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NICE National Institute for Health and Care Excellence

Givosiran for treating acute hepatic porphyria [ID1549]

2nd Evaluation meeting – Chair's presentation

ERG: PenTAG

Technical team: Fatima Chunara, Sally Doss, Jasdeep Hayre

Chair: Peter Jackson

Company: Alnylam Pharmaceuticals

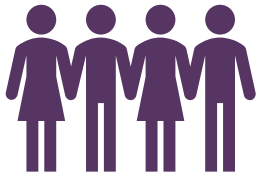
15th September 2021

Givosiran (Givlaari, Alnylam Pharmaceuticals)

Marketing authorisation	Treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older (MA received 2 March 2020)
Mechanism of action	Small interfering ribonucleic acid (siRNA) targeting delta aminolevulinic acid synthase 1 (ALAS1) messenger ribonucleic acid (mRNA) blocking production of the enzyme ALAS1 is an enzyme early in the haem pathway
Administration	**Subcutaneous injection once a month** (2.5 mg/kg)
Price	£41,884.43 per 189 mg/vial If the technology is approved it will be provided to the NHS with a confidential discount (simple PAS)

Disease Background

Acute hepatic porphyria (AHP) prevalence



- Rare inherited metabolic disorder
- Prevalence of symptomatic acute intermittent porphyria (the most common type) is ~5.4 per million in Europe (about 300 people in England)
- 10% of people experience recurrent acute porphyria attacks (at least 4 in 12 months)
  - Currently 27 people are treated for recurrent attacks in the UK
  - 1 to 3 people starting treatment every year; similar number stop treatment
- Most people are diagnosed in their 20's or 30's; predominantly female

Causes

- Gene mutations that lead to defective enzymes in the haem pathway
- Build up of porphyrin precursors in the liver and other tissues
  - High levels of porphobilinogen (PBG), aminolevulinic acid (ALA), porphyrin

4 types of acute porphyria (different genes in haem pathway mutated):

- Aminolevulinate dehydrase porphyria (ADP)
- Acute intermittent porphyria (AIP) – most common type; most people with recurrent attacks have AIP; highest symptom burden
- Hereditary coproporphyria (HCP)
- Variegate porphyria (VP)

Disease background: chronic symptoms

Treatment centres

National Acute Porphyria Service (NAPS) provides acute care support and clinical advice for people with:

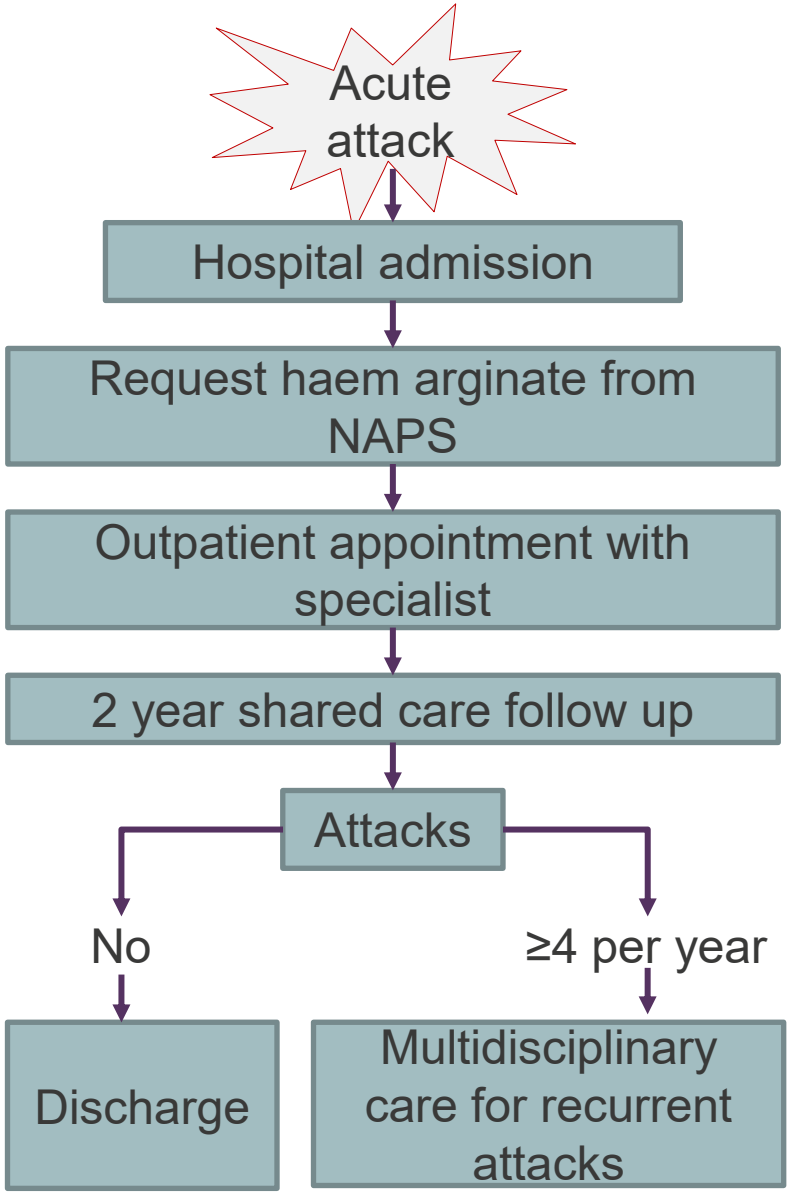
- Isolated acute attacks requiring haem arginate treatment
- Recurrent acute attacks

