Therefore, the decision to exclude US patients may be reasonable (although it should be noted that patients from other geographical regions including Australia, Central America and Asia were still included). The ERG considered that [redacted] kg was somewhat lower than the average weight of the adult UK female population (which is estimated to be approximately 70 kg). The company provided OWSA which increased the average patient weight to [redacted] kg; however, results were not sensitive to this. The ERG noted that this was because the number of givosiran vials used to treat a patient who weighs [redacted] kg and [redacted] kg, is the same.

Limited clinical advice to the ERG confirmed that AHP predominantly affects women; however, the current number of female patients managed in the UK was suggested to be slightly lower i.e. 82% (the company assumed 86% in their base case). For completeness, the ERG conducted a scenario analysis which reduced the proportion of females in the model to 82% (Sections 6.2.1 and 6.2.3).

The ERG further noted that the proportion of patients experiencing chronic symptoms i.e. chronic pain, neurological and psychiatric symptoms were not reported in ENVISION. The prevalence of chronic conditions used in the economic model was therefore based on published literature (see Section 4.2.8).

Table 28: Baseline patient characteristics included in the model

Patient characteristics	Modelled parameter
Starting age (years)	41.64
Weight (kg)	[redacted]
Percentage of females	85.7%

4.2.4. Interventions and comparators

Within the economic analysis the company compared givosiran (as a prophylactic once monthly subcutaneous (SC) injection) plus BSC to BSC alone. BSC was assumed to consist of medicine and HCRU associated with the treatment of acute attacks and long-term chronic symptoms (Section 4.2.9.1). As noted in Sections 2.2 and 2.3, the ERG was aware that several prophylactic treatments were currently used within the UK to treat AHP patients including off-

label prophylactic IV heme and GnRH analogues (as well as liver transplantation). However, the company did not compare givosiran to these treatments.

4.2.4.1. Prophylactic IV heme

The company stated that prophylactic IV heme was not considered as a comparator (or included within the BSC treatment arm) given that off-label use is explicitly prohibited in the summary of product characteristics (SmPC)[28]. The SmPC states that "*NORMOSANG should not be used as a preventive treatment since available data is too limited and long term administration of regular infusions carries the risk of iron overload*." However, clinical input to the ERG confirmed that prophylactic IV heme is currently widely used off-label to treat AHP patients in the UK (see Section 2.3). Due to the contradiction surrounding current prophylactic IV heme use in practice and the licensed indication, the ERG acknowledged that it was unclear whether a comparison versus prophylactic IV heme would be appropriate.

4.2.4.2. GnRH analogues

In its clarification response, the company stated that GnRH analogue prophylaxis was not considered a relevant comparator as only a small number of female patients with repeated premenstrual acute attacks receive treatment (in ENVISION only 4.3% of patients were receiving GnRH analogue for prophylaxis of attacks). Furthermore, the company noted that an audit of the NAPS database highlighted a wide variation in UK clinical practice with respect to duration and monitoring of GnRH analogue use (as well as the specific drugs used, and the treatment of side effects). The ERG considered that a cost utility analysis versus prophylactic GnRH analogues would introduce further uncertainty, given the lack of robust comparative efficacy data and the variability surrounding GnRH analogue use in practice (see Section 2.3).

4.2.4.3. Liver Transplant

The company stated that liver transplant had not been considered as a relevant comparator in the economic model given that it is rarely performed. Clinical advice to the ERG confirmed that liver transplants are relatively rare and therefore, the ERG considered the exclusion of liver transplant as a relevant comparator to be reasonable.

4.2.5. Perspective, time horizon and discounting

The time horizon used in the base case analysis was a lifetime (60 years or 122 cycles). The proportion of patients alive at Year 60 was approximately 5%. The company justified the use of

a lifetime horizon on the basis that AHP is a chronic and incurable hereditary disease requiring long-term specialist management. Overall, the ERG considered a lifetime horizon to be appropriate for use in the base case as it is sufficiently long to capture the important differences in costs and outcomes between givosiran and BSC.

However, based on clinical opinion to the ERG, it may be plausible for a proportion of AHP patients to remain asymptomatic post-menopause (whereby active treatment is no longer required). As such, a shorter time horizon may adequately capture the key differences in costs and benefits between treatment arms. The ERG noted that the company did not provide sensitivity analysis which reduced the time horizon and the model did not include functionality to allow the time horizon to be varied by the ERG.

The company selected a six month cycle length in the base case analysis on the basis that this reflected the duration of the ENVISION study. The company clarified in response to ERG's query about this model parameter that the six-month cycle length also matches the intervals between routine clinic visits for monitoring of AHP patients, as set out in AHP evaluation and management recommendations from the Porphyrias Consortium and in the NHS Standard Contract for Severe Acute Porphyria Service. Based on clinical input to the ERG, it was confirmed that monitoring for AHP patients is conducted primarily on a six monthly basis (although this may vary on an individual patient basis). The use of a six-month cycle length therefore seemed reasonable; however, the ERG noted that the company neither considered an alternative cycle length nor included it in the sensitivity analysis

The ERG had no concerns surrounding discounting. Costs and benefits were discounted at 3.5%, which reflects NICE guidance. All costs and outcomes were estimated from an NHS and PSS perspective.

4.2.6. Treatment effectiveness and extrapolation

Patients entered the model in either the symptomatic, recurrent or severe health state (starting distribution based on baseline data from ENVISION), and moved through health states based on treatment-specific transition probabilities which were estimated directly from ENVISION and ENVISION OLE. Death was included as an absorbing state. For the first modelled cycle (Month 0 to 6) the company applied treatment-specific transition probabilities from ENVISION to both treatment arms (Table 29 and Table 30). As outlined, during the six-month ENVISION study, a higher proportion of patients in the givosiran treatment arm transitioned into the asymptomatic

health state compared to the BSC arm, which was associated with a higher quality of life and lower costs compared to other modelled health states (no deaths occurred).

Table 29: Number of givosiran patients transitioning between health states from baseline to Month 6 (Cycle 1)

To / From	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]

Source: Alnylam, data on file.

Table 30: Number of BSC patients transitioning between health states from baseline to Month 6 (Cycle 1)

To / From	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]

Source: Alnylam, data on file.

4.2.6.1. Extrapolation of long-term clinical data

Due to the lack of long-term clinical data, the company made several assumptions surrounding the effectiveness of givosiran and BSC in the model. For givosiran, the company assumed that after 18 months (duration of ENVISION OLE), patients would continue to transition between health states (based on ENVISION OLE transition probabilities from Month 12 to 18), until Year 5. After Year 5 patients were then assumed to remain in their respective health states for the duration of the model. The company justified this assumption on the basis that available clinical data did not indicate a diminishing treatment effect whilst on treatment through year 3 of follow-up in the OLE. The ERG noted this assumption to be a key driver of the givosiran incremental QALY gain. As outlined in

Figure 2 patients transitioned to the asymptomatic state early and remained there for the duration of the model (albeit transition into the death state could occur).

The ERG acknowledged that clinical data (up to 18 months) appeared to demonstrate a continued treatment effect for patients receiving givosiran. However, due to the lack of long-term data there was considerable uncertainty surrounding the continued effect of givosiran in clinical practice. Clinician input to the ERG was sought in order to determine whether the company's assumption regarding the maintained treatment effect may be considered reasonable, or whether the efficacy of treatment may wane over time. Based on limited clinician feedback to the ERG, a continued treatment effect may be plausible, although long-term clinical data are needed to further validate this assumption.

To address uncertainty surrounding the long-term clinical effectiveness of givosiran, the ERG conducted three scenario analyses which explored the alternative efficacy assumptions (see Section 6.2). Given the lack of long-term data, the ERG considered that the use of available 18 month ENVISION OLE data to inform long term efficacy (transition probabilities frozen after 18 months), would reduce extrapolation uncertainty and would reflect observed clinical data (Sections 6.2.1 and 6.2.3)

Figure 2: Health state occupation over time (givosiran)

For BSC, the company made a simplifying assumption that patients remain in their respective health states (at six months) for the entire duration of the model i.e. transition probabilities are assumed to be 'frozen' and patients cannot improve (albeit transitions into the death state can occur). As outlined in Figure 3, most patients moved into the recurrent and severe health states early and remained there for the duration of the modelled horizon (transitions into the death state still possible). The company state that 'freezing' transition probabilities may be considered conservative given that the health status of patients is considered to worsen in the absence of an active disease modifying treatment (CS, Document B, p.90). The ERG queried this with clinical experts. Responses were limited, although one clinical expert reported that it could be plausible for a small proportion of patients to improve over time.

The ERG acknowledged uncertainty surrounding the company's approach given that the clinical data used to estimate long-term transition probabilities was short (six months), and it was unclear whether patients' disease severity would worsen considerably during this length of time. Clinical advice to the ERG was that disease severity may fluctuate naturally, and it is unclear

whether some patients may experience improvement over time. The ERG conducted a scenario analysis which extrapolated BSC transition probabilities from ENVISION to 18 months (in order to be in line with the duration of ENVISION OLE) (Section 6.2.1.2 and 6.2.3). Overall, the company's base case approach seemed reasonably conservative.

Figure 3 Health state occupation over time (BSC)

4.2.7. Key modelled assumptions

4.2.7.1. Menopause onset distribution

In the base case analysis the company captured menopause onset via a probability distribution by Greer et al (2003)[5], a Finnish study which assessed post-menopausal decline in vertebral bone mineral density in 3,198 women. The ERG noted that the company did not adequately justify the use of Greer et al, however, the company did provide a scenario analysis in the CS which estimated the probability of menopause onset by applying a normal distribution to the mean age and SD from the UK women's cohort study (Document B, p.102). The company stated the mean age of menopause onset in both Greer et al[5] and the UK women's cohort was similar (50.5 years) suggesting Greer to be reasonable source.

The ERG acknowledged that the mean age was similar between the two sources, however there was considerable difference with respect to the distribution fitted to the mean age of onset i.e. the company fitted a normal distribution (bell curve) to the UK Women's cohort, whilst the distribution in Greer et al[5] was irregular (although informed by data). Due to the differences in distribution, the per-cycle probability of menopause onset varied according to the source used. Given that the age of onset in the UK Women's cohort study represented more generalisable data to the target population, the ERG were of the opinion that this approach should have been used in the base case.

4.2.7.2. Proportion of patients continuing treatment after menopause

In the base case analysis the company assumed that 100% of asymptomatic patients would discontinue treatment with givosiran after menopause onset. The company justified this assumption based on input from clinical experts (CS Document B, p.85). Clinical advice to the ERG confirmed that after menopause onset, the majority of patients would likely no longer experience frequent attacks, however attacks may persist in a small proportion of patients. The ERG conducted a scenario analysis which assumed that 10% of patients would still experience and therefore require treatment with givosiran (see Section 6.2.1.5 and 6.2.3).

4.2.7.3. Neeleman et al (2018) as the primary source for prevalence of chronic symptoms

Due to the paucity of data, the company used a published study by Neeleman et al[4], to estimate both utility decrements associated with chronic symptoms as well as the per cycle cost of chronic symptoms (see Document B, p.99 outlining prevalence of AHP chronic conditions by health state). The ERG acknowledged that there is a lack of robust UK data outlining the prevalence of chronic symptoms in AHP patients and considered that the use of published literature, as a means of deriving proxy prevalence data may be reasonable. However, a key limitation pertained to the assumption that the prevalence data from this single study were generalisable to UK AHP patients.

