Givosiran for treating acute hepatic porphyria [ID1549]

Highly Specialised Technologies Evaluation Programme

Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters
St Luke's Campus
Heavitree Road
Exeter
EX1 2LU

Authors

Caroline Farmer[1]
Brian O'Toole[1]
Madhusubramanian Muthukumar[1]
Sophie Robinson[1]
Fraizer Kiff[1]
Laura Trigg[1]
Tricia Gardiner[2]
Philip Newsome[3]
Louise Crathorne[1]
G.J. Melendez-Torres[1]

[1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter

[2] No affiliation

[3] University Hospitals Birmingham NHS Foundation Trust

Correspondence to

Caroline Farmer

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School South Cloisters St Luke's Campus Heavitree Road Exeter EX1 2LU 3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; c.farmer@exeter.ac.uk
Date completed	03/02/2021
Source of funding	This report was commissioned by the NIHR Systematic Reviews Programme as project number 13/31/81.
Declared competing interests of the authors	None
Acknowledgments	The authors acknowledge the administrative support provided by Mrs Sue Whiffin and Ms Jenny Lowe (both PenTAG).
Rider on responsibility for document	The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.
This report should be referenced as follows	Farmer, C., O'Toole, B., Muthukumar, M., Robinson, S., Kiff, F., Trigg, L., Gardiner, T., Newsome, P.N., Crathorne, L., Melendez-Torres, G. J. Givosiran for treating acute hepatic porphyria [ID1549]: A Highly Specialised Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2021.

Author Contributions:	
Caroline Farmer	Project lead, critical appraisal of the company submission, writing and editorial input
Brian O'Toole	Lead for the ERG's appraisal of the economic evidence, drafted economic sections of the report, writing and editorial input
Madhusubramanian Muthukumar	Critical appraisal of the economic evidence, checked and re-analysed the economic model, carried out further scenario analyses, and drafted economic sections of the report
Sophie Robinson	Critical appraisal of the literature search strategies, editorial review.
Fraizer Kiff	Critical appraisal of the clinical evidence
Laura Trigg	Critical appraisal of the clinical evidence
Tricia Gardiner	Clinical advice and review of draft report
Philip Newsome	Clinical advice and review of draft report

Author Contributions:	
Louise Crathorne	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report
G.J. Melendez-Torres	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report. Guarantor of the report.

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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
Key Issue 1	The lack of a comparison versus off label prophylactic treatment options	2.2; 2.3; 3.3; 4.2.4
Key Issue 2	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
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	4.2.9.2
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 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. 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	Long-term real world data outlining givosiran use in clinical practice would help reduce uncertainty surrounding this issue.

Report sections	4.2.9.3
might help to resolve this key 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).

Report sections	1.4, 4.2.7 and 4.2.3
	• 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.
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]
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

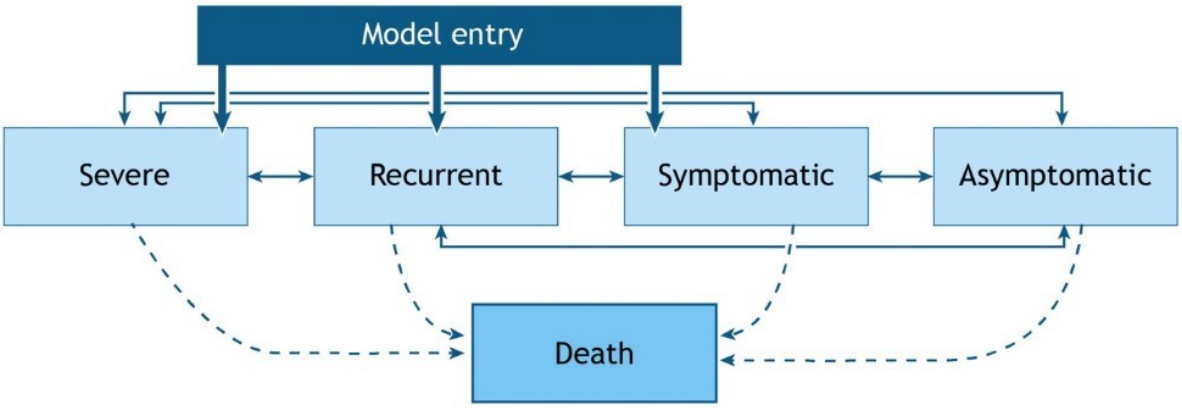
The ERG acknowledged there is limited published evidence available with respect to the classification of AHP disease severity. However, the decision to rely upon a single study may not be considered robust, particularly as Neeleman et al[4] was a non UK based study (The

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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