NAPS includes 2 National Acute Porphyria Centres (NAPCs) and outreach services provided in 2 Regional Porphyria Centres

Current treatments for recurrent attack

UK clinical guidelines by the British and Irish Porphyria Network (updated 2017) treatments may include:

- Prophylactic haem arginate intravenous infusion – 2 to 4 a month **(outside of marketing authorisation)**
- Avoidance of known triggers
- Gonadotropin analogues
- Liver transplant



ECM1 summary (1/2)

Population	Adults and young people aged 12 years or older with **recurrent severe** attacks of AHP *(narrower than marketing authorisation which includes adults and young people aged 12 years or older with AHP)*
Subgroups	Not included because of low numbers Evidence is mainly from people with acute intermittent porphyria (AIP)
Comparators	Best supportive care **Not included** in analysis were: • prophylactic intravenous haem (haem arginate) • GnRH analogues
Outcomes	

Scope	Submission	Model
Numbers of acute attacks	Yes	Yes
Porphyrin precursor concentrations in urine	Yes	No
Neurological impairment	No – considered major omission by ERG	
Autonomic function	No	No
Mortality	Yes	Yes
AE of treatment	Yes	Yes
HRQoL (for patients and carers)	Yes	Yes

ECM1 summary (2/2)

Clinical trial	ENVISION phase 3 randomised, double-blind, placebo-controlled with 30-month open-label extension (N=94) Phase I/II trial dose finding (N=17)
Key results	Annualised attack rate at 6 months (ENVISION): • Givosiran: 3.2 (95% CI 2.25 to 4.59) • Comparator: 12.5 (95% CI 9.35 to 16.76)
Model	Markov model; 5 health states asymptomatic, symptomatic, recurrent, severe and death
Company ICER versus BSC	£[redacted] per QALY gained (PAS included)(ERG corrected model)
Company incremental QALYs versus BSC	9.32
Committee preferred ICER versus BSC	£[redacted] per QALY gained (includes all committee preferences*)
Technical team incremental QALYs versus BSC	8.98

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BSC: best supportive care; ICER: incremental cost effectiveness ratio; QALY: Quality adjusted life years
* UK cohort data for menopause onset distribution and health state utilities based on RRMS

ECD recommendation

The committee was **minded not to recommend** givosiran as an option for treating acute hepatic porphyria in people 12 years and older.