The ERG noted that Neeleman et al[4] was an observational study conducted in the Netherlands, which assessed the medical and financial burden of AIP patients over a 56-year period (from 1960 to 2016). The ERG noted that the majority of patients were either symptomatic (n=24) or asymptomatic (n=53) and that relatively few patients had recurrent AIP (n=11). Furthermore, approximately 55% of recurrent patients were smokers (which may potentially increase the prevalence of certain chronic symptoms). Due to the small number of patients and differences in

baseline characteristics between patients in ENVISION and those in Neeleman et al, the ERG considered the prevalence data used in the economic model to be an area of considerable uncertainty.

4.2.7.4. Mortality

The model captured general population mortality i.e. age and gender specific all-cause mortality, which was adjusted to reflect the proportion of females within the analysis, and AHP specific mortality hazard ratio (HR) 1.31 (95% CI 1.0, 1.8), based on a published study by Baravelli et al.[29] This was applied to each modelled health state for both givosiran and BSC; i.e. mortality did not differ according to treatment or health state. The company stated that this 'conservative' approach was adopted due to the lack of givosiran mortality data, noting that no patients died during ENVISION. The ERG acknowledged that the approach may be considered conservative.

4.2.8. Health-related quality of life

The company adopted a utility decrement approach to estimate the base case utility values. As outlined in the CS (Document B, Section 10.6), the utility of the general population was adjusted for gender and age, and then disutilities associated with acute attacks and long-term chronic symptoms were applied to estimate health state utility values (Table 31). The company stated that this approach allowed for AHP-related disutilities to be considered independent of cohort age. To estimate the age and gender adjusted baseline value, the company used a published equation by Ara and Brazier et al (2011)[30], resulting in a baseline value of 0.886 (which varied in the model on a per cycle basis based on patient age and gender). Overall, the ERG considered that a utility decrement approach to estimating health state utility values was largely appropriate and has been used in previous NICE technology appraisals (TAs), including caplacizumab (TA667).

Table 31: Modelled health state disutilities

Health state	Utility decrement
Asymptomatic	[redacted]
Symptomatic	[redacted]
Recurrent	[redacted]
Severe	[redacted]

Due to the lack of HRQoL data surrounding chronic symptoms in patients with AHP, utility decrements were derived from published literature that reported HRQoL data for other conditions (which the company deemed to be similar in terms of impact on chronic pain, neurological and psychiatric symptoms). These utility decrements were then weighted by the prevalence of each chronic symptom, based on proportions by Neeleman et al[4]. The company noted that Neeleman et al. did not report the proportion of patients with multiple concurrent chronic conditions. Therefore, the company used the approach by Ara and Brazier (2017)[31] to derive these utilities as mentioned in the CS (Document B, p.77). The health state utility decrements used in the economic model are outlined in Table 31.

With respect to chronic pain, the company identified three potential studies which reported HRQoL data, these were Stafford et al (2012)[32] for migraine, Hoxer et al (2019)[33] for haemophilia, and McDermott et al (2006)[34] for neuropathic pain. The ERG noted that the company opted to use the study by McDermott et al in the base case analysis, which reported utility values for mild, moderate and severe neuropathic pain. In order to estimate neuropathic pain disutility, the company subtracted the average utility value (of mild, moderate and severe health states) from the general population estimate. This resulted in a modelled disutility of (-0.383). The company justified the use of McDermott et al[34] on the basis that neuropathic pain was a better proxy for chronic pain in AHP than chronic pain in haemophilia (as reported in Hoxer et al[33]) and that pain scores reported in Stafford et al[32] were specific to migraine attacks.

The ERG was unable to confirm the similarity of AHP to other progressive/neurological conditions in terms of their chronic pain impact via clinical advice, due to the small number of AHP treated patients in the UK and the heterogeneity of the disease. Therefore, the most appropriate source of disutility was considered a subject of uncertainty. Furthermore, McDermott et al. was associated with considerable generalisability concerns i.e. the mean age of the population was 62 years, approximately 49% were male and most patients experienced neuropathic pain as a result of diabetes (23%). Based on a review of Hoxer et al (2019), baseline characteristics of study participants appeared more generalisable to those in ENVISION, however the study was limited in that HRQol was not elicited directly from haemophilia patients but rather a sample of the general UK population. The ERG acknowledged that using a chronic pain utility decrement from Hoxer et al (-0.19), increased the ICER for givosiran by approximately 16%.

For neurological pain, the company used a study by Sullivan et al (2017)[35] and selected the utility decrement reported for 'other hereditary and degenerative neuropathy' diseases (reported to be -0.097) on the basis that this avoids restricting disutility to a specific neurological measure. The ERG was unable to confirm the value as the supplementary table was not included in the paper provided by the company. However, the ERG agreed with the company's statement that the disutility for neuropathic pain was relatively low when compared to other modelled disutilities, and therefore could be considered conservative. For psychiatric disutility, the company stated that patients with AHP experience a wide range of psychiatric symptoms including depression, anxiety, insomnia and psychosis, and therefore used a study by Ara and Brazier et al (2011)[30], which reported HRQoL values for multiple psychiatric symptoms. The modelled disutility associated with psychiatric symptoms was estimated to be -0.27.

Overall, the ERG noted the company's use of non-AHP disutilities from published literature was subject to uncertainty. However, given the lack of long-term UK specific chronic symptom data in patients with AHP, the approach of using published literature values for broadly similar conditions could be considered reasonable. In order to address uncertainty surrounding modelled utility values, the ERG has conducted scenario analyses using alternative utility assumptions (see Section 6.2.1 and 6.2.3).

The ERG acknowledged that HRQoL data were collected in the ENVISION study; however, these data were not utilised in the company's base case. During the clarification process, the company stated that the data were not used primarily because they lacked face validity in that there was a poor correlation between AAR and EQ-5D; i.e. some patients with a high number of attacks reported high utility (close to 1) whilst some patients with few attacks reported low utility. The company further stated that the inconsistent results may be due to the small sample size of patients within the ENVISION study and the fact that patients had the disease for a relatively short period of time (therefore the full impact of chronic symptoms may not have been adequately captured). Overall, the ERG agreed that the company's justification for not using direct EQ-5D data from ENVISION seemed reasonable. However, for completeness, the company was asked to provide the utility values based on EQ-5D data from the ENVISION study (Table 32). Note that the mean EQ-5D at baseline was calculated by ERG from these values and has been reported as well in Table 32. The ERG conducted several scenario analyses using EQ-5D data from ENVISION (see 6.2.1.4 and 6.2.3).

Table 32: Utility values based on EQ-5D data from ENVISION

Health state	Mean EQ-5D (6 months)	Mean EQ-5D (average of baseline and 6 months)	Calculated: Mean EQ-5D (baseline)
Asymptomatic	[redacted]	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D, EuroQol 5-dimensions questionnaire

It should be noted that the health state utility values derived from similar conditions as well as the EQ-5D data from ENVISION as mentioned above were applied with the age-adjusted multiplier calculated as described in Ara and Wailoo (2012; online appendix, p 3)[36].

4.2.8.1. Acute attack disutility

The company modelled the impact of an acute attack on patient HRQoL, using data reported by patients in the EXPLORE study[18]. EXPLORE, a natural history study, aimed to characterise the natural history and clinical management of AHP patients with recurrent attacks. HRQoL (specifically during attacks) was assessed as a secondary outcome using the EQ-5D-5L and data were elicited from patients at baseline, 6 months and 12 months.

To estimate the disutility of an acute attack the company subtracted the mean utility of a patient experiencing an attack ([redacted]) from the mean utility whilst 'attack free' ([redacted]) resulting in an acute attack disutility of ([redacted]). This disutility was applied for a duration of 7.2 days, which was the mean attack duration observed in EXPLORE. Based on expert opinion to the ERG, the duration appeared reasonable, albeit there is likely to be variation in practice. OWSA provided by the company indicated that the ICER was moderately sensitive to a reduction in average attack duration. When reduced to 5.9 days the ICER increased by approximately 13%.

The ERG noted that the use of EXPLORE as the primary data source for estimating attack disutility was subject to some uncertainty given the differences in key patient characteristics between those in ENVISION and those in EXPLORE (in terms of prior prophylactic IV heme use, percentage of patients receiving opioids and median number of attacks in the prior six or 12 months). With respect to these baseline differences, it appeared that patients in EXPLORE were 'more severe' than those in ENVISION. As such the ERG noted that use of HRQol data from EXPLORE may not be fully generalisable to the modelled population (as represented by

patients in ENVISION). The company further stated that it was not possible to use HRQol data from ENVISION to estimate the disutility of an acute attack given that only [redacted] of the EQ-5D assessments in the ENVISION trial were administered during an attack. Overall, the ERG agreed with the company that ENVISION data were unlikely to be robust and suitable for use in the base case, given the paucity of attack disutility data. Therefore, the company's decision to use of EXPLORE data, appeared reasonable.

The company conducted sensitivity analysis which removed the disutility associated with an acute attack (results available within the company's model but not presented in the CS). The ERG noted that results were relatively sensitive to this analysis, which had an upward impact on the ICER; however, the scenario lacked plausibility given that some disutility would be expected.

4.2.8.2. Carer disutility

The company included carer disutility in its base case analysis. Disutilities were taken from a published study by Acaster et al (2013),[7] a UK observational study which assessed the HRQoL impact on carers who treat multiple sclerosis (MS) patients. The study elicited online responses from 200 carers using multiple questionnaires including the EQ-5D and compared these to 200 responses from a matched control group (non-carers). Carers completed the Patient-determined Disease Steps Scale (PDSS), an outcome measure used to assess MS disability. As noted in Table 33, the company made a simplifying assumption that carer disutility at different stages of MS would provide a suitable proxy for AHP health states. During clarification (question B8), the ERG asked the company to provide further rationale for this assumption. The company responded noting that MS is likely to provide a reasonable proxy on the basis that both MS and AHP predominantly affect women in their reproductive years, impose a HRQoL burden with respect to both chronic and acute effects, and that both diseases can be categorised according to disease severity.

Table 33: Base case carer disutility included in the model

Health state	Carer disutility
Asymptomatic (assumed to equal Stage 1 MS)	-0.002
Symptomatic (assumed to equal Stage 2 MS)	-0.045
Recurrent (assumed to equal Stage 4 MS)	-0.142
Severe (assumed to equal Stage 5 MS)	-0.160

Abbreviations: MS, multiple sclerosis

Overall, the ERG considered carer disutility to be appropriate for inclusion in the base case, given that patients with AHP are likely to require ongoing carer support, particularly in the recurrent and severe health states. However, the following concerns may introduce uncertainty into the analysis:

- There may be generalisability concerns surrounding the assumption that carer disutility associated with MS is applicable to AHP. Although the ERG acknowledged and broadly agreed with the company's points regarding the similarities between the conditions, the assumption underpinning the correlation between AHP health states MS stages was not supported/validated by published literature. Clinical opinion was sought by the ERG to validate the company's assumption; however, neither clinicians were able to confirm the assumption. The company provided an OWSA, which varied carer disutility in each health state. Results were somewhat sensitive to a reduction in carer disutility within the recurrent and severe health states. Reducing carer disutility in the recurrent health state to -0.020 resulted in a [redacted] increase in the ICER, whilst reducing carer disutility in the severe health state to -0.052 resulted in a [redacted] increase in the ICER.
- Clinical advice to the ERG noted that carers were likely to be required when patients experienced chronic pain and other debilitating symptoms. However, it is uncertain whether patients would require a carer in each health state, particularly the less severe states i.e. asymptomatic, where impact on patient physical and cognitive functioning is likely to be minimal. When the ERG adjusted the model by removing carer disutility for these health states, the impact on the ICER was minor.

