NICE National Institute for Health and Care Excellence

Givosiran for treating acute hepatic porphyria [ID1549]

1st Evaluation meeting – lead team presentation

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Company: Alnylam Pharmaceuticals

Committee meeting: 13 May 2021

Disease background

Disease background

Acute hepatic porphyria (AHP) is a 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 theses experience recurrent acute porphyria attacks (at least 4 in 12 months)
  - currently 26 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

Cause

- gene mutations that lead to defective enzymes in the haeme 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 – diagnosis

Diagnosis

- is often delayed and there is a risk of misdiagnosis because of the heterogeneity of disease presentation and symptoms (can be misdiagnosed for example as gastrointestinal disorders, neurological/neuropsychiatric disorders, gynaecological disorders and abdominal conditions requiring surgery
- urine test for porphobilinogen (PBG), aminolevulinic acid (ALA), and porphyrin levels
- genetic tests are available but not routinely used
  - help to confirm initial diagnosis
  - identify specific type

Disease background – attacks

- Too much porphyrin can damage nerve cells and provoke life-threatening acute attacks and long-term debilitation

Attack triggers

- some medications
- hormones (for example oestrogen and progesterone)
- alcohol
- smoking
- stress
- fasting

Symptoms

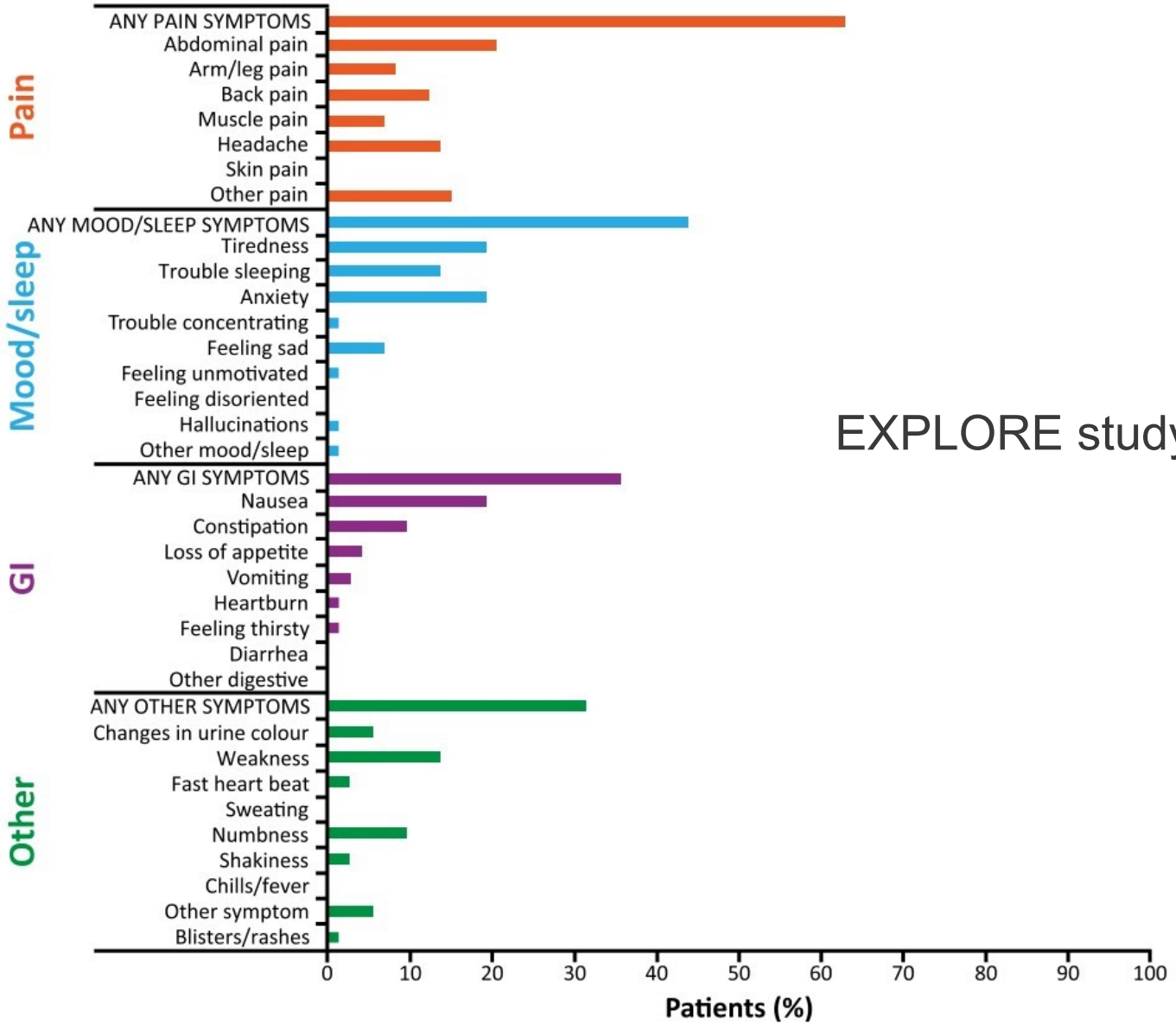
- severe acute and chronic pain
- weakness and fatigue
- long-term complications such as renal impairment
- hypertension and loss of venous access
- psychological impact and anxiety
- severe hyponatraemia (low sodium)
- seizures and arrhythmias