Further information requested from the company for the 2nd ECM:

- A revised clinical and cost-effectiveness analysis comparing givosiran with prophylactic haem arginate and including the committee's preferred assumptions
- An exploratory analysis of how the starting age for treatment affects cost effectiveness
- An exploratory analysis of how the number of people stopping treatment at menopause in both arms of the clinical trial affects cost effectiveness.

Committee preferences at ECM1

Issue	Committee preference	Incorporated by company?
Comparator	Prophylactic haem arginate	Yes
Long-term effectiveness of givosiran	Allowing people to move between health states in the first 18 months after which they remain in the same health state in the givosiran arm	No: based on latest data*
Long-term effectiveness of BSC	Allowing people to move between health states in the first 6 months after which they remain in the same health state in the best supportive care arm	Yes
Time on treatment extrapolation	Using the log-logistic model to extrapolate time on treatment	Yes
Time on treatment duration for women	Continuing treatment until menopause for most women and throughout the time horizon of the model for men and some women	Yes
Quality of life data	Using utilities from relapsing–remitting multiple sclerosis	No: original approach kept
Opioid dependency	Including the costs of opioid dependency	Yes

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BSC: best supportive care

*Based on latest OLE data, transitions extrapolated to 3-years (recycle of last observed probabilities up to year 3, then freeze)

ECD consultation responses

Consultation comments received from

- The British Porphyria Association
- Global Porphyria Advocacy Coalition
- International Porphyria Patient Network
- National Acute Porphyria Services at Cardiff and Vale University Hospital and King's College Hospital

Company response

- The company submitted additional evidence and a new economic analysis against a comparator of prophylactic haem arginate

Summary of consultation comments (1)

High unmet need, limited effectiveness and acceptability of current treatments (1/2)	
Gonadorelin analogues	• Rarely used in the UK • Not suitable for males • Limited efficacy in a minority of female patients in whom recurrent attacks are clearly premenstrual
Liver transplantation	• Last resort when other therapies are no longer effective or when acute attacks are associated with recurrent life threating complications • Associated with a new set of health problems: for example, many people also develop impaired renal function, which then requires a combined liver and kidney transplant with additional risks and complications

Summary of consultation comments (2)

High unmet need, limited effectiveness and acceptability of current treatments (2/2)

Haem arginate infusions 1 to 4 times per month is the main management strategy for severe recurrent attacks but has no evidence base and limited benefit

Prophylactic haem arginate has some effect on reducing attack frequency but people remain very unwell:

- Disabling pain, other chronic symptoms, breakthrough attacks (requiring extra infusions) and hospital admissions
- Highly dependent on haem arginate and on maintaining central venous access
- Delays in their regular treatment can result in life threatening attacks

Comparators

- The opinion of clinical experts should be given more weight regarding this
- There is no clear distinction between prophylactic haem arginate and haem arginate to treat an acute attack in people with recurrent severe attacks
- Haem arginate was used in the ENVISION trial to treat acute attacks if deemed necessary by the treating physician

"…A young patient with acute intermittent porphyria whose infusion was delayed for two days had a very severe attack complicated by paralysis and respiratory arrest. This delay occurred because of difficulties with venous access, which is a particular problem associated with frequent haem arginate infusions."

Summary of consultation comments (3)

Age at model entry

- Unlikely that the majority of people will need to continue givosiran until the menopause
- People who start givosiran treatment early are likely to need only short periods of treatment (e.g. a few years)
- Age of diagnosis of acute porphyria is often in mid-20s
- Age at which recurrent attacks are more likely to start is between 30s and 40s
- Although anyone newly diagnosed might become eligible to receive givosiran if they started recurrent attacks, **this is unlikely to be until their 30s or 40s.**

Stopping treatment / length of treatment

- Research suggests that people with shorter duration of recurrent attacks:
  - Respond more quickly and completely
  - Do not relapse when givosiran is stopped
  - Can be offered a treatment break after a short period of treatment with givosiran
- However, people with established recurrent attacks for many years may require a longer spell of treatment before the biochemistry reduces to nearer normal levels – even if attack symptoms stop rapidly. These people might need longer periods of treatment