4.2.9. Resources and costs

4.2.9.1. Medicine acquisition costs

Medicine acquisition costs were included in the model for givosiran based on a list price of £41,884.43 per 189 mg/vial. The company stated that the cost was sourced from the Monthly Index of Medical Specialties (MIMS), which was an appropriate source. According to the SmPC for givosiran, treatment is to be administered at 2.5 mg/kg. Vial sharing was not considered in the analysis and relative dose intensity was estimated to be [redacted] based on ENVISION. The model therefore estimated the per cycle treatment cost of givosiran to be [redacted].

The ERG acknowledged that the dose used in the economic model to estimate medicine costs was based on the average weight of European (EU) patients within the ENVISION study

(estimated to be [redacted]), and representing a total dose per administration of [redacted]. In the CS (Document B, p.98), the company justified the exclusion of US patients when determining the average patient weight, on the basis that EU patients were likely to be more representative of UK patients. The ERG understood that differences in patient characteristics (particularly weight) are likely to exist between the US and UK patients. Therefore, the company's rationale for attempting to estimate a more generalisable average patient weight appeared to be reasonable. As noted in Section 4.2.3, the company provided additional scenario analyses which varied patient weight in the model; however, this did not have a material impact on the ICER.

For BSC, no prophylactic treatment cost was considered in the model; however, medicine acquisition costs associated with the treatment of acute attacks were considered i.e. IV heme and management of its side effects, pain medications, antiemetics, antihistamines and antipsychotics. These costs were also applied to patients in the givosiran treatment arm who experienced an acute attack. The ERG considered that costs were largely valued based on appropriate sources including electronic market information tool (eMIT) and MIMS (Table 34).

During clarification (question B9) the company was asked to comment on the source used to identify the list of medicines provided during an acute attack (as well as other resource use assumptions in the model; see Section 4.2.9.2). The company subsequently confirmed that resource use estimates were derived from face-to-face and telephone clinician interviews. The ERG noted that the sample of clinicians was small (n=3); however, they appeared to be lead consultants for NAPS and therefore the estimates could be considered reasonable. Overall, additional resource use data collected directly from ENVISION would have been useful to further validate modelled resource use assumptions.

Table 34 List of medicines costs included in the model.

Medicine	Unit Cost (price per pack)	Source
Acute IV heme	£1,737	MIMS
Albumin	£54.62	Lloyds Pharmacy
Morphine	£6.84	eMIT
Fentanyl	£5.05	eMIT
Codeine	£3.69	eMIT
Cyclizine (IV)	£4.08	eMIT
Ondansetron (IV)	£1.05	eMIT

Medicine	Unit Cost (price per pack)	Source
Cinnarizine (oral)	£4.48	eMIT
Promethazine	-	-
Chlorpromazine	£2.02	eMIT
Prochlorperazine	£0.92	eMIT

Abbreviations: eMIT, electronic market information tool; IV, intravenous; MIMS, monthly index of medical specialties

4.2.9.2. Resource use associated with acute attacks

The base case analysis included costs associated with the treatment of acute attacks. A full list of HCRU was not provided in the company CS but was available in the company's model (see HCRU tab). In addition to medicine costs outlined in Section 4.2.9.1, patients experiencing acute attacks were assumed to require visits from healthcare professionals (nurse practitioners, physicians, pain specialists, physiotherapists and dieticians), require inpatient resource use (ambulance, accident and emergency [A&E] attendance, hospital stay, intensive care unit [ICU] stay), as well as investigative tests whilst in hospital. The full list of HCRU assumptions can be found in the HCRU tab of the company's model. Unit costs were valued using the Personal Social Services Research Unit (PSSRU) and inflated to 2017 and 2019 estimates where appropriate.

The ERG noted that the intensity of resource use provision varied depending on the setting. Although resource use estimates were based on NAPS clinician input, the ERG identified that several resource use assumptions were associated with uncertainty (Table 35).

Table 35: Key resource use assumptions

Resource use assumption	Modelled input
% of acute attacks treated at home	15%
% of acute attacks treated as outpatient visit	5%
% of acute attacks treated in hospital	80%
Length of hospital stay	7.2 days

Based on clinical input to the ERG, it was confirmed that the majority of attacks were likely to be treated within a hospital setting, indicating that the company's base case assumption of 80% may be reasonable. However, the ERG acknowledged uncertainty surrounding the proportion, based on OWSA results provided by the company. When the proportion of hospitalised attacks

was reduced to 64%, the ICER increased by approximately 28%. As an exploratory analysis, the ERG conducted a scenario which reduced the proportion of attacks to 50% (Sections 6.2.1.7 and 6.2.3).

Table 36: Costs associated with treating acute attacks

Acute attack	Unit Cost
Home	[redacted]
Urgent health care visit	[redacted]
Hospital	[redacted]

4.2.9.3. Treatment discontinuation

Treatment discontinuation in the model (which accounted for unplanned interruptions in dosing) was captured via a time on treatment (ToT) curve, simulating the proportion of patients discontinuing givosiran within each model cycle. Patients who stopped treatment with givosiran were no longer assumed to receive benefit; i.e. treatment effectiveness was assumed to reflect that of BSC and patients could no longer transition between health states. As noted on p.91 of the CS, the company extrapolated ToT by fitting a log logistic parametric function to the Kaplan-Meier (KM) curve from the ENVISION and ENVISION OLE studies (discontinuation data available up to 18 months)

The ERG noted that the company's rationale for selecting the log logistic was not clear in the CS. Based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) scores provided by the company, the log logistic was similar to other curves including the Weibull, Gompertz and log normal (CS Document B, Table 51 p.91). The exponential curve appeared to provide the best fit resulting in the lowest AIC and BIC scores, however this was not selected for use in the base case as it produced constant discontinuation rates.

The ERG considered that there was some uncertainty surrounding the company's base case approach to estimating treatment discontinuation, described as follows;

- The fully parametric extrapolation approach as outlined in Figure 4 below, highlighted that the parametric functions do not provide an adequate fit to the KM curve i.e. discontinuation is underestimated from zero to eight months and overestimated from 10-16 months. The ERG considered that a piecewise approach would provide a more accurate representation

of discontinuation during the study period and therefore would reduce overall uncertainty. This approach was conducted as an ERG scenario analysis (Section 6.2.1.3 and 6.2.3).

- The company did not provide sensitivity analysis assessing the impact of using alternative treatment discontinuation curves on the ICER. As such, the ERG considered that uncertainty surrounding treatment discontinuation was not adequately captured in the model. For completeness, the ERG has conducted a scenario analysis using the Gompertz curve (Sections 6.2.1.3 and 6.2.36.2.1.3).

Figure 4: Modelled treatment discontinuation

Abbreviations: KM, Kaplan-Meier; ToT, time on treatment

4.2.9.4. Administration *costs*

Givosiran is administered as a subcutaneous (SC) treatment once per month. Within the CS, the company assumed that the cost of administration would be £37, based on a Band 5 nurse visit (one hour) and used PSSRU 2019. Given that BSC did not include a prophylactic treatment, no administration costs were considered. The company did provide OWSA which increased the hourly administration cost of givosiran to £44; however, this did not have a material impact on the ICER. The ERG noted that administration assumptions were not considered to be a key driver of the ICER.

4.2.9.5. Monitoring costs

The ERG considered the company's estimated monitoring costs to be somewhat underestimated. In the CS (Document B, p.33), the company stated that liver function tests should be performed prior to initiating treatment and repeated monthly during the first six months. The ERG noted that the company's model appeared to include the cost of liver function tests as part of an acute attack when patients are hospitalised; however, the model did not appear to include the treatment specific monitoring costs associated with givosiran as outlined in the CS. Therefore, the ERG conducted a scenario analysis incorporating this assumption (Sections 6.2.1.13 and 6.2.3).

The ERG noted that the cost of a liver function test was valued using NHS reference costs (2016/17); however, the company used the cost of a full pulmonary function test as a proxy for a liver function test, as this was not available in NHS tariffs (estimated to be £226). The ERG confirmed that there was no single unit cost for liver function test, therefore the company's proxy costing approach seemed reasonable (albeit the precise unit cost was subject to some uncertainty).

4.2.9.6. Opioid addiction costs

Opioid addiction costs were included in the model for patients in the recurrent and severe health states. Given that a higher proportion of BSC patients entered and remained in the recurrent and severe health states opioid addiction costs were substantially higher in the comparator arm i.e. £36,431 versus £2,167 respectively (or 16 times higher). The company justified the inclusion of these costs on the basis that frequent use of opiates (particularly when high doses are used for pain management in AHP), can lead to an increased risk of addiction. Data from ENVISION appeared to demonstrate that fewer patients in the givosiran arm were using analgesics; however, the analgesic sparing effect appeared to reduce during ENVISION OLE. The ERG was not aware of robust long-term data demonstrating the impact of givosiran on opioid addiction.

The per cycle cost of addiction per patient was estimated to be £1,381 based on a published study by Shei et al. (2015)[37] and the prevalence of opioid addiction was assumed to be 82% in both the recurrent and severe health state as per Neeleman et al. (2018)[4]. During the clarification process the company was asked to comment on the per cycle cost used in the base case. The £1,381 figure reported by Shei et al. (2015)[37] appeared to reflect the per patient annual incremental health care costs of prescription opioid abuse. The company confirmed that its base case estimate reflected the annual cost therefore should be divided by two to reflect the six-month (per cycle) cost i.e. £691 (Section 5.1.1).

Whilst not a key driver of the ICER, the ERG considered that givosiran 'savings' associated with a reduction in opioid use may not be appropriate for inclusion in the base case analysis as there are concerns surrounding the appropriateness and generalisability of Shei et al (2015)[37] and Neeleman et al (2018)[4] which were used to estimate opioid addiction costs. The ERG conducted a scenario analysis which removed opioid addiction costs (Sections 6.2.1.8 and 6.2.3).

4.2.9.7. Adverse *event costs*

The model included costs associated with severe treatment related AEs (Table 37). The per cycle incidence rates were based on data from ENVISION (Safety Analysis Set)[22] which reported that a higher proportion of patients receiving givosiran experienced asthaenia, iron overload and headache compared to BSC. The unit cost for each AE was estimated to be £109, and was valued using PSSRU 2019 (based on one hour of medical consultant time).

Table 37: Adverse event costs included in the model

Adverse event	Unit Cost
Asthaenia	£109
Lipase increased	
Iron overload	
Headache	

The ERG considered PSSRU to be an appropriate source, however the following uncertainties were identified surrounding the company's handling of AE costs.

- It was unclear why all AEs were assumed to require identical resource use. During the clarification stage (question B10), the company was asked to comment and noted that this was a simplifying assumption. The company further stated that if the number of visits were increased to three, this would have a marginal impact on the ICER, increasing it by [redacted]
- Costs associated with treating CKD were not included in the analysis. As noted previously, two patients in the givosiran arm were hospitalised for CKD; however, the company did not include incidence of CKD in the model on the basis that data are scarce. The ERG noted that AE costs in the givosiran treatment arm may be somewhat underestimated; however, overall AEs were not considered to be a key driver of incremental results.

- Based on the serious AE data reported in the Safety Analysis Set[22], the ERG considered that the company's justification for including the list of AE's in Table 37 was not robust and that the list may not fully reflect the most frequently occurring serious AE's.

4.3. Managed access agreement

In order to address uncertainty surrounding how givosiran will be used in clinical practice, the company submitted a further economic model outlining how givosiran may be evaluated within a managed access agreement (MAA; CS, Document B, p122). The MAA model adjusted the cost of givosiran (relative dose intensity) by [redacted]. In addition, the company stated that a patient access scheme (PAS) discount will be submitted for givosiran as part of an MAA (the ERG noted that this has not yet been accepted for implementation). The complete list of assumptions used to estimate the MAA model ICER are provided in Table 38.

