Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende givosiran til behandling af akut hepatisk porfyri

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. givosiran
2. Forhandlingsnotat fra Amgros vedr. givosiran
3. Ansøgers endelige ansøgning vedr. givosiran

Medicinrådet

Response document for DMC

Company response to Draft Recommendation of the Medicines Council on givosiran for the treatment of acute hepatic porphyria

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Alnylam Sweden AB is thankful that the Danish Medicines Council (DMC) has been able to review our submission for GIVLAARI® (givosiran) for the treatment of acute hepatic porphyria (AHP), a rare, debilitating, and potentially life-threatening genetic disease. We note that key results of our base-case cost-effectiveness analysis (CEA) have been reported in the DMC's Draft Recommendation, including the high gain in quality-adjusted life-years (QALYs) for patients who receive givosiran in comparison with patients on best supportive care (BSC).

Alnylam believes that the company-submitted base-case CEA is an appropriate measure for decision-making. We look forward to collaborative discussions with the DMC with the goal of enabling Danish patients to have access to this innovative therapy, joining patients in other European countries where givosiran is already approved for reimbursement.

It is beyond the scope of this brief response to address the Draft Recommendation's conclusions point-by-point, so we have limited this response to the following two observations, namely:

- Givosiran fills an important therapeutic gap for patients with AHP in Denmark.
- The cost-effectiveness model presented by Alnylam is generalizable to Denmark.

1. Givosiran addresses a major unmet need for patients with AHP in Denmark

A positive recommendation for givosiran would address a major unmet need for patients with AHP in Denmark, as no other licensed therapies are available for this devastating disease. AHP is a serious chronic condition driven by overproduction of heme intermediates in the liver [1-5]. The disease is characterized by acute neurovisceral attacks in which patients experience excruciating abdominal pain and other debilitating symptoms, including nausea, vomiting, constipation, seizures, and neuropsychiatric symptoms [6]. The extent of the debilitation that AHP patients suffer during acute attacks is extreme, with patients describing the pain in terms such as "*not compatible with life*", "*not of this world",* and "*like being disemboweled, having a hot pan shoved into your intestines or into your abdomen while having your ribs filleted*" [7, 8]. Repeated attacks severely impair patients' health-related quality of life (HRQoL), social functioning, and ability to work [8, 9].

Most patients with recurrent attacks develop chronic conditions, such as chronic pain, neurological symptoms, psychiatric disorders, and hypertension [10]. At least some chronic conditions of AHP appear to be due to repeated autonomic and peripheral nerve damage during acute attacks [11]. Long-term complications include liver cancer and chronic kidney disease [12, 13], and may result from direct effects of elevated levels of toxic heme intermediates [14].

Before givosiran, patients lacked an approved, disease-modifying treatment for AHP, leaving them at risk for acute attacks and the ongoing accumulation of clinical, HRQoL, and economic burden [15]. Givosiran has demonstrated immense value as the only therapy that targets the underlying AHP disease process, thereby preventing attacks and addressing ongoing chronic pain [16]. Givosiran decreases levels of key toxic heme intermediates to near-normal levels [16, 17]. By reducing accumulation of these intermediates, givosiran significantly reduces or prevents the occurrence of porphyria-related attacks and also decreases other aspects of disease burden.

Over the 6-month double-blind period of the pivotal phase 3 randomized controlled trial (RCT) of givosiran, ENVISION, which enrolled patients with a history of repeated attacks, patients in the givosiran arm experienced a significant 73% mean reduction in annualized attack rate (AAR) relative to placebo [16]. Continuing improvement was demonstrated in the ENVISION open-label extension, during which all patients received givosiran: 86% of patients originally randomized to givosiran in the double-blind period and 92% of those originally in the placebo group were completely attack-free in the final 3 months of the 36-month treatment period [18]. These results affirm the urgency of providing patients with AHP in Denmark with access to givosiran, a high-value treatment for this devastating condition.

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2. Alnylam's cost-effectiveness model is generalizable to Denmark

The Draft Recommendation states that the DMC did not arrive at a single fair health-economic analysis as the basis for evaluating givosiran, suggesting that the CEA conducted by Alnylam contains uncertainty. Alnylam has invested considerable care to mitigate any uncertainties in our CEA, including extensive dialogue with other leading health technology assessment agencies, which found the analysis to be appropriate for decision-making. In addition, to help ensure generalizability of our CEA to patients with AHP in Denmark, many assumptions—including the proportion of asymptomatic women who stop treatment after menopause—were informed by clinical expert input from Denmark. We remain available to engage with the DMC to resolve any uncertainties.