Summary of consultation comments (4)

Quality of life	
EQ-5D issues	• EQ-5D does not capture extent of givosiran benefits • Not validated for AHP (sensitivity to disease characteristics is unknown) • Measures present day QoL but AHP is characterised by intermittent symptoms • HST committee has previously accepted that EQ-5D is not suitable for capturing intermittent symptoms (e.g. HST13, volanesorsen)
QoL data	In absence of strong data and with RRMS utilities having similarities and differences, the committee should note: 1. **Gill et al. 2021*:** demonstrates burden of illness with AHP is high across all patients, regardless of frequency of attacks, and AHP negatively affects patients and caregivers alike 2. **Qualitative testimonials** from people experiencing recurrent attacks 3. Data from people who were able to **directly compare life on haem arginate and life on treatment with givosiran**. Haem arginate has been noted by patients to be an effective treatment that stops them from dying, but it does not provide the immense improvements to every aspect of a patient's life that givosiran does.

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*Considered in its unpublished format by the ERG in their original report

Summary of consultation comments (5)

Use of givosiran	
Starting givosiran at diagnosis of recurrent attacks	• Fewer chronic symptoms and co-morbidities • Rapid effect on biochemistry and symptoms • Expected to respond better than people who switch to givosiran after being managed with haem arginate for many years
Tachyphylaxis	• Not been seen in people treated with givosiran • Response improves over time, with gradually improving urine biochemistry (falling urine porphobilinogen concentrations) and fewer chronic symptoms.
Liver transplants	• Transplants are performed when haem arginate is no longer an option. This cures AHP but is associated with accompanying lifelong adverse consequences, symptoms of different nature and health risks • Givosiran could prevent these adverse effects in people with AHP while at the same time saving valuable donor organs for other groups of patients
Dosing	• Some people can tolerate less than monthly dosing

Updated ENVISION-OLE data

ENVISION-OLE: updated data

- Company provided updated data from the ENVISION-OLE study (not used to inform the revised economic analysis post-ECD [given time constraints*])
- [redacted]
- [redacted]

	AAR	Placebo/Givosiran (N=46)	Givosiran/Givosiran (N=48)	All Givosiran (N=94)
Historical	Month 18 (OLE)			
	n	45	48	93
	Median (Q1, Q3)	1.62 (0, 2.94)	0.58 (0, 3.24)	0.72 (0, 3.13)
	Mean (SEM)	2.44 (0.49)	2.54 (0.62)	2.50 (0.42)
New	Month 36 (OLE)			
	n	[redacted]	[redacted]	[redacted]
	Median (Q1, Q3)	[redacted]	[redacted]	[redacted]
	Mean (SEM)	[redacted]	[redacted]	[redacted]

ERG: overall effect of givosiran on AAR is likely to be clinically meaningful to people with AHP

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*Full finalisation and quality control of all outputs are expected to be completed on [redacted]

AAR: annualised attack rate; AHP: acute hepatic porphyria; SEM: standard error of mean

ENVISION-OLE: updated data

Attack rate in the ENVISION trial and open-label extension

ENVISION-OLE: updated safety data

[redacted]

Summary risk of adverse events between 18- and 36- months

N (%) patients with ≥1:	18 months	36 months
AE	[redacted]	[redacted]
Study drug–related AE	[redacted]	[redacted]
SAE	[redacted]	[redacted]
Study drug–related SAE	[redacted]	[redacted]
Severe AE	[redacted]	[redacted]
Study drug–related severe AE	[redacted]	[redacted]
AE leading to discontinuation	[redacted]	[redacted]
Study drug–related AE leading to discontinuation	[redacted]	[redacted]
Death	[redacted]	[redacted]