Table 38: Assumptions used in the estimation of the MAA analysis

MAA assumptions	Additional information
Inclusion of a PAS for givosiran	[redacted]
[redacted] (based on feedback from NAPS clinicians)	[redacted]
Proportion of patients [redacted]	[redacted]
Percentage of patients [redacted]	[redacted]
Duration of [redacted]	[redacted]
Average proportion of patients [redacted]	[redacted]

Abbreviations: ALA, delta aminolevulinic acid; MAA, managed access agreement; NAPS, National Acute Porphyria Service; PAS, patient access scheme; PBG, porphobilinogen; RDI, relative dose intensity; SmPC, summary of product characteristics

The ERG noted the following concerns surrounding the company's proposed MAA:

- The ERG understood that the proposed MAA (including the PAS discount) was under negotiation and therefore should be considered a scenario analysis. However, for completeness, the ERG presented two sets of results, one set incorporating the company's MAA assumptions and another set that removes the MAA assumptions. These dual results have been presented for the company's base case, ERG scenario analyses and ERG preferred base case (see Section 5.1 and Section 6.2.3). Due to the uncertainty surrounding the MAA assumptions outlined above, the ERG considered that the results incorporating the MAA analysis should be interpreted with caution.

- The MAA impacts on givosiran costs only; i.e., the analysis does not adequately capture changes in HRQoL associated with stopping treatment. As such the analysis may be considered overly simplistic.

- The ERG noted that [redacted] were not supported by clinical evidence. Clinical advice to the ERG acknowledged that there is considerable uncertainty surrounding how givosiran will be used in practice i.e. it is unclear whether patients who are achieving clinical benefit with treatment will continue to receive givosiran or whether they would stop treatment. Furthermore, based on NAPS clinical advice it is likely that the frequency and severity of AHP symptoms will diminish over time, therefore patients are unlikely therefore to require lifelong treatment.

The ERG acknowledged that until long-term data are collected there is considerable uncertainty surrounding how givosiran will be used in clinical practice. Due to the limitations highlighted above, the ERG considered the company's MAA analysis to be subject to a high degree of uncertainty.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

The company submitted a corrected model during clarification. The corrected model resolved questions B14 (ToT applied for modelled time horizon) and B15 (annual cost of opioid addiction corrected for cycle length). The ERG therefore referred to this corrected model when presenting the results in the sections below unless otherwise stated. The ERG noted that cross references to the CS have been included in the narrative for completeness, but results reflect those provided by the company with the corrected model during clarification (question B14 and question B15).

5.1.1. Company's base case results

The company's base case results are provided in Table 39**.** Table 39

For givosiran compared with BSC, the deterministic and probabilistic incremental costs are [redacted] and [redacted] and the incremental QALYs are 9.32 and 8.74 with incremental cost-effectiveness ratios (ICERs) of [redacted] and [redacted] per QALY gained, respectively.

Table 39. Base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained (ICER)
Company deterministic base case					
Givosiran	[redacted]	[redacted]	-	-	-
BSC	[redacted]	[redacted]	[redacted]	9.32	[redacted]
Company probabilistic base case					
Givosiran	[redacted]	[redacted]	-	-	-
BSC	[redacted]	[redacted]	[redacted]	8.74	[redacted]

Abbreviations: QALYs, quality adjusted life years

5.1.2. Company's sensitivity analyses

5.1.2.1. One-way sensitivity analysis

The company presented a deterministic OWSA with the model parameters included as presented in the clarification response (Table 15). Where data were available, parameters were

varied using 95% confidence intervals, otherwise upper and lower bounds were varied by a standard error of 10% of the mean (base case) value.

A tornado plot was used to present the OWSA results in the clarification response (clarification Figure 5) for the comparison of givosiran versus BSC, with the ICER (£/QALY) as the outcome of interest. As per the tornado plot, the results were most sensitive to the intercept of the log-logistic function to extrapolate ToT, the discount rates on costs and outcomes, the proportion of females in the cohort, and age at initiation of treatment with givosiran.

5.1.2.2. Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) to explore the impact of parameter uncertainty when the model parameters were varied as per the respective distributions (CS, Document B, Section 12.4.3, Table 65). The PSA was run for 1,000 iterations. The PSA results are provided in Table 39.

The cost effectiveness acceptability curve (CEAC) indicated that the probability of givosiran being cost-effective at a £100k threshold was [redacted].

5.1.2.3. Scenario analyses

The company conducted several scenario analyses to assess the impact of alternative settings and model assumptions and the structural uncertainties on the base case results. Scenario analysis results were provided in the CS (Document B, Section 12.4.2, Table 64), and subsequently updated using the corrected model as summarised in Table 40. Note that the company did not provide results for the scenario analyses in the corrected model submitted during clarification.

Table 40: Outcomes of company scenario analyses relative to company base case

Scenario	Impact on incremental costs	Impact on incremental QALYs	ICER	% change from company base case
Company base case	[redacted]	9.32	[redacted]	-
Givosiran efficacy: recycling up to Year 3	↑	↓	[redacted]	[redacted]
Probability of menopause onset based on a normal distribution fitting mean age of	↑	↓	[redacted]	[redacted]

Scenario	Impact on incremental costs	Impact on incremental QALYs	ICER	% change from company base case
menopause and SD of UK women's cohort study[2]				
BSC efficacy: DB ENVISION for Cycle 1, then probability of disease worsening up to year 5	↓	↓	[redacted]	[redacted]
Mortality scenario analysis	↑	↑	[redacted]	[redacted]
Alternative assumption for prevalence of chronic conditions	↓	↑	[redacted]	[redacted]
Alternative caregiver disutility Assumption 1	↔	↓	[redacted]	[redacted]
Alternative caregiver disutility Assumption 2	↔	↓	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; DB, double blind; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years; SD, standard deviation; UK, United Kingdom

↑ increase relative to company base case; ↓ decrease relative to base case; ↔ no change relative to base case

5.2. Managed access agreement

The company provided results assuming a managed access agreement which primarily included [redacted] as mentioned in the CS (Appendix F). Further details on the MAA assumptions can be found in Section 4.3. These results are provided for completeness, but the ERG noted that a MAA has not yet been agreed.

The results were presented in the CS (Document B, Table 81), and updated subsequently using the corrected model as provided in Table 41.

Table 41: Deterministic results (including MAA assumptions)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained (ICER)
Company deterministic case with MAA					
Givosiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	9.32	[redacted]

Abbreviations: BSC, best supportive care; MAA, managed access agreement; QALYs, quality adjusted life years

5.3. Model validation and face validity check

The company provided the quality checklist used to assess the model via a series of validation tests in the CS (Section 12.7.4, Table 74).

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The ERG identified several limitations within the company's base case and has explored the impact of alternative parameter values and assumptions, which the ERG considered more plausible.

This section is organised as follows:

- Section 6.1 details the impact of errors identified in the ERG's validation of the executable model.
- Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. These analyses were conducted within the company's corrected base-case analysis. The scenario analyses presented in Section 6.2 focus on exploring the key issues and uncertainties around the company's base case assumptions.
- Section 0, the ERG base-case is presented based on a combination of the exploratory analyses presented in Section 6.2.

6.1. ERG corrections and adjustments to the company's base case model

The company resolved the identified errors in response to the ERG clarification questions B14 and B15 and provided a corrected model as mentioned in Section 5.1.1. In addition, the ERG identified a minor error in the PSA macro. However, it did not have any impact on the results.

6.2. Exploratory and sensitivity analyses undertaken by the ERG

As noted throughout the report, the ERG identified several uncertainties surrounding the company's modelled parameters and assumptions. The ERG has therefore conducted multiple scenario analyses exploring the impact of these uncertainties on the ICER. See Section 6.2.1 for a description of each scenario and Section 6.2.3 for results.

6.2.1. Scenario analyses

6.2.1.1. Scenario 1: Givosiran efficacy

The ERG considered there to be uncertainty surrounding the company's approach to extrapolating givosiran long-term clinical efficacy (Section 4.2.6). Three scenario analyses were conducted by the ERG to explore the impact of using alternative efficacy assumptions. These

assumptions varied the source of efficacy data (ENVISION only vs. ENVISION OLE), and the length of time patients were allowed to continue to transition between health states.

- In Scenario 1a) givosiran clinical efficacy was assumed to be based on ENVISION and OLE data (and transition probabilities were frozen after 18 months). Given the lack of long-term data, the ERG considered this scenario minimised uncertainty and therefore included this assumption within the ERG preferred base case. This scenario resulted in an increased ICER for givosiran when compared to the company's base case, as patients were no longer capable of transitioning/improving up to year 5 (see Section 6.2.3a).
- In Scenario 1b), the ERG assumed that treatment efficacy would last until year 3 i.e., patients were assumed to move between health states based on transition probabilities from ENVISION OLE (12-18 months) which was assumed to continue until 36 months, and thereafter transition probabilities were frozen. This analysis was undertaken in order to explore the impact of a potential of a maintained treatment effect (after the observed trial period). This resulted in an increased ICER versus the company's base case as givosiran efficacy extrapolation was based on 3 years instead of 5 years (see Section 6.2.3b).
- Finally, in Scenario 1c) the ERG sought to determine the impact of basing givosiran long-term efficacy on ENVISION data only i.e., transition probabilities at six months were extrapolated to 18 months and then frozen thereafter). Although the analysis is helpful in exploring the impact on ICER when only ENVISION trial data are considered for givosiran, the ERG noted that considering efficacy data from the OLE study was appropriate despite its limitations. Given that the efficacy of givosiran within the first 6 months of ENVISION was lower than the ENVISION OLE period (Document B, p.89), this scenario resulted in an increased ICER for givosiran (Section 6.2.3c)).

Further scenarios exploring alternative freezing points for transition probabilities for givosiran are presented as part of a two-way analysis. It was noted that the earlier givosiran efficacy/transition probabilities were frozen, the higher the increase in ICER, as shown in Section 6.2.2.

6.2.1.2. Scenario 2: BSC efficacy

In the base case analysis BSC transition probabilities were frozen at six months in the ENVISION study i.e., further transitions were not possible after six months. The company stated that this was a relatively conservative assumption, as patients would likely get worse over time.

For completeness, the ERG conducted a scenario analysis which extended BSC transition probabilities to 18 months (to be in line with the duration of the OLE study), and then assumed patients remained in their respective health states for the duration of the time horizon. This scenario analysis resulted in a lower ICER for givosiran. This was due to the fact that more patients were entering the recurrent and severe health states, thus leading to higher BSC costs and disutilities (see Section 6.2.3 for results).

Further scenarios exploring alternative freezing points for transition probabilities for BSC are presented as part of a two-way analysis. It was noted that the sooner the BSC efficacy/transition probabilities were frozen, the greater the increase in ICER, as shown in Section 6.2.2.

6.2.1.3. Scenario 3: Time on treatment

In the base case analysis, the company extrapolated ToT via a fully parametric approach using the log-logistic curve (Section 4.2.9.3). To sufficiently address uncertainty surrounding modelled time on treatment, the ERG conducted two scenario analyses.

- In Scenario 3a) a piece wise approach was used to model ToT whereby the KM curve from ENVISION was used until 18 months, and the log-normal curve was used for extrapolating to the remaining duration of the model. The ERG considered the log-normal curve to be the second best-fitting curve (after the exponential), based on AIC and BIC scores and visual inspection. Please note that though the log-normal distribution was fitted to the entire duration of ToT KM curve, a piecewise approach was preferred because of the fitted curve's deviation from the observed KM curve.
- Scenario 3b) used the Gompertz distribution for extrapolation. Though the Gompertz curve was not found to be one of the best fits, ERG wished to explore this as a scenario given its considerable impact on the ICER and the ToT in the model being used to inform the monotonically decreasing discontinuation rates.