Attack severity

- Attack severity varies
  - mild attacks (mild pain, no vomiting, no paralysis, no hyponatraemia)
  - severe attacks require hospitalisation; recovery lasts 1 to 2 weeks

- Recurrent attacks are defined as 4 or more attacks in 12 months
- **Severe recurrent attacks are more common in people with AIP and women**

Disease background – chronic symptoms



EXPLORE study

Source: Gouya et al. 2020

Disease management and treatment pathway

Treatment centres

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

- people with isolated acute attacks requiring haem arginate treatment
- people with recurrent acute attacks

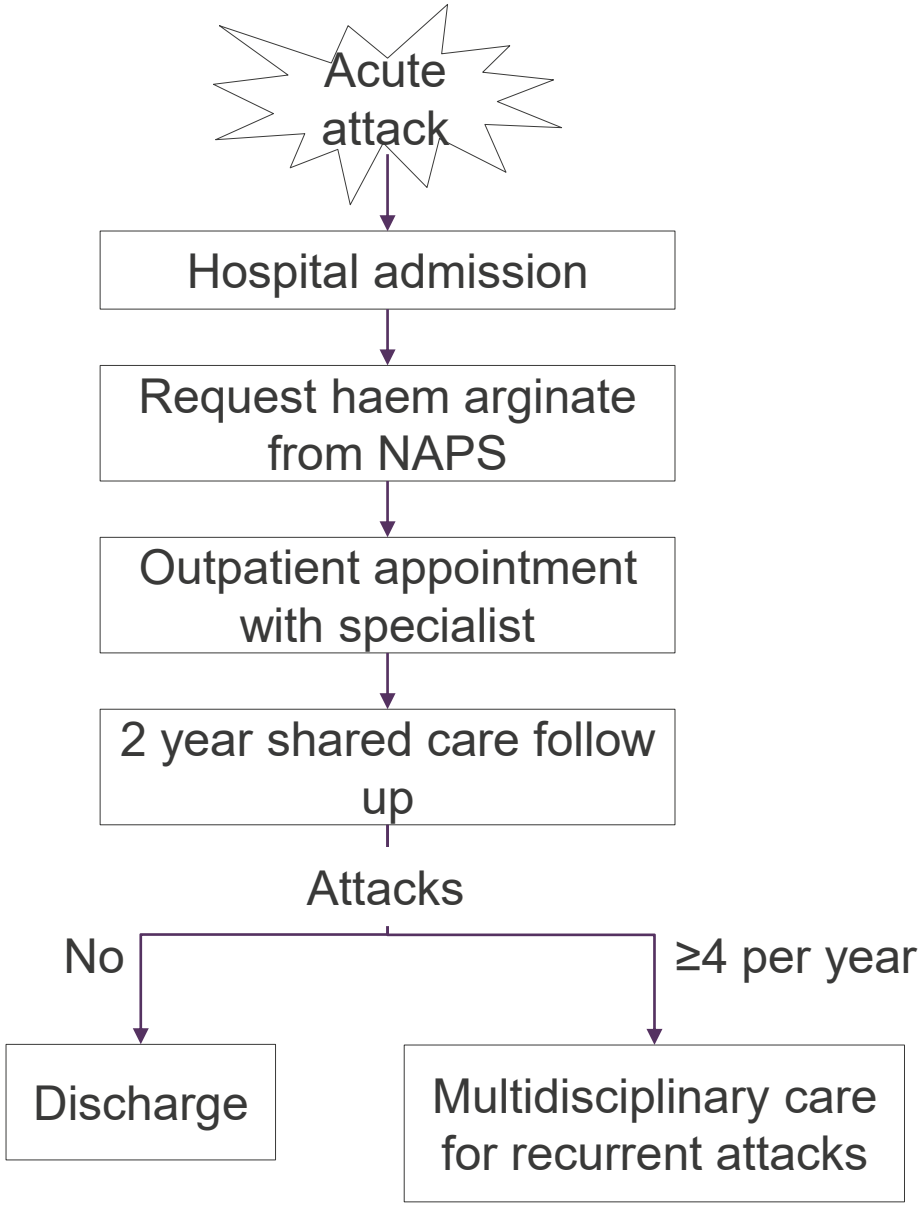
NAPS includes 2 National Acute Porphyria Centres (NAPCs) and outreach services provided in 2 Regional Porphyria Centres