In the Draft Recommendation, the DMC notes that there are very few patients who would be candidates for treatment with givosiran in Danish clinical practice, and concludes that this makes it difficult to assess whether the modelled patient population (which is based on the characteristics of patients in the ENVISION study) is comparable to the Danish patient population. In this regard, we wish to point out that ENVISION enrolled a high proportion of patients from Europe, including Nordic countries. Consequently, we are confident that the findings from ENVISION can be generalized to patients with AHP in Denmark.

The Draft Recommendation also expresses the belief that Danish patients with AHP have a lower AAR than observed in patients in the ENVISION trial. Alnylam would like to point out that with so few patients in Denmark, it is challenging to reach an accurate general conclusion about the severity of AHP in these patients. AHP has a variable and largely unpredictable disease course [2, 8, 19], such that a given patient who has few attacks one year may experience many the following year. Similarly, even one new (i.e., incident) patient in Denmark with a high AAR would represent a large increase in the overall attack burden in the country. In the face of such unpredictability in AAR over time in Denmark, we feel that the best approach is to base decisions on data from large, high-quality studies such as those we used in our CEA, namely ENVISION (N=94) [16]—the largest RCT ever conducted in AHP—and the long-term natural history study by Neeleman et al. (2018) (N=88) [13].

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3. References

1. Ramanujam, V.M. and K.E. Anderson, *Porphyria diagnostics - Part 1: A brief overview of the porphyrias.* Curr Protoc Hum Genet, 2015. **86**(1): p. 17.20.1-17.20.26.
2. Bissell, D.M. and B. Wang, *Acute hepatic porphyria.* J Clin Transl Hepatol, 2015. **3**(1): p. 17-26.
3. Wang, B., et al., *Acute hepatic porphyrias: review and recent progress.* Hepatol Commun, 2019. **3**(2): p. 193-206.
4. Laafi, J., et al., *Pro-oxidant effect of ALA is implicated in mitochondrial dysfunction of HepG2 cells.* Biochimie, 2014. **106**: p. 157-66.
5. Bissell, D.M., K.E. Anderson, and H.L. Bonkovsky, *Porphyria.* N Engl J Med, 2017. **377**(9): p. 862-872.
6. Anderson, K.E., et al., *Recommendations for the diagnosis and treatment of the acute porphyrias.* Ann Intern Med, 2005. **142**(6): p. 439-50.
7. American Porphyria Foundation, *The Voice of the Patient: Patient-Focused Drug Development Meeting - Acute Porphyrias*. 2017. p. 1-18.
8. Simon, A., et al., *Patient perspective on acute intermittent porphyria with frequent attacks: a disease with intermittent and chronic manifestations.* Patient, 2018. **11**(5): p. 527-537.
9. Gill, L., et al., *Burden of illness in acute hepatic porphyria (AHP): insights from patient and caregiver members of the British Porphyria Association. [Presented at the International Congress on Porphyrins and Porphyrias (ICPP) 2019, Milan, Italy, 8–11 September 2019]*. 2019.
10. Gouya, L., et al., *EXPLORE: a prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks.* Hepatology, 2020. **71**(5): p. 1546-1558.
11. Pischik, E. and R. Kauppinen, *An update of clinical management of acute intermittent porphyria.* Appl Clin Genet, 2015. **8**: p. 201-14.
12. Pallet, N., et al., *High prevalence of and potential mechanisms for chronic kidney disease in patients with acute intermittent porphyria.* Kidney Int, 2015. **88**(2): p. 386-95.
13. Neeleman, R.A., et al., *Medical and financial burden of acute intermittent porphyria.* J Inherit Metab Dis, 2018. **41**(5): p. 809-817.
14. Peoc'h, K., et al., *Hepatocellular carcinoma in acute hepatic porphyrias: A Damocles Sword.* Mol Genet Metab, 2019. **128**(3): p. 236-241.
15. Schmitt, C., et al., *Recurrent attacks of acute hepatic porphyria: major role of the chronic inflammatory response in the liver.* J Intern Med, 2018. **284**(1): p. 78-91.
16. Balwani, M., et al., *Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria.* N Engl J Med, 2020. **382**(24): p. 2289-2301.
17. Sardh, E., et al., *Phase 1 trial of an RNA interference therapy for acute intermittent porphyria.* N Engl J Med, 2019. **380**(6): p. 549-558.
18. Thapar, M., et al., *Efficacy and safety of givosiran in patients with acute hepatic porphyria: 36-month results of the phase 3 ENVISION randomised clinical trial [Presented at the International Liver Congress 2022, London, England, 22–26 June 2022].* J Hepatol, 2022. **77**(Suppl 1): p. S60-S61.
19. Naik, H., et al., *Experiences and concerns of patients with recurrent attacks of acute hepatic porphyria: A qualitative study.* Mol Genet Metab, 2016. **119**(3): p. 278-283.