Both the scenarios, Scenario 3a) and Scenario 3b) were found to increase the ICER. See section 6.2.3 for results.

6.2.1.4. Scenario 4: Health state utilities

The company's base case approach to estimating utilities within the model was subject to considerable uncertainty (Section 4.2.8). The ERG conducted three scenario analyses to explore the use of alternative values (see below).

- Scenario 4a): EQ-5D data were collected in the ENVISION study (Table 32); however, these data were not used in the company's base case analysis (Section 4.2.8). This scenario analysis therefore explores the impact of using HRQoL data directly elicited from patients in ENVISION. The ERG noted that due to the short-term nature of the study and counterintuitive values produced for the recurrent and severe health states, this scenario lacked face validity. See Section 6.2.3 for results.

- Scenario 4b): The ERG acknowledged that the higher utility estimate in the severe health state lacked face validity as mentioned in Section 4.2.8 and therefore opted to conduct a scenario analysis whereby the values for recurrent and severe health states were assumed to be the same as the symptomatic health state (Table 42). This approach appeared to estimate more plausible values (compared to the use of direct EQ-5D data); however, the ERG noted that the approach used a simplifying assumption and that utility values remained subject to uncertainty due to the limitations surrounding the ENVISION study i.e., short follow up and small patient numbers. See Section 6.2.3 for results.

Table 42: ERG adjusted values for recurrent and severe health states

Health state	Mean EQ-5D (6 months)	Calculated: Mean EQ-5D (baseline)
Asymptomatic	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]
Severe	[redacted]	[redacted]

EQ-5D, EuroQol 5-dimensions questionnaire; ERG, Evidence Review Group

- Scenario 4c): In Section 4.2.8 it was noted that in the absence of robust HRQoL data from AHP patients, 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). It should be noted that this scenario analysis replicated the company's approach to estimating carer disutility i.e. Expanded Disability Status Scale (EDSS) 1=asymptomatic, EDSS 2=symptomatic, EDSS 4= recurrent and EDSS 5=severe (Table 43).

Table 43: Health state utility values based on RRMS values from Hawton et al[1].

Health state	Mean EQ-5D
Asymptomatic	0.763
Symptomatic	0.719
Recurrent	0.596
Severe	0.438

Abbreviations: EQ-5D, EuroQol 5-dimensions questionnaire; RRMS, relapsing-remitting multiple sclerosis

All the three health state utility scenarios mentioned above resulted in an increased ICER (though with Scenario 4c the increase in ICER was marginal). See Section 6.2.3 for results.

6.2.1.5. Scenario 5: 10% of patients continue givosiran treatment after menopause

In the base case, the company assumed that 100% of patients who were asymptomatic at the age of menopause onset would discontinue givosiran. However, based on clinical opinion to the ERG, it may be plausible that a small proportion of patients who are asymptomatic would still receive the treatment. This scenario assumed that 10% of patients would continue to receive givosiran after menopause onset. The ICER is somewhat sensitive (with an upward impact) to this analysis due to the increased givosiran drug costs. See Section 6.2.3 for results.

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

In the base case analysis the company used a published study by Greer et al. (2003)[5] to estimate the per cycle probability of menopause onset. As noted in Section 4.2.7, there are generalisability concerns surrounding the use of this study as a means of estimating the probability of menopause in the model. In the CS, the company conducted a scenario analysis which used a normal distribution (fitting the mean and standard deviation age of menopause) from the UK Women's cohort study. The ERG considered that this source appeared more generalisable to the UK and therefore should have been used in the company's base case analysis. This scenario analysis resulted in an increased ICER. See Section 6.2.3 for results.

6.2.1.7. Scenario 7: Acute attack results in 50% hospitalisation rate

The ERG noted that cost of treating acute attacks in hospital was estimated to be high (i.e. [redacted]). Given that more patients in the BSC arm experienced acute attacks, the proportion of patients assumed to require hospitalisation was a key cost driver (see Section 4.2.9.2).

Based on clinical input to the ERG, the company's base case estimate appeared to be reasonable; however, in order to further explore the uncertainty, this scenario reduced the proportion of patients requiring hospitalisation to an arbitrarily selected value of 50%. This scenario increased the ICER substantially. See Section 6.2.3 for results.

6.2.1.8. Scenario 8: Opioid addiction costs removed

Although the ERG agreed that opioid addiction was a concern for patients with AHP, there were limitations around the generalisability of the data source used (Shei et al 2015[37]) to estimate opioid addiction costs within the base case analysis (Section 4.2.9.6). This scenario analysis therefore removed opioid addiction assumptions from the model. Opioid addiction is not considered to be a key driver of model results; therefore this scenario only had a marginal upward impact on the ICER. See Section 6.2.3 for results.

6.2.1.9. Scenario 9: Proportion of female patients in the model reduced to 82%

The company estimated the proportion of female patients in the model to be 86%, based on data from ENVISION (Section 4.2.3). Clinical opinion to the ERG indicated that the majority of patients are likely to be female in practice; however, suggested a lower proportion (approximately 82%) based on an unpublished 14 year follow up study[38] conducted with a UK AHP patient population. Given the model is heavily 'female orientated' with respect to modelled assumptions, this scenario analysis resulted in marginally increased ICER for givosiran. See Section 6.2.3 for results.

6.2.1.10. Scenario 10: Starting age reduced to 30 years

In the base case analysis, the company opted to use the age at screening (41.6 years) for the modelled starting cohort age (Section 4.2.3). This scenario analysis estimated the impact of using a starting age based on the age of diagnosis in ENVISION (30 years) on the ICER. Clinical advice to the ERG was that this assumption may be conservative as the availability of the NAPS specialist services has improved diagnosis of AHP, and new patients may be expected to be diagnosed earlier. Please note that this scenario increased the ICER substantially. See Section 6.2.3 for results.

6.2.1.11. Scenario 11: Time horizon reduced to 15 years

The ERG deemed a lifetime horizon to be reasonable for use in the base case; however, the company did not provide sensitivity analysis reducing the time horizon, thus introducing uncertainty (Section 4.2.5). This scenario explored the impact of reducing the time horizon to 15

years (arbitrary assumption [redacted]) and had substantially upward impact on the ICER given that the HRQoL benefit of givosiran is truncated at this earlier time point, whilst a considerable proportion of treatment costs have already been incurred. See Section 6.2.3 for results.

6.2.1.12. Scenario 12: Severe health state partially switched off

As noted in Section 4.2.2, there was some uncertainty surrounding the inclusion of the severe health state in the model. This scenario analysis explored the impact of partially switching off the severe health state. This was implemented by setting the entry cohort distribution at model start and the caregiver disutility for severe health state to zero. However, transitions into severe health states were still allowed and no further assumptions were made regarding the transitions.

This scenario had a considerable upward impact on the ICER. See Section 6.2.3 for results.

6.2.1.13. Scenario 13: Givosiran liver function tests included

As per the CS (Document B, Section 8.7), liver function tests need to be conducted for people on givosiran treatment prior to initiating the treatment and should be repeated monthly for the first six months of the treatment. However, this has not been included in the company's base case. Hence, this scenario explored the impact of including additional monitoring costs towards liver function test on the ICER. Nevertheless, there was no considerable impact on the ICER, as the additional monitoring costs for givosiran are only fixed costs for a definite time in the model and are minimal when compared to the drug acquisition costs of givosiran. See Section 6.2.3 for results.

6.2.2. Two-way sensitivity analyses (TWSA)

To explore further the robustness of the results while simultaneously varying any of the two key model parameters, ERG conducted the following two-way sensitivity analysis:

1. **Alternative time points for efficacy freezing:** Different time points for freezing the transitions between health states for givosiran versus that of the BSC
2. **Disease progression post-menopause:** Proportion of females in the model versus the proportion of females who could be symptomatic post-menopause and will continue to receive givosiran
3. [redacted]

All the above analyses resulted in an increased ICER as outlined in Section 6.2.3, Table 46 to Table 50. The analyses were run both with and without the MAA assumptions, except for TWSA 3 (as it is MAA specific).

6.2.3. Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The impact of the ERG's additional exploratory scenario and sensitivity analyses on the ICER was recorded by making the changes as described in Sections 6.2.1 and 6.2.2. Please note that the changes required for each scenario have been made individually and the percentage change from the corrected company base case along with the results has been presented in Table 44 and Table 45. For the TWSA, the parameters included were varied simultaneously and the subsequent impact on the ICER were recorded as shown in Table 46 to Table 50 .

Table 44: ERG exploratory analyses (excluding MAA assumptions)

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	£/QALY (ICER)	% change from company base case
ERG corrected company base-case	*5.1.1*	[redacted]	9.32	[redacted]	-
Scenario 1: Givosiran efficacy					
a) Clinical efficacy based on ENVISION and OLE data (TPs frozen after 18 months)	*6.2.1.1*	[redacted]	8.36	[redacted]	[redacted]
b) Clinical efficacy extrapolated to Year 3 (TPs frozen after 3 years)		[redacted]	9.26	[redacted]	[redacted]
c) ENVISION efficacy assumed to be maintained up to 18 months (OLE data not considered)		[redacted]	8.56	[redacted]	[redacted]
Scenario 2: BSC efficacy data from ENVISION extended to 18 months	*6.2.1.2*	[redacted]	9.14	[redacted]	[redacted]
Scenario 3: ToT extrapolation					
a) KM curve until 18 months and Log- normal for extrapolation beyond	*6.2.1.3*	[redacted]	9.32	[redacted]	[redacted]
b) Gompertz		[redacted]	9.30	[redacted]	[redacted]
Scenario 4: Health state utility values					
a) Utilities based on EQ-5D data from ENVISION	*6.2.1.4*	[redacted]	5.11	[redacted]	[redacted]
b) Recurrent and severe ENVISION utilities adjusted by ERG		[redacted]	5.66	[redacted]	[redacted]
c) AHP utilities based on RRMS values in Hawton et al[1])		[redacted]	9.02	[redacted]	[redacted]
Scenario 5: 10% of patients assumed to require treatment after age of menopause onset	*6.2.1.5*	[redacted]	9.31	[redacted]	[redacted]

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	£/QALY (ICER)	% change from company base case
Scenario 6: The per cycle probability of menopause onset based on mean age from UK Women's cohort study[2] (fitting a normal distribution).	*6.2.1.6*	[redacted]	9.31	[redacted]	[redacted]
Scenario 7: Proportion hospitalised for acute attack reduced to 50%	*6.2.1.7*	[redacted]	9.32	[redacted]	[redacted]
Scenario 8: Opioid addiction costs removed	*6.2.1.8*	[redacted]	9.32	[redacted]	[redacted]
Scenario 9: Proportion female reduced to 82%	*6.2.1.9*	[redacted]	9.30	[redacted]	[redacted]
Scenario 10: Starting cohort mean age reduced to 30 years	*6.2.1.10*	[redacted]	10.71	[redacted]	[redacted]
Scenario 11: Time horizon reduced to 15 years	*6.2.1.11*	[redacted]	5.12	[redacted]	[redacted]
Scenario 12: Severe health state 'partially switched off'	*6.2.1.12*	[redacted]	8.24	[redacted]	[redacted]
Scenario 13: Patients treated with givosiran require monitoring prior (and once monthly for first 6 months)	*6.2.1.13*	[redacted]	9.32	[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; OLE, open label extension; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; ToT, time on treatment; TPs, transition probabilities

Table 45: ERG exploratory analyses (including MAA assumptions)