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



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)

Patient and carer perspective

Patient and carer organisations submission

- **Submissions from 2 organisations – British Porphyria Association (BPA), Global Porphyria Advocacy Coalition (GPAC)**

Unmet need	• Current treatments do not prevent attacks or reduce chronic symptoms • Need for preventative treatments of acute attacks • Available prophylactic treatment is haem arginate which is used outside its marketing authorisation
High symptom burden	• Extreme pain, nausea, vomiting, constipation, hyponatremia, seizures, muscle weakness, paralysis

Quality of life	• Recurrent attacks are significant burden on the lives of patients and carers
	  • burden on physical and mental wellbeing
	  • burden on functioning, including work/study and family relationships
	• EQ-5D may not capture potential benefit of a reduction in acute attacks
	  • change in pain from acute attacks makes little difference compared with chronic pain
	  • changes in disability and psychological outcomes may not be sufficiently captured using EQ-5D

"Life is affected in every aspect, it's the little things like losing your independence, but also having to plan life so carefully. It's a relentless managing of everything …"

Patient and carer organisations submissions

The technology

Elimination ↓ or reduction ↓ of:

- ↓ acute attacks (no hospital admissions)
- ↓ acute pain
- ↓ ↓ chronic pain
- ↓ Fatigue and improved sleep patterns
- ↓ ↓ nausea and sickness

Improvement in:

- ↑ sleep patterns
- ↑ strength and general physical ability
- ↑ general wellness; ability to fully take part in daily activities such as personal care, housework, childcare, work and study

Prevention of:

- further decline in venous access, reduced reliance on portacaths and, in some cases, improvements to veins
- further iron overload with chance to treat it effectively to bring levels back to normal
- repeated episodes of paralysis associated with attacks, leading to neurological recovery

Administration is

- simple and less invasive compared with intravenous haem arginate
- less time-consuming, requires fewer ancillary and personnel resources (including considerably fewer nursing time/visits) and fewer physical and mental pressures

Patients are less reliant on carers and family members for personal and medical care

Clinical perspective

Clinical perspective

- **National Acute Porphyria Service at Cardiff and Vale University Health Board and Kings College Hospital**

Current treatment – main-stay is prophylactic haem arginate:

- about 95% of people with recurrent attacks get haem arginate
- use is outside of marketing authorisation; not investigated in clinical trials for prophylaxis
- 2 to 4 doses per month given intravenously at home
- reduces the frequency and severity of attacks
- requires access to vein via central venous catheter
- side effects - difficulty maintaining central venous access, iron overload that can cause chronic hepatic inflammation

Current treatment – gonadotropin analogues

- management of hormonally-driven attacks in women
- suppress ovulation, may be helpful for a short period of up to 2 years
- oestrogen deficiency side effects
- rarely used

Technology

- patient convenience; fewer administrations (1 per month); subcutaneous injection
- less healthcare resource
- treatment duration is currently unknown
- few reported side effects; mild

NHS England and Improvement

NHS England and Improvement perspective

- There are no national NHSE clinical commissioning policies for acute hepatic porphyria
- Commissioned service exists as part of the National Acute Porphyria Service (NAPS) since 2012/13. Patients are seen in outpatient clinics across the country
- The technology will not alter the current pathway of care
- Givosiran is available through clinical trials
- Technology would be administered through HSS under existing arrangements
- The technology would provide an important alternative treatment option. Administration is different to haem arginate (subcutaneous injection versus infusion); both can be delivered by homecare
- Healthcare resource might be reduced because of reduction in complications
- Initially delivery within the HSS using shared care protocols; longer term delivery via homecare
- No additional investment needed
- Access to the technology would significantly improve the quality of life of all patients with severe recurrent acute porphyria

Appraisal summary

Appraisal summary (1/2)

Best supportive care is the only comparator considered in the model
Population considered in appraisal is narrower than in MA

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 heme (heme 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

Appraisal 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	£XXXXXX per QALY gained (PAS included)(ERG corrected model)
Company incremental QALYs versus BSC	9.32
Technical team preferred ICER versus BSC	£XXXXXX per QALY gained (PAS included)
Technical team incremental QALYs versus BSC	8.20
BSC: best supportive care; ICER: incremental cost effectiveness ratio; QALY: Quality adjusted life years	