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PY: patient-year

Company post-ECM1 approach

Summary of company post-ECM1 approach

	Company base-case	ERG	Impact
Comparator	Prophylactic haem arginate	Considered appropriate	
Long-term effectiveness of givosiran	Based on latest OLE data, transitions extrapolated to 3-years (recycle of last observed probabilities up to year 3, then freeze)	Considered appropriate	
Chronic costs	Based on updated literature search	Considered acceptable	
Utilities	Maintain original approach	RRMS utilities	
Menopause onset	Based on distribution of age from Finnish study: Greer et al. (2003)	UK Women's Cohort study	

New company scenarios		Impact
Starting age	Starting age at 37	
ToT assumption	% of asymptomatic female cohort discontinuing post-menopause reduced by 10%	

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Model driver **Unknown impact** **Small impact**

RRMS: relapsed-remitting multiple sclerosis; open-label extension; ToT: time on treatment

Prophylactic haem arginate effectiveness

Data sources: Marsden et al. (2015): clinical benefit seen in 50% to 70% of people (clinical expert: 70% more probable) and Neeleman et al. (2018): 51.3% AAR reduction

Company approach and rationale	
Base case: 36%	• 70% of people benefit from 51% AAR reduction • **Considered an overestimate**: only considers reduction in attack frequency (and not other symptoms of AHP*) • Clinical expert: % achieving symptomatic improvement would be substantially lower than 70%
Scenario: 26%	• 50% of people benefit from 51% AAR reduction
Scenario: 51%	• 100% on prophylactic haem arginate benefit from 51% AAR reduction • **Considered clinically implausible**: implies effectiveness is approaching that of givosiran (conflicts with clinical opinion)
Scenario: 10%	• To model the minimum average incremental benefit expected

ERG

- Not convinced by company's interpretation that 51.3% AAR reduction from Neeleman et al. is *conditional* on treatment response (AAR could be influenced by a number of factors that do not relate to treatment response)
- Some basis to consider the scenario of an absolute AAR reduction of 51% as plausible as the base-case estimate

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AAR: annualised attack rate
*Such as chronic pain, neurological dysfunction and psychiatric symptoms

Prophylactic haem arginate: time to maximum effect and treatment waning

Time to maximum effect + time over which the effect is sustained (amortisation period)*	
Background	• Median duration: 4.2 years (Marsden et al.) to 6.5 years (Neeleman et al.) • Clinical input: prophylaxis would reach a maximum in first year of treatment and then plateau out to approximately 5 years before starting to wane
Company approach	• Base-case: 5 years • Range considered reasonable: 4 years to 7 years • Scenarios: 18 months, 3, 4, 6 and 7 years
Treatment waning	
Background	• Prophylactic haem arginate is associated with tachyphylaxis • Clinical input: efficacy declines over time, such that the acute attack rate gradually increases
Company approach	• Base-case: 23 years** • Scenarios: no waning, 3-years, 7-years (max. length of amortisation period)

The company acknowledge the uncertainty surrounding the long-term effectiveness of prophylactic haem arginate and provided 2-way and 3-way threshold analyses to test uncertainty with respect to AAR reduction, amortisation and waning of treatment effect.

*As defined by the company. In practice within the model, this is the time at which the state distribution of patients peaks in terms of utility benefits for distribution of patients by health state

**Corresponds to the observation period over which Schmitt et al. (2018) reported an increase in recurrent AIP patients due to hemin prophylaxis use

Scenario analyses: starting age and menopause assumptions

Starting age

- **Base-case assumption:** 42-years
- **Scenario analysis: 37-years.** This is:
  - Similar to (but younger than) the lower bound of the 95% confidence interval for age at baseline in the ENVISION EU populations (37.9 years)
  - Younger than the median age at baseline in the EXPLORE natural history study (38 years)
- Concordance of evidence from ENVISION and EXPLORE supports 37 years being the lowest plausible starting age for a prevalent cohort of these patients

Time on treatment – menopause assumption

- Uncertain whether all asymptomatic female patients would discontinue treatment upon menopause onset
- **Base-case assumption:** all females discontinue treatment at menopause
- **Scenario analysis:** percentage of asymptomatic female cohort discontinuing post-menopause reduced by 10% (i.e. 90% of these people went off treatment)