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	ICER £/QALY	% change from company base case
ERG corrected company base-case	*5.2*	[redacted]	9.32	[redacted]	-
Scenario 1: Givosiran efficacy					
a) Clinical efficacy based on ENVISION and OLE data (TPs frozen after 18 months)	*6.2.1.1*	[redacted]	8.36	£169,369	[redacted]
b) Clinical efficacy extrapolated to Year 3 (TPs frozen after 3 years)		[redacted]	9.26	£99,071	[redacted]
c) ENVISION efficacy assumed to be maintained up to 18 months (OLE data not considered)		[redacted]	8.56	£148,563	[redacted]
Scenario 2: BSC efficacy data from ENVISION extended to 18 months	*6.2.1.2*	[redacted]	9.14	£18,510	[redacted]
Scenario 3: ToT extrapolation					
a) KM curve until 18 months and Log-normal for extrapolation beyond	*6.2.1.3*	[redacted]	9.32	£124,323	[redacted]
b) Gompertz		[redacted]	9.30	£187,620	[redacted]
Scenario 4: Health state utility values					
a) Utilities based on EQ-5D data from ENVISION	*6.2.1.4*	[redacted]	5.11	£173,193	[redacted]
b) Recurrent and severe ENVISION utilities adjusted by ERG		[redacted]	5.66	£156,376	[redacted]
c) AHP utilities based on RRMS values in Hawton et al[1])		[redacted]	9.02	£98,178	[redacted]
Scenario 5: 10% of patients assumed to require treatment after age of menopause onset	*6.2.1.5*	[redacted]	9.31	£107,756	[redacted]

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	ICER £/QALY	% change from company base case
Scenario 6: The per cycle probability of menopause onset based on mean age from UK Women's cohort study[2] (fitting a normal distribution).	*6.2.1.6*	[redacted]	9.31	£107,567	[redacted]
Scenario 7: Proportion hospitalised for acute attack reduced to 50%	*6.2.1.7*	[redacted]	9.32	£176,832	[redacted]
Scenario 8: Opioid addiction costs removed	*6.2.1.8*	[redacted]	9.32	£96,932	[redacted]
Scenario 9: Proportion female reduced to 82%	*6.2.1.9*	[redacted]	9.30	£106,202	[redacted]
Scenario 10: Starting cohort mean age reduced to 30 years	*6.2.1.10*	[redacted]	10.71	£194,823	[redacted]
Scenario 11: Time horizon reduced to 15 years	*6.2.1.11*	[redacted]	5.12	£326,441	[redacted]
Scenario 12: Severe health state 'partially switched off'	*6.2.1.12*	[redacted]	8.24	£144,710	[redacted]
Scenario 13: Patients treated with givosiran require monitoring prior (and once monthly for first 6 months)	*6.2.1.13*	[redacted]	9.32	£95,093	[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; OLE, open label extension; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; ToT, time on treatment; TPs, transition probabilities

Table 46: TWSA: Alternative time points for efficacy freezing (without MAA assumptions)

		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; TWSA, two-way sensitivity analyses

Table 47: TWSA: Alternative time points for efficacy freezing (with MAA assumptions)

		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; ICER, incremental cost-effectiveness ratio; MAA, managed access agreement; QALY, quality-adjusted life year; TPs, transition probabilities; TWSA, two-way sensitivity analyses

ICER > £100k/QALY

ICER < £100k/QALY

Table 48. TWSA: Disease progression post-menopause (without MAA assumptions)

		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

Table 49. TWSA: Disease progression post-menopause (with MAA assumptions)

		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: ICER, incremental cost-effectiveness ratio; MAA, managed access agreement; QALY, quality-adjusted life year; TWSA, two-way sensitivity analyses

ICER > £100k/QALY

ICER < £100k/QALY

Table 50. TWSA: [redacted] (MAA)

		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: ICER, incremental cost-effectiveness ratio; MAA, managed access agreement; QALY, quality-adjusted life year; TWSA, two-way sensitivity analyses

ICER > £100k/QALY

ICER < £100k/QALY

6.3. ERG's preferred assumptions

The ERG preferred base case ICER (excluding MAA assumptions) is outlined in Table 51 and the ERG preferred base case ICER (including MAA assumptions) is outlined in Table 52.

Table 51: ERG preferred base case (excluding MAA assumptions)

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
Company base-case	*5.1.1*	[redacted]
Scenario 1: Givosiran transition probabilities based on OLE data (frozen at 18 months)	*4.2.6 and 6.2.3*	[redacted]
Scenario 3: ToT extrapolated using piecewise approach (KM curve + log Normal cure)	*4.2.8 and 6.2.3*	[redacted]
Scenario 4c: AHP utilities based on RRMS values in Hawton et al[1]	*4.2.9.3 and 6.2.3*	[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).	*4.2.7 and 6.2.3*	[redacted]
Scenario 8: Opioid addiction costs removed	*4.2.9.6 and 4.2.9.64.2.9.64.2.9.6*	[redacted]

Abbreviations: AHP, acute hepatic porphyria; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; MAA, managed access agreement; OLE, open-label extension; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; ToT, time on treatment; UK, United Kingdom

Table 52: ERG preferred base case (including MAA assumptions)

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
Company base-case	*5.1.1*	[redacted]
Scenario 1: Givosiran transition probabilities based on OLE data (frozen at 18 months)	*4.2.6 and 6.2.3*	[redacted]
Scenario 3: ToT extrapolated using piecewise approach (KM curve + log Normal cure)	*4.2.8 and 6.2.3*	[redacted]
Scenario 4: AHP utilities based on RRMS values in Hawton et al[1]	*4.2.9.3 and 6.2.3*	[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).	*4.2.7 and 6.2.3*	[redacted]
Scenario 8: Opioid addiction costs removed	*4.2.9.6 and 4.2.9.64.2.9.64.2.9.6*	[redacted]

Abbreviations: AHP, acute hepatic porphyria; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; MAA managed access agreement; OLE, open-label extension; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; ToT, time on treatment; UK, United Kingdom

6.4. Conclusions of the cost-effectiveness section

Based on the ERG preferred base case results (excluding MAA assumptions), givosiran resulted in ICER of [redacted], based on an incremental cost of [redacted] and incremental QALY gain of 8.20.

The ERG considered the company's economic model (with and without MAA assumptions) to include a number of highly uncertain assumptions and the ICER was found to be sensitive to variation in these key model assumptions (see Section 6.2.3). The ERG acknowledged that the company had provided the best possible efficacy evidence available for givosiran (using data from ENVISION and the ENVISION OLE). However, the studies were short-term and there was considerable uncertainty around long term extrapolation assumptions used in the model for both givosiran and BSC treatment arms.

Furthermore, there was a lack of robust data regarding the impact of givosiran on long-term HRQoL of AHP patients. The use of published literature by the company to estimate utility decrements was limited by generalisability concerns and therefore the appropriateness of the modelled values was subject to uncertainty. The ERG considered that longer term HRQoL and clinical efficacy data and would be useful in addressing the limitations and uncertainties identified within this technology appraisal.

7. END OF LIFE

The ERG considered that givosiran does not meet NICE end of life criteria:

- The treatment is not indicated for patients with a short life expectancy, normally less than 24 months and;
- There is insufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional three months, compared to current NHS treatment.

8. SUBMISSIONS FROM PRACTITIONER AND PATIENT GROUPS

8.1. National Acute Porphyria Service at Cardiff and Vale University Health Board and Kings College Hospital

A statement was received from each of the NAPS services, which provided comments on the epidemiology of the target population, the current treatment pathway, and the potential use and implementation of treatment with givosiran.

Overall, the comments regarding the epidemiology of the target population were consistent with the evidence presented by the company. There were two notable exceptions: firstly, regarding prognosis, where in contrast to the company, it was claimed that the frequency and severity of attacks in the target population would be expected to reduce over patients' lifetimes. Secondly, both stakeholders estimated the current target population would be smaller than that estimated by the company (26 patients vs 35), and that not all these patients would be expected to switch to givosiran if available. The trial populations were considered to be relevant to practice, and both clinicians noted that treatments may be similar between centres and internationally.

The current treatment pathway described by stakeholders is consistent with the ERG's understanding. Both stakeholders highlighted several advantages of givosiran as compared to IV heme prophylaxis; including patient convenience, as givosiran requires fewer administrations and in time can be administered at home. Relatedly, givosiran is expected to require less healthcare resource. Finally, the stakeholders highlighted risks associated with IV heme prophylaxis.

The stakeholders did not expect treatment with givosiran to require significant changes in service configuration. Due to the risk of anaphylaxis reported in the trial evidence, both stakeholders considered that early treatments with givosiran should be administered in hospital, before being administered at home.

Stakeholders considered that the efficacy of givosiran is likely to vary between patients, due to the variable nature of the disease. In practice, stakeholders considered it unlikely that patients would require lifelong treatment, and would favour options to start and stop treatment where considered appropriate by a multi-disciplinary team.

8.2. British Porphyria Association (BPA)

A statement was received from The British Porphyia Association (BPA), accompanied by an unpublished manuscript[39] and series of case studies of patients with AHP who experience recurrent acute attacks.

The statement highlighted an unmet need for preventative treatment for acute attacks. The stakeholder outlined the limitations of current treatments, and stated that patients report that these do not prevent attacks or reduce chronic symptoms of AHP.

The statement provided an insight into the significant burden of recurrent attacks on the lives of both patients and carers. This includes burden on physical and mental wellbeing, but also for functioning, including work/study and family relationships. The stakeholder echoed the company's concerns that the EQ-5D may not capture the potential benefit of a reduction in acute attacks. This is because a change in pain from acute attacks may make little change to the pain reported by patients with chronic pain. In addition, the stakeholder suggested that changes in disability and psychological outcomes may not be sufficiently captured using the EQ-5D.

8.3. Global Porphyria Advocacy Coalition (GPAC)

A statement was received by The Global Porphyria Advocacy Coalition (GPAC), accompanied by an unpublished manuscript[39] (the same manuscript as provided by the BPA). The GPAC is an international company supporting porphyria agencies, including the BPA, and the statement generally concurred with the statement provided by BPA. The stakeholder further highlighted the significant burden of the disease on the lives of patients and their carers, and the unmet need for treatment. Furthermore, the stakeholder concurred with the view of the BPA that trial outcomes may not sufficiently capture the true impact of the disease on the lives of patients and carers.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Givosiran for treating acute hepatic porphyria [ID1549]

You are asked to check the ERG report from Peninsula Technology Assessment Group (PenTAG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5:00pm** on **Monday 15 February 2021** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the evaluation committee and will subsequently be published on the NICE website with the evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Preamble

Alnylam would like to express our sincere appreciation for the time and effort invested by the ERG in its review of our evidence submission for givosiran for acute hepatic porphyria (AHP) and our follow-up clarifications. We are especially grateful for the ERG's timely review considering the challenges that COVID undoubtedly posed to the reviewers.

Overall, we are gratified that the ERG has recognised the strengths of our submission, and we acknowledge many of the limitations identified in the report, reflecting the evidence gaps typical of any disease as rare as AHP. However, one disappointing aspect of the current HST process is that, unlike in the STA process, the company has no right of reply to the ERG report and thus we are unable to comment in this pro forma response on some of the ERG's preferences and assumptions stated within the report with which we disagree, or to present additional evidence which could have addressed some of ERG's uncertainties. Nevertheless, we would like to emphasise that we completely understand and respect the remit of this stage in the current process. We have therefore restricted our input in the following tables to a limited number of specific amendments to correct factual imprecision where this could potentially result in misinterpretation by committee, and which we believe will therefore further improve the report overall.