Clinical evidence – completed and ongoing studies

Study name and acronym	Study design	Intervention / Comparator	Population
ENVISION (Phase III) and ENVISION OLE	Randomised, double blind, placebo-controlled (6 months duration) Open-label extension (up to 18 months)	Givosiran 2.5 mg/kg versus placebo, Sodium Chloride 0.9% Best supportive care in both arms	N=46 (givosiran) N=43 (placebo) Men and women, ≥12 years; severe recurrent attacks (at least 2 attacks in the last 6 months requiring hospitalisation urgent healthcare visit or prophylactic IV heme at home)
Phase I/II	Randomised Dose finding 3 parts/cohorts (A, B, C)	Part C: givosiran versus placebo	Part C: N=13 (givosiran) N=4 (placebo). Men and women, ≥12 years; at least 2 attacks in the 6 months before the trial

Clinical evidence – Baseline characteristics in ENVISION

	ENVISION	
	Givosiran n=48	Placebo n=46
Age, mean (SD)	40.1 (12.1)	37.4 (10.5)
Female, n (%)	43 (90)	41 (89)
Years since diagnosis, mean (SD)	11.1 (11.2)	8.3 (8.5)
AHP type, n(%) AIP (HMBS) AIP (unidentified) HCP VP	 46 (96) 0 1 (2) 1 (2)	 43 (94) 2 (4) 0 1 (2)
Attacks in last 6 months, median (IQR)	8 (4 to 18)	7 (4 to 14)
Attacks in last 12 months, median (range)	–	–
Daily chronic symptoms between attacks, n (%)	23 (48)	26 (57)
Ever diagnosed with neuropathy, n (%)*	XX (XX)	XX (XX)
Prior hemin prophylaxis, n (%)	20 (42)	18 (39)
Opioids between attacks, n (%)	14 (29)	13 (28)
GnRH analogue use, n (%)*	4.3% across both arms	

Source: Balwani et al (2020) N Engl J Med 382:2289-2301

*source ERG report table 14

Clinical evidence – ENVISION trial effectiveness

	ENVISION (6 months)		ENVISION OLE (18 months)
	Placebo (n=43)	Givosiran (n=46)	Placebo/givosiran (n=43)
Acute attacks	12.5 (95% CI 9.35 to 16.76)	3.2 (95% CI 2.25 to 4.59)	
		Relative reduction: 74% (95% CI 59% to 84%)	82% (95% CI 75% to 87%)
Attacks requiring hospitalisation	3.21 (95% CI 1.98 to 5.20)	1.65 (95% CI 0.98 to 2.78)	0.94 (NR)
		Relative reduction: 49% 95% CI -4% to 75%	Relative reduction: 73% (95% CI 57% to 84%)
Attacks requiring urgent healthcare visit	7.53 (95% CI 5.13 to 11.05)	1.22 (95% CI 0.73 to 2.05)	1.56 (NR)
		Relative reduction: 84% (95% CI 69% to 91%)	83% (95% CI 75% to 89%)
Attacks requiring acute IV hemin administration	NR Total attacks: 32	NR Total attacks: 3	0.06
		NR	Relative reduction: 96% (95% CI 81% to 99%)

CI: confidence interval; NR nor reported; OLE: open label extension

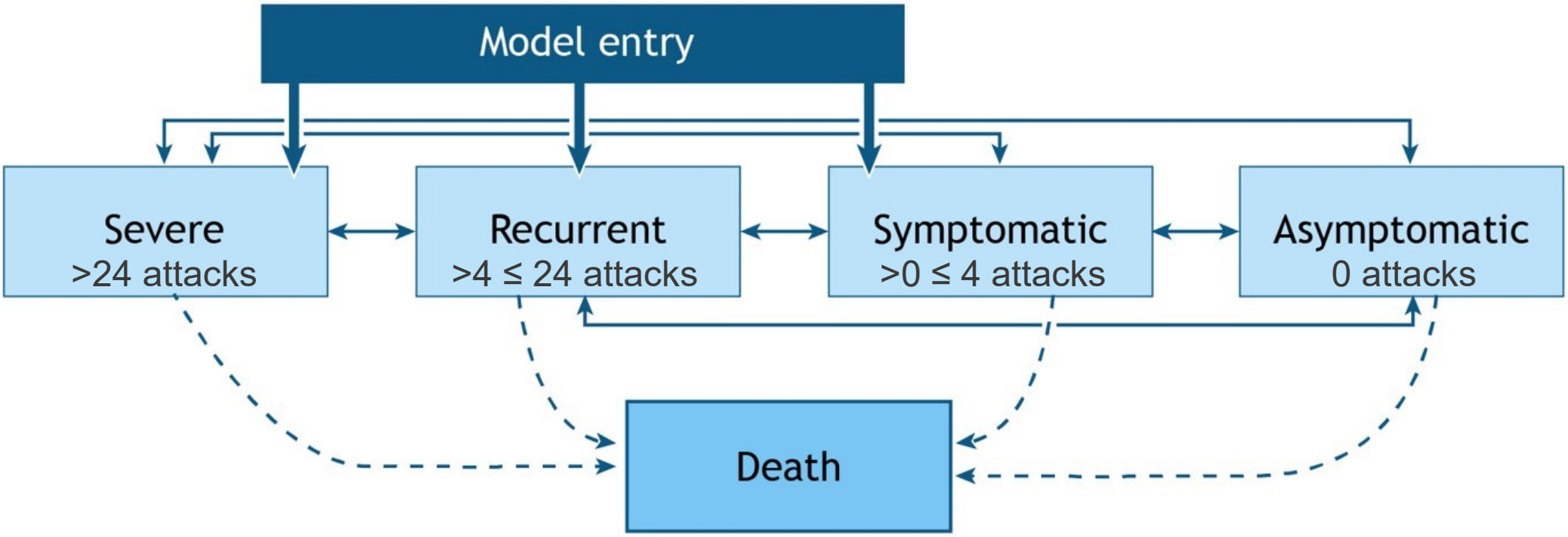
Clinical evidence – ENVISION trial quality of life