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Medicinrådet

Response document for DMC

Factual accuracy and confidential information check of the
Draft Recommendation of the Medicines Council on givosiran for the treatment of acute hepatic porphyria

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1. Factual accuracy check

Description of problem	Description of proposed amendment	Justification for amendment
Section 1.4, page 18: "Hæmin tilføres dagligt i op til 4 døgn. [Haemin is given daily for up to 4 days.]" This sentence does not accurately reflect the approved dosing regimen for hemin according to the SmPC: "The recommended daily dose is 3 mg/kg once daily for four days … the course of the treatment may be repeated under strict biochemical surveillance if there is inadequate response after the first course of treatment." [1]	In the quoted sentence, Alnylam recommends clarifying that hemin is given daily for four days, and this course may be repeated if there is inadequate response after the first course of treatment.	The suggested edit will avoid an inaccurate characterization of the approved dosing for hemin.
Section 2.3.1, page 26: "Dog bemærker Medicinrådet, at en del af patientpopulationen reelt har oplevet færre årlige anfald end de 4, som er angivet som inklusionskriterie. I EPAR'en angives, at minimumsværdierne af den historiske AAR er 0 [4], og der er således inkluderet patienter, der ikke har oplevet anfald i 6 mdr. forud for studiestart. [However, the Medical Council notes that part of the patient population actually experienced fewer annual seizures than the 4 specified as inclusion criteria. The EPAR states that the minimum value of the historical AAR is 0 [4], and thus patients who have not experienced seizures for 6 months prior to study entry are included.]" The quoted text is inaccurate because it implies that multiple patients in ENVISION had not experienced acute attacks in the 6 months prior to study entry. On the the contrary, the minimum AAR of 0 relates solely to one patient in the placebo group who did not meet the inclusion criterion of a history of at least 2 composite	Alnylam recommends deletion of the two quoted sentences.	The suggested edit will avoid an inaccurate characterization of the patient population included in the ENVISION trial.

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Description of problem	Description of proposed amendment	Justification for amendment
porphyria attacks, since the patient had 2 attacks that were treated at home without intravenous hemin, which was identified as a protocol deviation [2].		
Section 2.5, page 51: "Blandt alle patienter, der har modtaget givosiran i ENVISION og ENVISION OLE (n=111) [Among all patients who received givosiran in ENVISION and ENVISION OLE (n=111)]" Page 52: "Blandt de 111 patienter, der har modtaget givosiran i ENVISION og ENVISION OLE [Among the 111 patients who received givosiran in ENVISION and ENVISION OLE]" These statements are incorrect because ENVISION and its OLE included only 94 patients. This "n=111" includes also the Phase 1/2 study.	Alnylam recommends revision of the quoted statements to read "Among patients who received givosiran in placebo-controlled and open-label clinical studies (n=111)" for alignment with the SmPC [3].	The suggested edits will avoid an inaccurate description of the size of the patient population included in ENVISION.

2. Confidential information check

Location of incorrect marking	Description of incorrect marking
Table 0-1, page 9 Table 3-1, page 55	Hospital costs and patient costs should be redacted as these are results derived from the company's confidential model.
Figure 2-1, page 33 Figure 2-2, page 37 Figure 2-4, page 43 Figure 2-5, page 44 Figure 2-7, page 47 Figure 2-8, page 48 Figure 8-1, page 71	It is unclear if the graphs will be redacted, as currently only the figure captions and footnotes are highlighted as confidential. Alnylam requests that the graphs be redacted as these 36-month data have not been published.