Alnylam welcomes the announcement on February 4th of NICE's method review of the HST process, and the undertaking to enable company feedback on ERG reports in future. As we understand that this "right to reply" does not apply to our givosiran submission initiated under the existing process, we will wait to raise issues related to the ERG's preferred assumptions and justifications at the next opportunity, in committee.

Response to ERG Report

Issue 1 Characterisation of clinical expert input on natural history of AHP in patients on best supportive care (BSC)

Description of problem	Description of proposed amendment	Justification for amendment
Section 2.1, page 24: "The company argued that, if left untreated, patients would not experience an improvement in symptoms (CS Document B, p. 72); however, this was at odds with a submission from a NAPS clinician, who stated that symptoms are likely to diminish with time (see Section 8.1)." We believe this statement is a misinterpretation of the NAPS clinician's input, based on the following more detailed account given by the ERG on page	Alnylam requests deletion of the quoted sentence on page 24.	AHP patients with repeated acute attacks —the target population for givosiran—will accumulate irreversible damage over time if repeated attacks persist.[1,2] The disease course of AHP is variable, but according to a lead author on the unique long-term natural history study of 88 patients by Neeleman et al. (2018),[3] who is a leading global expert on treating patients with AHP: "For patients who have recurrent attacks, the clinical condition is on average getting worse." It is critical to recognise

86: “The company state that ‘freezing’ transition probabilities may be considered conservative given that the health status of patients is considered to worsen in the absence of an active disease modifying treatment (CS, Document B, p.90). The ERG queried this with clinical experts. Responses were limited, although one clinical expert reported that it could be plausible for a small proportion of patients to improve over time [our emphasis].” This expert’s response does not support the ERG’s apparent conclusion on page 24 that patients’ symptoms *are likely to* diminish with time—on the contrary, the clinician is clearly suggesting, with strong caveats (i.e., “could be plausible”), that only a small minority of patients *might* improve over time. The expert’s response does not pertain to the disease trajectory for the average patient with repeated attacks.		that this expert clinician is attesting to the disease course for the average patient who would be eligible for givosiran—i.e., a patient suffering from repeated acute attacks. In contrast, the clinical expert cited by the ERG is undoubtedly referring to a small proportion of all patients with AHP, who would on average have much milder disease than the population targeted by givosiran. Repeated acute attacks result in progressive nerve damage, leading to ongoing symptoms including chronic pain, urinary incontinence, motor weakness, and potentially even permanent paralysis.[3,4] It is thus incorrect to imply that symptoms are likely to (meaning, on average) diminish with time in the absence of disease-modifying treatment. Deletion of the quoted sentence will avoid this incorrect implication. AHP patients are also at elevated risk for progressive long-term complications, including chronic kidney disease (CKD), hepatocellular carcinoma (HCC), and hypertension.[3,5-7] As explained in CS Section 12.2.1, long-term complications are not considered in the cost-effectiveness model (CEM) because incidence data are poor or unavailable and there is no evidence that the conditions will improve with improvements in AHP health states. On the contrary, even if a small subset of patients receiving BSC might experience resolution of acute symptoms, there is no rationale for believing that long-term complications could resolve, especially considering that levels of the toxic haem intermediates ALA and PBG would remain elevated. However, the quoted sentence could be misinterpreted as referring to all symptoms

		including these long-term complications, leaving the incorrect impression that CKD and HCC spontaneously diminish over time. Deletion of this sentence will pre-empt this misunderstanding.

Issue 2 Characterisation of the impact of givosiran on mortality

Description of problem	Description of proposed amendment	Justification for amendment
Table 4, page 31: "Mortality was included but not considered a key driver of the ICER. Givosiran did not result in an incremental life year gain compared to BSC." Alnylam is concerned that this statement is likely to be misinterpreted. Equal survival is merely a model assumption, not based on actual mortality data for givosiran vs BSC, which does not exist at present. In reality there is every reason to expect there will be an incremental life-year gain for givosiran vs. BSC given that givosiran controls the levels of toxic haem intermediates that drive not only acute attacks but also chronic conditions.	Alnylam proposes replacement of the quoted text with the following sentence: "In the absence of available data on whether givosiran conveys a survival benefit, the company applied the same mortality rate in all health states, as a result of which the model did not yield a mortality difference between the givosiran and BSC arms."	The proposed amendment will avoid leaving the incorrect impression that there is clinical evidence of no incremental life-year gain for givosiran vs. BSC, and will clarify that this is merely a consequence of a model assumption.

Issue 3 Characterisation of ENVISION OLE follow-up

Description of problem	Description of proposed amendment	Justification for amendment
Section 3.2.2.1, page 38: "The ERG also noted that evidence in the CS beyond the 18-month follow-up showed significant missing data (this may be due to ongoing data collection at this time point)." The use of the term "missing data" is misleading,	Alnylam proposes editing the sentence along the following lines: "The ERG also noted that evidence in the CS beyond the 18-month follow-up reflected lower sample sizes due to ongoing data collection after this time point."	The requested amendment will avoid the incorrect and negative implication that there are substantial missing data or dropouts in the OLE.

as the lower sample sizes beyond 18 months in the submitted data are merely due to the fact that at data cut-off for the 18-month analysis not all patients had yet reached time on treatment beyond 18 months.		

Issue 4 Characterisation of clinical effect of givosiran by location of treatment for attacks

Description of problem	Description of proposed amendment	Justification for amendment
Section 3.2.3.2, page 60: "Overall, the data suggest that givosiran results in a reduction in all types of attack measured in ENVISION and ENVISION OLE, though there is evidence that the effect may be greater for those attacks that are currently treated without hospitalisation." Alnylam is concerned that the second half of this sentence proposes a real difference in effectiveness of givosiran for different locations of attack treatment, when no such conclusions can be drawn reliably since the results are not adjusted for the differences in treatment practice in different countries or any other potential confounders. The type (i.e., location of treatment) of attack should not be regarded as a proxy of efficacy, but rather should be considered as a health system characteristic. Furthermore, these subgroup results are impacted by the diminished sample sizes, so any lack of apparent significance is likely a consequence of loss of statistical power rather than a real reflection of diminished clinical effect.	Alnylam proposes deletion of the phrase "though there is evidence that the effect may be greater for those attacks that are currently treated without hospitalisation"	The proposed deletion would avoid leaving the impression that there is a clear and real difference in efficacy of givosiran depending on the location of attack treatment. There are a number of factors that complicate such an interpretation. First, it would be misleading to report apparent trends without acknowledging all the uncontrolled confounding factors based on local treatment practice, such as the propensity to admit a patient to hospital as opposed to treating in an outpatient setting (or even receiving treatment for an attack at home) in different countries represented in ENVISION. Second, there are statistical power considerations that argue against drawing such an inference—ENVISION was powered for a composite primary endpoint of annualised attack rate (AAR), rather than any given component of the composite endpoint. As a result, we consider it is misleading to draw any such inferences that givosiran has less efficacy on any component of the composite endpoint (i.e., hospitalisation), on the basis of the low sample size of such events which may lead to erroneous conclusions. Notably, individual

		components of the composite primary endpoint were not pre-specified primary or secondary endpoints; rather, these AAR categories were simply defined to ensure capturing of acute attacks requiring major specific medical intervention that can be objectively measured.

Issue 5 Characterisation of pain and analgesic use results in ENVISION

Description of problem	Description of proposed amendment	Justification for amendment
Section 3.2.3.2, page 66: [re pain and analgesic usage endpoints] "As noted in Section 3.2.2.6, all of these analyses were post-hoc, and therefore should be considered exploratory and at a higher risk of bias." All of these pain and analgesic usage endpoints were pre-specified in the ENVISION protocol[8] and are thus not post hoc analyses. Daily worst pain over 6 months and change from baseline in the SF-12 PCS at 6 months were pre-specified secondary endpoints. Daily worst pain and analgesic usage at 12 months were pre-specified exploratory endpoints.	Alnylam requests deletion of the quoted sentence.	The requested deletion will correct the inaccurate statement that these are post hoc analyses.
Section 3.2.3.2, page 66: "However, while the reduction in AAR was maintained in ENVISION OLE, findings from ENVISION OLE showed an increase in overall use of pain relief between 12- and 18-months in both the placebo/givosiran and givosiran/givosiran arms. As shown in Table 21, at the 12- and 18-month follow-ups, there was no consistent difference in pain relief to that used by the placebo arm in the double-blind phase."	Alnylam requests either deletion of the quoted text or addition of a comprehensive explanation of the issues with these data post–month 12.	The requested amendment will avoid leaving the misleading impression that the analgesic use data after month 12 can be relied upon as showing a real increase in use of pain relief rather than merely an artefact of different data collection methodology before vs. after month 12.

Alnylam wishes to emphasise that any analyses of analgesic data after month 12 cannot be considered to be reliable, because data collection using the eDiary, which included capture of opioid and non-opioid analgesic use, was only performed from month 0 through month 12. After month 12, medication use was captured only through the concomitant medication forms of the CRF, which could not be analysed with reference to eDiary records as was done prior to month 12. This discrepancy confounds comparison of medication use prior to month 12 with utilisation after month 12. Consequently, the analgesic data beyond month 12 should be regarded as unreliable, and do not support the ERG's conclusion that actual use of pain medications increased from month 12 to month 18.		
Section 3.2.3.2, page 67: "However, the lack of a demonstrable effect of pain relief in ENVISION OLE casts doubt on the reliability of the effect in ENVISION, and at this stage the ERG regarded that it is not possible to conclude that givosiran is associated with a meaningful reduction in pain relief." This statement directly contradicts the conclusion of the EMA following their review of the evidence, including data from the OLE presented during the D90 response to questions. The EMA's recognition that givosiran is associated with a meaningful reduction in pain relief is reflected by reporting in SmPC Table 2 of the significant difference between givosiran and placebo in daily pain score, and the statement regarding the SF-12 results: "there was consistent evidence of effect favouring	Alnylam proposes deletion of this sentence.	The proposed deletion will remove a discordant conclusion that conflicts with the givosiran label as approved by the EMA following their review of the evidence.

this medicinal product in bodily pain".[9] Notably, the SF-12 bodily pain results represent a clinically meaningful finding, as these reveal that patients felt better and experienced less interference in their normal activities due to pain.		
Section 3.2.3.2, page 67: "These data are replicated below (Table 18), and show no obvious change in pain during attacks between those treated with givosiran and placebo." As in the preceding quotation, this statement directly contradicts the conclusion of the EMA following their evidence review. Please see above for further details.	Alnylam proposes deletion of this sentence.	The proposed deletion will remove a discordant conclusion that conflicts with the givosiran label as approved by the EMA following their review of the evidence.
Section 3.2.3.2, page 69, Table 18: the reported pain scores are not identified as change from baseline.	Alnylam requests the following edit to the caption to their Table 18: "Change from baseline in daily worst pain during and between acute attacks in ENVISION and ENVISION OLE: AIP"	The requested correction will clarify what the numbers in Table 18 represent and avoid misinterpretation that these are absolute values.