- ENVISIONS collected EQ-5D-5L data
  - Mapped to EQ-5D-3L

	ENVISION (6 months) Placebo (n=43)	Givosiran (n=46)
Least square mean change in visual analogue scale	2.8	6.8
	Treatment difference: 4.0 (-3.3, 11.4)	
Least square mean change in utility	-0.008	0.021
	Treatment difference: 0.03 (-0.03, 0.09)	

Health economics

Company model – Markov model



Patient characteristics	Modelled parameter
Starting age (years)	41.64
Weight (kg)	XXXX
Percentage of females	85.7%

Model input and model assumptions

- Model inputs are based on ENVISION, ENVISION OLE and natural history study

Assumptions	In key issues
Disease severity based on frequency of acute attacks and presence of chronic symptoms	No
No excess mortality due to AHP attack	No
Disutilities for (1) acute attacks (2) chronic health states	Yes (issue 4)
Average duration of acute attack is 7.3 days	No
Treatment of acute attacks: 80% hospital, 5% outpatient setting, 15% home setting	No
Transition probabilities in givosiran arm based on ENVISION OLE • data extrapolated to 5-years • after 5 years, cohort remains stable	Yes (issue 3)
Transition probabilities in BSC arm based on ENVISION • after 6 months, cohort remains stable	Yes (issue 3)
Following treatment interruption, transitions for best supportive care are applied	No
Mortality hazard ratio mortality is 1.3 versus general population	No
Caregiver disutilities based on caregiver HRQoL for multiple sclerosis	Yes (issue 4)
BSC no costs related to pharmacologic therapy or treatment administration	No

Key issues

Key issues

Issue	Impact
1 Lack of a comparison versus other prophylactic treatment options	
2 Generalisability of the ENVISION trial to NHS practice	
3 Long-term clinical effectiveness of givosiran and BSC	
4 Quality of life data and utility values used within the model	
5 Treatment discontinuation and time on treatment	
6 Patient baseline characteristics and other model assumptions	 

NICE  Model driver  Unknown impact  Small impact

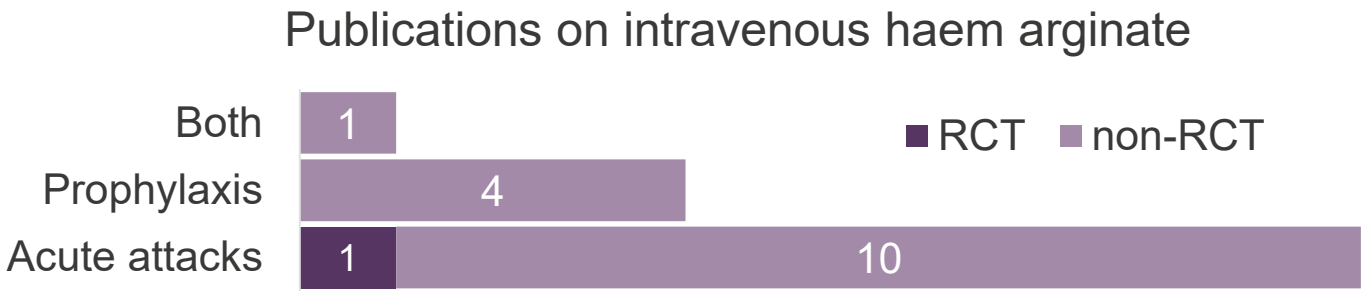
Issue 1: Comparison versus prophylactic treatments