Issues for discussion

Issue 1: Approach to utilities

Background	Company approach	Committee preference
	Utility decrements due to chronic conditions calculated based on literature	ERG approach: RRMS utility values as best available proxy Rationale: company approach of summing the effect of single chronic symptoms is flawed

Company post-ECM1 approach: original base-case maintained

- RRMS utilities cannot be expected to capture the HRQoL burden of AHP
- Qualitative research with AHP patients suggests that the main drivers of HRQoL impairment are chronic conditions such as chronic pain, neurologic symptoms, and psychiatric symptoms.
- Disutilities of AHP health states are unlikely to be similar to disutility of patients in RRMS stages because chronic symptoms of AHP are substantially different from those in RRMS

Company approach

State	Utility decrement	SE
Asymptomatic	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]
Severe	[redacted]	[redacted]

ERG approach

State	Utility values
Asymptomatic	0.763
Symptomatic	0.553
Recurrent	0.719
Severe	0.438

Which approach to utilities is preferred?

AHP: acute hepatic porphyria; HRQoL: health-related quality of life; RRMS: relapsed-remitting multiple sclerosis

Issue 2: menopause onset data source

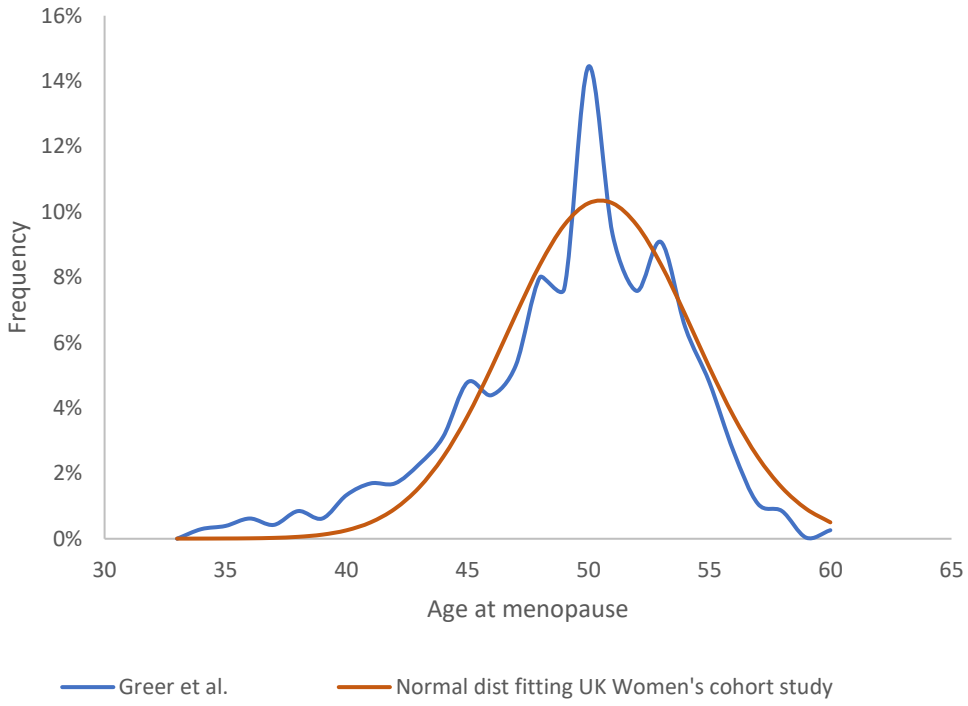
ECM1: company preference	ECM1: committee preference
Finnish cohort study (Greer et al)	UK Women's cohort study

Company ECM2: maintains preference for Greer et al. Scenario analysis with Women's Cohort Study also presented.

ERG: maintains preference for UK Women's cohort study (more generalisable to UK)

- Mean age (50.5 years) is similar between sources but there is considerable difference in distributions (bell curve used for UK Women's cohort study, irregular (but informed by data) distribution with Finnish study
- Per cycle probability of menopause onset might be different between Finnish and UK cohort

Scenario analysis using Greer al. data



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Which data source for menopause onset is preferred?