Issue 6 Characterisation of Neeleman et al. (2018)

Description of problem	Description of proposed amendment	Justification for amendment
Section 4.2.2, page 78: "However, the decision to rely upon a single study may not be considered robust, particularly as Neeleman et al was a non UK based study (The Netherlands), which aimed to determine the financial burden of AIP." Although healthcare resource use and associated costs are certainly reported in this publication, a key focus of this study was the prevalence of symptoms and long-term complications, i.e., the medical burden of AHP, the investigation of which	Alnylam proposes to replace "financial burden" with "burden of illness".	The proposed amendment would avoid unfairly discounting the relevance of the real-world clinical data from this study. The objectives statement in this publication makes clear that it is not merely a financial study: "… in order to get a better insight into the burden of AIP, we studied the prevalence of porphyria symptoms and complications, in addition to the costs related to recurrent porphyric attacks and compared them to symptomatic porphyria cases and asymptomatic gene carriers

was, at a minimum, the co-primary objective. Alnylam considers the ERG report's description of the study goal as merely determining financial burden to be misleading.		in a case-control study design."[3] Notably, we did not use healthcare resource utilisation data from Neeleman et al. (2018) in our CEM.
Section 4.2.7.3, page 88: "The study included a small number of patients with AIP (11 recurrent, 24 symptomatic and 53 asymptomatic)." In the context of the extreme rarity of AHP, this study is a remarkable achievement and one of the largest cohorts ever reported. Alnylam considers the description of the sample of 88 patients as "as small number" to be misleading in this context.	Alnylam proposes to delete "a small number of" from the quoted sentence.	The proposed deletion will avoid mischaracterising what is in fact the longest-term natural history study ever conducted in AHP, and one of the largest.

Issue 7 Characterisation of Alnylam's rationale for CEM cycle length

Description of problem	Description of proposed amendment	Justification for amendment
Section 4.2.5, page 83: "The company selected a six month cycle length in the base case analysis on the basis that this reflected the duration of the ENVISION study. The ERG did not consider the company's rationale to be appropriate, as the cycle length should reflect clinically important events such as monitoring. Based on clinical input to the ERG, it was confirmed that monitoring for AHP patients is conducted primarily on a six monthly basis (although this may vary on an individual patient basis)." Alnylam provided this same rationale regarding monitoring in our response to ERG question B1, but our response is not acknowledged in the ERG report.	Alnylam requests revision of the quoted text along the following lines: "The company selected a six-month cycle length in the base case analysis on the basis that this reflected the duration of the ENVISION study. The company clarified in response to ERG's query about this model parameter that the six-month cycle length also matches the intervals between routine clinic visits for monitoring of AHP patients, as set out in AHP evaluation and management recommendations from the Porphyrias Consortium and in the NHS Standard Contract for Severe Acute Porphyria Service. Based on clinical input to the ERG, it was confirmed that monitoring for AHP patients is conducted primarily on a six monthly basis (although this may vary on an individual patient	The requested amendment will incorporate the relevant details of Alnylam's response to ERG question B1 and avoid the incorrect implication that the company disagrees with the clinical input received by the ERG.

	basis)."	

Issue 8 Description of rationale for ERG scenario analysis on model cohort starting age (Scenario 10)

Description of problem	Description of proposed amendment	Justification for amendment
Section 6.2.1.10, page 112: "This scenario analysis estimated the impact of using a starting age based on the age of diagnosis in ENVISION (30 years) on the ICER. Clinical advice to the ERG was that this assumption may be conservative as the availability of the NAPS specialist services has improved diagnosis of AHP, and new patients may be expected to be diagnosed earlier. Please note that this scenario increased the ICER substantially." ERG's choice of 30 years is based on age at diagnosis in the ENVISION phase 3 trial, whereas our submitted base-case value of 41.64 years was based on patient age at baseline in ENVISION. As we explained in our response to ERG question B18, age at diagnosis does not reflect the current "snapshot" of the age distribution of patients who would initiate givosiran today. The fact that the ERG report states, "Clinical advice to the ERG was that … new patients may be expected to be diagnosed earlier [our emphasis]" confirms that the experts are referring to age at diagnosis for incident patients, not the age distribution of prevalent patients who would start givosiran now.	Alnylam requests addition of a sentence following the quoted text clarifying that age at diagnosis of AHP is not representative of the starting age for givosiran treatment because the patients who would start treatment with givosiran today include prevalent patients who may have been diagnosed years or decades ago.	The requested amendment will serve as a disclaimer that Scenario 10 substitutes age at diagnosis/incident patients for age at treatment initiation/prevalent patients. With the slow accrual of new AHP patients over time due to the low incidence of this rare disease, it will be many years before age at diagnosis can serve as a proxy for age at initiation of givosiran. Furthermore, age at diagnosis is likely to grossly underestimate the age at which patients would be eligible for givosiran because genetic testing/family screening can lead to diagnosis many years or even decades prior to symptoms that would lead to initiating givosiran. For example, the minimum age at diagnosis in ENVISION was 5 years old but the minimum age at baseline was 19 years.[10] The requested amendment will help the reader to interpret this scenario correctly as an exploration of sensitivity of the CEM results to starting age, rather than being a clinically realistic setting.

Issue 9 Description of methodology for ERG scenario analysis switching off Severe health state (Scenario 12)

Description of problem	Description of proposed amendment	Justification for amendment
Section 6.2.1.12, page 113: "This scenario analysis explored the impact of switching off the severe health state. This was implemented by setting the entry cohort distribution at model start and the caregiver disutility for severe health state to zero. This scenario had a considerable upward impact on the ICER." It is unclear from this description what rules the ERG applied to transitions into the Severe health state. Without a clearer explanation the reader cannot evaluate this scenario.	Alnylam requests addition of text clarifying whether or not transitions into the Severe health state were possible, and if not, how was this exclusion implemented in the ERG's adaptation of the model.	Even if no patients enter the CEM in the Severe health state, patients could theoretically still transition into the Severe health state. Alternatively, removing the Severe health state entirely would imply redefining the Recurrent health state as AAR>4, and thus the mean AAR and transition probabilities in the Recurrent health state would require adjustment. Without such changes, the results obtained would be computationally flawed and clinically meaningless. The requested amendment will clarify whether or not this transition was allowed in the ERG's adaptation of the model for Scenario 12, and allow the reader to judge the appropriateness of the method implemented.

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Givosiran for treating acute hepatic porphyria [ID1549]

Highly Specialised Technologies

Evaluation Programme

Addendum #1

ERG base case and scenario analyses using the newly approved PAS for givosiran

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Produced by

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1. INTRODUCTION

The purpose of this addendum is to provide the results of the ERG base case and scenario analyses following the approval of the PAS discount for givosiran (confirmed to the ERG in correspondence with NICE on 19/04/2021).

The analyses reported herein update the results tables provided in Section 6.2 and 6.3 of the ERG report. The analyses incorporate the corrections made to the company model by the ERG, in addition to the ERG's preferred assumptions as they are stated in the report. Please note that the PAS now approved for givosiran was included in the ERG's scenario analyses incorporating the assumptions for the proposed managed access agreement (MAA) for givosiran. This addendum therefore only provides an update to the ERG analyses that did not incorporate these assumptions.

2. EXPLORATORY AND SENSITIVITY ANALYSES UNDERTAKEN BY THE ERG

The results of the ERG's scenario analyses updated to include the new PAS are summarised below in Table 1.

Table 1: ERG exploratory analyses (excluding MAA assumptions)

Preferred assumption	Section in ERG report	Incremental costs (£)	Incremental QALYs	£/QALY (ICER)	% change from company base case
ERG corrected company base-case	***Error! Reference source not found.***	[redacted]	9.32	[redacted]	-
Scenario 1: Givosiran efficacy					
a) Clinical efficacy based on ENVISION and OLE data (TPs frozen after 18 months)	***Error! Reference source not found.***	[redacted]	8.36	[redacted]	[redacted]
b) Clinical efficacy extrapolated to Year 3 (TPs frozen after 3 years)		[redacted]	9.26	[redacted]	[redacted]
c) ENVISION efficacy assumed to be maintained up to 18 months (OLE data not considered)		[redacted]	8.56	[redacted]	[redacted]
Scenario 2: BSC efficacy data from ENVISION extended to 18 months	***Error! Reference source not found.***	[redacted]	9.14	[redacted]	[redacted]
Scenario 3: ToT extrapolation					
a) KM curve until 18 months and Log-normal for extrapolation beyond	***Error! Reference source not found.***	[redacted]	9.32	[redacted]	[redacted]
b) Gompertz		[redacted]	9.30	[redacted]	[redacted]
Scenario 4: Health state utility values					

Preferred assumption	Section in ERG report	Incremental costs (£)	Incremental QALYs	£/QALY (ICER)	% change from company base case
a) Utilities based on EQ-5D data from ENVISION	***Error! Reference source not found.***	[redacted]	5.11	[redacted]	[redacted]
b) Recurrent and severe ENVISION utilities adjusted by ERG		[redacted]	5.66	[redacted]	[redacted]
c) AHP utilities based on RRMS values in Hawton et al[1])		[redacted]	9.02	[redacted]	[redacted]
Scenario 5: 10% of patients assumed to require treatment after age of menopause onset	***Error! Reference source not found.***	[redacted]	9.31	[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).	***Error! Reference source not found.***	[redacted]	9.31	[redacted]	[redacted]
Scenario 7: Proportion hospitalised for acute attack reduced to 50%	***Error! Reference source not found.***	[redacted]	9.32	[redacted]	[redacted]
Scenario 8: Opioid addiction costs removed	***Error! Reference source not found.***	[redacted]	9.32	[redacted]	[redacted]
Scenario 9: Proportion female reduced to 82%	***Error! Reference source not found.***	[redacted]	9.30	[redacted]	[redacted]
Scenario 10: Starting cohort mean age reduced to 30 years	***Error! Reference source not found.***	[redacted]	10.71	[redacted]	[redacted]
Scenario 11: Time horizon reduced to 15 years	***Error! Reference source not found.***	[redacted]	5.12	[redacted]	[redacted]
Scenario 12: Severe health state 'switched off'	***Error! Reference source not found.***	[redacted]	8.24	[redacted]	[redacted]
Scenario 13: Patients treated with givosiran	***Error! Reference***	[redacted]	9.32	[redacted]	[redacted]

Preferred assumption	Section in ERG report	Incremental costs (£)	Incremental QALYs	£/QALY (ICER)	% change from company base case
require monitoring prior (and once monthly for first 6 months)	***source not found.***				

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; OLE, open label extension; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; ToT, time on treatment; TPs, transition probabilities

3. ERG PREFERRED ASSUMPTIONS

The results of the ERG base case updated to include the PAS for givosiran are provided below in Table 2.

Table 2: ERG preferred base case (excluding MAA assumptions)

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
Company base-case	***Error! Reference source not found.***	[redacted]
Scenario 1: Givosiran transition probabilities based on OLE data (frozen at 18 months)	***Error! Reference source not found.*** *and* ***Error! Reference source not found.***	[redacted]
Scenario 3: ToT extrapolated using piecewise approach (KM curve + log Normal cure)	***Error! Reference source not found.*** *and* ***Error! Reference source not found.***	[redacted]
Scenario 4c: AHP utilities based on RRMS values in Hawton et al[1]	***Error! Reference source not found.*** *and* ***Error! Reference source not found.***	[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).	***Error! Reference source not found.*** *and* ***Error! Reference source not found.***	[redacted]
Scenario 8: Opioid addiction costs removed	***Error! Reference source not found.*** *and* ***Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.***	[redacted]

Abbreviations: AHP, acute hepatic porphyria; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; MAA, managed access agreement; OLE, open-label extension; QALY, quality adjusted life year; RRMS, relapsing-remitting multiple sclerosis; ToT, time on treatment; UK, United Kingdom

4. CONCLUSIONS OF THE COST-EFFECTIVENESS SECTION

Based on the ERG preferred base case results including the PAS for givosiran (and excluding MAA assumptions), givosiran resulted in an ICER of [redacted], based on an incremental cost of [redacted] and an incremental QALY gain of 8.20. As noted in the ERG report, the ERG considered that there remains a significant amount of uncertainty surrounding the clinical efficacy of givosiran, and that longer term HRQoL and clinical efficacy data would be useful in addressing the limitations and uncertainties identified within this technology appraisal.