Background

Current treatments	Used in clinical practice	Used in model
Best supportive care	Yes	Yes
Intravenous haem arginate	Outside MA	No
Gonadatrophin analogues	Outside MA	No
Liver transplant	Not routinely used; rare	No
MA: marketing authorisation		

Studies on effectiveness of comparators

- Best supportive care = comparator in ENVISION (defined by treating clinicians, included management of chronic symptoms and acute attacks)
- Intravenous haem arginate – no robust evidence for prophylaxis, no comparative evidence



- Gonadotropin analogues – high variability in NHS clinical practice (type, length, monitoring)

Issue 1: Comparison versus prophylactic treatments

ERG comments

- Comparators should reflect treatments used in clinical practice (even if used outside their marketing authorisation)
- Acknowledge limitation of data for intravenous haem and gonadotropin analogues
- Inclusion in model would increase uncertainty
- Agrees with company not to include but cautions that this doesn't represent clinical practice

Is best supportive care the most relevant comparator for the model?

Does the model adequately reflect current clinical practice?

Issue 2: Generalisability of ENVISION to NHS practice

Background

- ENVISION is main trial, included:
  - people with acute intermittent porphyria (AIP) (n=89); only 4 had other AHPs
  - older people; people with fewer chronic symptoms
- ENVISION was international trial; 4 people from Britain (4.3% of participants)
- ENVISION OLE included 2 doses; 1.25 mg/kg (n=37) and 2.5 mg/kg (n=56)

Issues

- ENVISION
  - might include more people with 'less severe' symptoms of AHP than seen in NHS clinical practice
  - best supportive care in other countries might be different than in NHS clinical practice
- ENVISION OLE
  - givosiran dose might differ from NHS clinical practice

ERG comments

- Unclear what factors affect disease prognosis, and efficacy of givosiran
- Aware that AHP is heterogeneous and smaller trials can't represent full target population
- Aware that baseline characteristics influence model outcomes (see Issue 6)

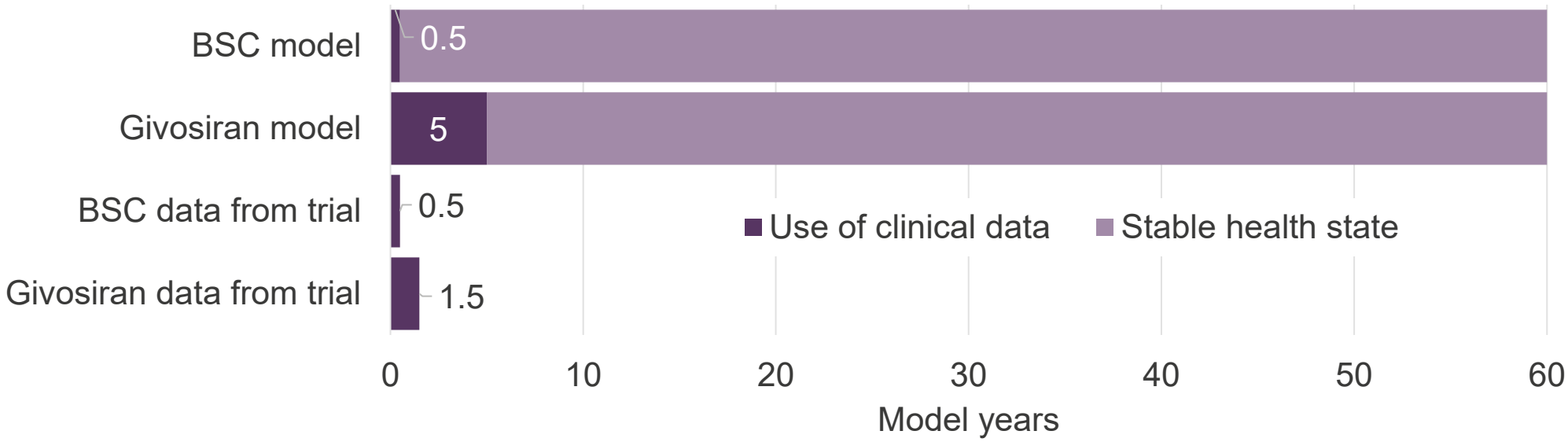
What patient characteristics affect treatment outcomes?

Are results from ENVISION generalisable to people seen in the NHS?