Additional areas of uncertainty

Additional areas of uncertainty that cannot be resolved. Committee should be aware of these when making its recommendations

Issue	Summary of ERG comments
Updated clinical efficacy data	Updated data from ENVISION OLE: • Was limited to AAR and graphical representations of ALA and PBG levels • Did not include a breakdown of AAR according to resource need • Did not include subgroup data*

Updated safety data	• Nature of drug-related serious and severe AEs not reported
	  • [redacted]
	  • [redacted]
	  • [redacted]
	  • [redacted]
	• Data suggest that:
	  • [redacted]
	  • [redacted]
	  • ERG opinion: Givosiran should initially be administered in a specialist centre, and may benefit from proposals to introduce breaks in treatment (although the ERG note that the clinical efficacy of this approach has not been evaluated).

AAR: annualised attack rate; ALA: aminolaevulinic acid; PBG: porphobilinogen [redacted]

Cost-effectiveness results vs. prophylactic haem arginate – PAS included

	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	
Company	Givosiran vs. hemin prophylaxis (base-case)	[redacted]	8.76	[redacted]	>100,000
	Starting age = 37 years	[redacted]	9.34	[redacted]	>100,000
	10% Asymptomatic women continue treatment after menopause onset	[redacted]	8.76	[redacted]	>100,000
	Time of menopause: UK Women's Cohort Study	[redacted]	8.76	[redacted]	>100,000
	Health-state utilities based on RRMS proxy values (Hawton et al. 2016)	[redacted]	7.85	[redacted]	>100,000
ERG	Company base case with UK Women's Cohort time of menopause + RRMS utilities	[redacted]	7.85	[redacted]	>100,000
	Company base-case + starting age = 30 years	[redacted]	10.13	[redacted]	>100,000

NICE RRMS: relapsed-remitting multiple sclerosis

Cost-effectiveness results vs. BSC – PAS included

	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	
Company	Givosiran vs. BSC	[redacted]	9.26	[redacted]	>100,000
Company	Starting age = 37 years	[redacted]	9.85	[redacted]	>100,000
Company	10% Asymptomatic women continue treatment after menopause onset	[redacted]	9.26	[redacted]	>100,000
Company	Time of menopause: UK Women's Cohort Study	[redacted]	9.26	[redacted]	>100,000
Company	Health-state utilities based on RRMS proxy values (Hawton et al. 2016)	[redacted]	8.98	[redacted]	>100,000
ERG	Company base case with UK Women's Cohort time of menopause + RRMS utilities	[redacted]	8.98	[redacted]	>100,000
ERG	Company base-case + starting age = 30 years	[redacted]	10.66	[redacted]	>100,000

NICE BSC: best standard care; RRMS: relapsed-remitting multiple sclerosis

Threshold analyses

In addition to the standard cost-effectiveness analysis, the company also conducted threshold analyses:

1. **Two-way threshold analysis (AAR reduction x time to maximum effect + time of sustained effect [*amortisation period*])**
   - To explore the impact on the ICER of varying AAR reduction and amortisation period of prophylactic haem arginate, holding waning of effect for prophylactic haem arginate at the base case value of 23-years

2. **Three-way threshold analysis (AAR reduction x time to maximum effect + time of sustained effect [amortisation period] x waning effectiveness)**
   - To explore the impact on the ICER of varying AAR reduction, amortisation period, and waning of effect for hemin prophylaxis

Two-way threshold analysis results

Company

Amortisation of effect	Hemin prophylaxis AAR reduction (total effect)			
	10%	26%	36%	51%
18 months	**********	**********	**********	**********
3 years	**********	**********	**********	**********
4 years	**********	**********	**********	**********
5 years	**********	**********	**********	**********
6 years	**********	**********	**********	**********
7 years	**********	**********	**********	**********