Issue 3: Long-term clinical effectiveness of givosiran and BSC

Background

- ENVISION OLE provides data up to 18 months for givosiran and 6 months for BSC
- Model uses data from ENVISION and OLE for transition probabilities and treatment effectiveness for up to 5 years



Issue 3: Long-term clinical effectiveness of givosiran and BSC

ERG comments

- Company's long-term effectiveness assumptions are uncertain
- Alternative effectiveness assumptions are valuable
- Transition probabilities and associated assumptions are key driver of the model
- Scenario analyses

Scenario	Data source	Stable health state from year	Impact on ICER
Base case – givo	*ENVISON + OLE*	*5*	
1a – givo	ENVISION + OLE	1.5	↑
1b – givo	ENVISION + OLE	3	↑
1c – givo	ENVISION	1.5	↑
Base case – BSC	*ENVISION*	*0.5*	
2 – BSC	ENVISION	1.5	↓

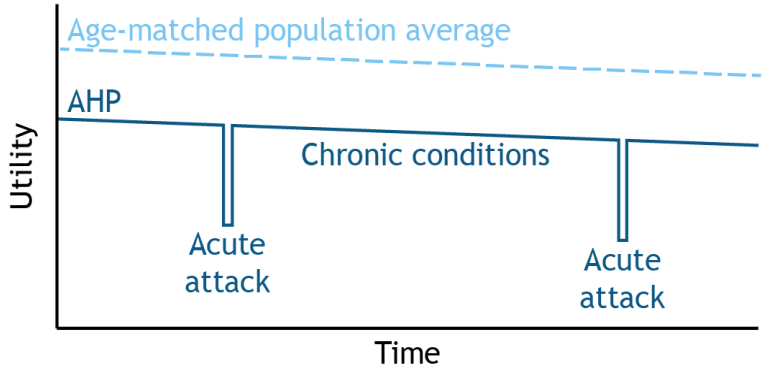
Are ENVISION and OLE the most appropriate data sources?

At what time point is AHP stable when treated with givosiran or BSC?

Issue 4: Quality of life data and utility values within the model

Background

- EQ-5D-5L data collected in the ENVISION, not used in model
- Model uses utility decrement estimates for:
  - chronic conditions from non-AHP sources
  - acute attack from AHP source other then ENVISION



State	Utility decrement	SE	Source
Acute attack	XXXXXX	XXXX	EXPLORE
Chronic symptoms/comorbidities			
Pain	-0.383		McDermott et al. (2006)
Neurological	-0.097		Sullivan et al. (2011)
Psychiatric	-0.272		Ara and Brazier (2011)
Asymptomatic	XXXXXX	XXXX	
Symptomatic	XXXXXX	XXXX	
Recurrent	XXXXXX	XXXX	
Severe	XXXXXX	XXXX	
Caregiver disutility by health state			
Asymptomatic	-0.002	0.053	Acaster et al. (2013) Multiple sclerosis study
Symptomatic	-0.045	0.057	
Recurrent	-0.142	0.062	
Severe	-0.160	0.055	

Issue 4: Quality of life data and utility values within the model

ERG comments

- Utility and disutility estimates are uncertain
- Acknowledges that chronic symptoms, such as chronic pain, comorbid health conditions, and neurological impairment influence HRQoL
- Reductions in attack rate may not alone lead to significant change in patients' HRQoL
- Provided scenario analyses

Scenario	Data source	Impact on ICER
Base case	*Utility decrement from published literature*	
4a	EQ-5D data ENVISION	↑
4b	EQ-5D data adjustment for recurrent and severe health state	↑
4c	Utility values for people with relapsing-remitting multiple sclerosis (chronic and progressive condition with relapse)	↔

Health state	Mean EQ-5D (6 months)	Mean EQ-5D (baseline)	RRMS
Asymptomatic	XXXXXX	XXXXXX	0.763
Symptomatic	XXXXXX	XXXXXX	0.719
Recurrent	XXXXXX	XXXXXX	0.596
Severe	XXXXXX	XXXXXX	0.438
*adjusted value, RRMS relapsing-remitting multiple sclerosis			

What is the most appropriate approach to estimate utility values?

Is it appropriate to use EQ-5D data from ENVISION in the model?

Is it appropriate to use utility values from people with RRMS appropriate as proxy?

Issue 5a: Time on treatment

Background – time on treatment

- Short follow up in trial (up to 18 months)
- Company fitted parametric models on time on treatment Kaplan-Meier curves from ENVISION and ENVISION OLE
- Company used log-logistic curve to extrapolate

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

Issue 5a: Time on treatment

ERG comments – time on treatment

- uncertainty surrounding how givosiran will be used in clinical practice and therefore how long patients will remain on treatment
- Scenario analyses

Scenario	Parametric fit	Impact on ICER
Base case	*Log-logistic*	
3a	Piece-wise (Kaplan Meier and log-normal)	↑
3b	Gompertz	↑

Is a piece-wise curve or the log-logistic curve the most appropriate approach to fit time on treatment data?

Issue 5b: Treatment discontinuation

Background

- Uncertainty how givosiran will be used in clinical practice
  - Length of time patients will get treatment
  - Whether and when treatment will restart after treatment break

ERG comments

- Mixed responses from clinical experts
- Likely to be substantial individual variation
- There might be stop start criteria
- Lifelong treatment might be plausible if patient receiving treatment as long as they experiencing clinical benefit
- Any analysis around treatment discontinuation is highly exploratory and subject to major limitations

How would givosiran be used in clinical practice?

Is lifelong treatment with givosiran plausible?

Issue 6: Baseline characteristics and model assumptions (1)

Starting age of model cohort

- **Company** used a starting age of 41.64 years
- **Trial**
  - average age at screening was 38.8 ± 11.4 years
  - average age of diagnosis was approximately 30 years

- **ERG's** clinical experts suggest that most plausible starting age is below 41.64 years
  - Used starting age of 30 years

Is 41.64 years a plausible starting age for people who get givosiran?

Issue 6: Baseline characteristics and model assumptions (2)

Costs of opioid dependency

- **Company** included costs of opioid dependency for recurrent and severe health states
  - Cost were based on published literature

- **ERG** highlights that there is no robust data on givosiran and opioid dependency
  - Concerns around appropriateness and generalisability of sources for costs of opioid dependency
  - Excludes these costs

Is it appropriate to include cost of opioid dependency for recurrent and severe health states?

Issue 6: Baseline characteristics and model assumptions (3)

Proportion of patients experiencing chronic symptoms

- **Company**
  - used results from a natural history study (EXPLORE)
- **Trial**
  - chronic symptoms i.e. chronic pain, neurological and psychiatric symptoms not reported

- **ERG**
  - prevalence of chronic symptoms in people with AHP based on single study from the Netherland (Neeleman *at el.* 2018)
  - lack of robust UK data
  - Unit costs were largely dated (2008 to 2016) and derived from unconventional sources (for example The Guardian)

Are the company's sources for chronic symptoms and cost associated with chronic symptoms appropriate?

Issue 6: Baseline characteristics and model assumptions (4)

Menopause onset

- **Company**
  - Used data from Finish cohort study to estimate per cycle probability of menopause onset
  - Presented scenario analysis which used a normal distribution (fitting the mean and standard deviation age of menopause) from the UK Women's cohort study
  - Assumes all patients who are asymptomatic at menopause stop treatment

- **ERG**
  - Per cycle probability of menopause onset might be different between Finish and UK cohort
  - Prefers UK Women's cohort study
  - Acknowledged that majority of patients likely to discontinue at menopause onset
  - Assumed 10% of patients continue givosiran treatment after menopause onset

Cost effectiveness results – PAS included

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	
Company base case				
ERG corrected company base case	£XXXXXX	**9.32**	£XXXXXX	>100,000
Scenario 1: Givosiran transition probabilities based on OLE data (frozen at 18 months)	£XXXXXX	**8.36**	£XXXXXX	>100,000
Scenario 3: ToT extrapolated using piecewise approach (KM curve + log Normal cure)	£XXXXXX	**9.32**	£XXXXXX	>100,000
Scenario 4c: AHP utilities based on RRMS values in Hawton et al[1]	£XXXXXX	**9.02**	£XXXXXX	>100,000
Scenario 6: The per cycle probability of menopause onset based on mean age from UK Women's cohort study[2] (fitting a normal distribution).	£XXXXXX	**9.31**	£XXXXXX	>100,000
Scenario 8: Opioid addiction costs removed	£XXXXXX	**9.32**	£XXXXXX	>100,000
ERG's preferred assumptions	£XXXXXX	**8.20**	£XXXXXX	>200,000

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	
	Adjusted	Unadjusted
Company base case		
ERG corrected company base case	9.32	17.28
ERG's preferred assumptions	8.20	15.6

Innovation and equality considerations

- Acute hepatic porphyria predominantly affects young women
- Pregnant women
  - No data available
- Haem arginate and liver transplant may not be acceptable for certain patient groups
- Travel to porphyria centres for treatment may be difficult for those with disabilities or limited financial resources

Are there any equality issues to consider in particular, in applying the marketing authorisation of givosiran and access for people with protected characteristics?

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 the 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

Key issues

Issue	Impact
1 Lack of a comparison versus prophylactic treatment options	
2 Generalisability of the ENVISION trial to NHS practice	
3 Long-term clinical effectiveness of givosiran and BSC	
4 Quality of life data and utility values used within the model	
5 Treatment discontinuation and time on treatment	
6 Patient baseline characteristics and other model assumptions