ERG

Amortisation of effect	Hemin prophylaxis AAR reduction (total effect)			
	10%	26%	36%	51%
18 months	**********	**********	**********	**********
3 years	**********	**********	**********	**********
4 years	**********	**********	**********	**********
5 years	**********	**********	**********	**********
6 years	**********	**********	**********	**********
7 years	**********	**********	**********	**********

Incorporates committee ECD preferences (inc. RRMS utilities) + extrapolation of givosiran efficacy to 3 years, updated costs for chronic conditions and per cycle probability of menopause onset based on mean age from UK Women's Cohort (fitting a normal distribution)

Three-way threshold analysis results – company (1/2)

AAR reduction	Waning of effect (time from when total effect is reached)				
	Amortisation of effect	No waning of effect	3 years	7 years	23 years
10%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]
26%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]

Three-way threshold analysis results – company (2/2)

AAR reduction	Waning of effect (time from when total effect is reached)				
	Amortisation of effect	No waning of effect	3 years	7 years	23 years
36%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]
51%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]

Three-way threshold analysis results – ERG (1/2)

AAR reduction	Waning of effect (time from when total effect is reached)				
	Amortisation of effect	No waning of effect	3 years	7 years	23 years
10%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]
26%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]

Incorporates committee ECD preferences (inc. RRMS utilities) + extrapolation of givosiran efficacy to 3 years, updated costs for chronic conditions and per cycle probability of menopause onset based on mean age from UK Women's Cohort (fitting a normal distribution)

Three-way threshold analysis results – ERG (2/2)

AAR reduction	Waning of effect (time from when total effect is reached)				
	Amortisation of effect	No waning of effect	3 years	7 years	23 years
36%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]
51%	18 months	[redacted]	[redacted]	[redacted]	[redacted]
	3 years	[redacted]	[redacted]	[redacted]	[redacted]
	4 years	[redacted]	[redacted]	[redacted]	[redacted]
	5 years	[redacted]	[redacted]	[redacted]	[redacted]
	6 years	[redacted]	[redacted]	[redacted]	[redacted]
	7 years	[redacted]	[redacted]	[redacted]	[redacted]

Incorporates committee ECD preferences (inc. RRMS utilities) + extrapolation of givosiran efficacy to 3 years, updated costs for chronic conditions and per cycle probability of menopause onset based on mean age from UK Women's Cohort (fitting a normal distribution)

QALY weighting

- ICER greater than £100,000 per QALY, judgements take account of the **magnitude of benefit** and the additional **QALY weight** that would be needed to support recommendation
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Number of additional QALYs (X)	Weighting	
Less than or equal to 10	1	
11 to 29	Between 1 and 3 (equal increments)	
Greater or equal to 30	3	
Scenario	**Incremental QALYs**	
Compared with prophylactic harm arginate	Discounted	Undiscounted
Company base case	8.76	16.43
ERG's preferred assumptions	7.85	15.63
Compared with BSC	Discounted	Undiscounted
Company base case	9.26	17.18
ERG's preferred assumptions	8.98	17.23

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

Back-up slides

Clinical evidence – haem arginate prophylaxis transition probabilities (1/2)

Number of patients transitioning between health states from baseline to time of achieving total AAR reduction with hemin prophylaxis

1. 10% relative reduction applied to best supportive care annualised attack rate

From / To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic	*	*	*	*	*
Symptomatic	*	*	*	*	
Recurrent	*	*		*	
Severe	*	*	*	*	*
Total	*	*			

2. 26% relative reduction applied to best supportive care annualised attack rate

From / To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic	*	*	*	*	*
Symptomatic	*	*	*	*	
Recurrent	*	*		*	
Severe	*	*	*	*	*
Total	*	*		*	

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AAR: annualised attack rate; BSC: best supportive care

Clinical evidence – haem arginate prophylaxis transition probabilities (2/2)

Number of patients transitioning between health states from baseline to time of achieving total AAR reduction with hemin prophylaxis

3. 36% relative reduction applied to best supportive care annualised attack rate

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

4. 51% relative reduction applied to best supportive care annualised attack rate

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

NICE

AAR: annualised attack rate