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Location of incorrect marking	Description of incorrect marking
Figure 8-2, page 73 Figure 8-3, page 76 Figure 8-7, page 80	
Table 3-2, pages 56–57	All company values for annualized attack rate in each health state, health-state distribution of patients at the start of the model, utility values, and incremental QALY should be redacted, as these are directly derived from patient-level data, are not public and will not be made public. In addition, change in ICER has not been redacted for the scenarios on weight distribution, costs associated with chronic symptoms, and costs associated with chronic symptoms. These values should be redacted for consistency with the other changes in ICER reported in this table.

References

1. Orphan Europe SARL. *NORMOSANG 25 mg/ml, concentrate for solution for infusion Summary of Product Characteristics*. 19 June 2019 [cited 14 November 2019]; Available from: https://www.recordatirarediseases.com/sites/www.recordatirarediseases.com/files/inline-files/Normosang_ProductInformation.pdf.
2. Balwani, M., et al., *Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria.* N Engl J Med, 2020. **382**(24): p. 2289-2301.
3. Alnylam Netherlands B.V. *Givlaari (givosiran 189 mg/mL solution for injection) Summary of Product Characteristics*. 22 June 2022 [cited 14 December 2022]; Available from: https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf.

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Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

24.01.2023

MGK/ECH

Forhandlingsnotat

Dato for behandling i Medicinrådet	22.02.2023
Leverandør	Alnylam Sweden AB
Lægemiddel	Givlaari (givosiran)
Ansøgt indikation	Behandling af akut hepatisk porfyri (AHP) hos voksne og unge i alderen 12 år og ældre.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Givlaari (givosiran):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Givlaari	189 mg/ml	1 stk.	361.169,00	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

[redacted]

Aftaleforhold

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen lægemidler i konkurrence til Givlaari til den ansøgte indikation. Tabel 3 viser de årlige lægemiddeludgifter for Givlaari.

Tabel 2: Årlige lægemiddeludgifter

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Antal pakninger pr. år	Lægemiddeludgift pr. år (SAIP, DKK)
Givlaari	189 mg/ml	1 stk.	2,5 mg/kg SC hver måned	[redacted]	12*	[redacted]

*Baseret på vægt under 75,5 kg. Det antages at der anvendes 1 pakning pr. behandling.

Status fra andre lande

Land	Status	Kommentar	Link
Norge	Ikke anbefalet		https://nyemetoder.no/metoder/givosiran-givlaari
Sverige	Delvis anbefalet	Til patienter som har haft mindst fire sygdomsrelaterede anfald, der har krævet indlæggelse inden for de sidste 12 måneder	Givlaari ingår i högkostnadsskyddet med begränsning (tlv.se)
England	Delvis anbefalet	Til patienter med klinisk bekræftede svære tilbagevendende anfald (4 eller flere indenfor 12 måneder)	https://www.nice.org.uk/guidance/hst16/chapter/1-Recommendations

Konklusion

[redacted]

Application for the assessment of Givlaari™ (givosiran) for patients with acute hepatic porphyria

Confidential information is highlighted in yellow in this application

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1. Basic information

Contact information	
Name	**Jan Westerblad**
Title	General Manager, Nordic Region, Alnylam Sweden AB
Phone number	+47 48401490
E-mail	jwesterblad@alnylam.com
Name	**Anees Malik**
Title	Associate Director, Market Access, Alnylam UK Limited
Phone number	+44 7917 820691
E-mail	amalik@alnylam.com

Overview of the pharmaceutical	
Proprietary name	Givlaari™
Generic name	Givosiran
Marketing authorization holder in Denmark	Alnylam Sweden AB
ATC code	A16AX16
Pharmacotherapeutic group	Various alimentary tract and metabolism products
Active substance(s)	Givosiran
Pharmaceutical form(s)	Solution for injection (subcutaneous injection, SC)
Mechanism of action	Givosiran is a double-stranded small interfering ribonucleic acid (siRNA) that causes degradation of aminolevulinate acid synthase 1 (ALAS1) messenger ribonucleic acid (mRNA) in hepatocytes through RNA interference, resulting in a reduction of induced liver ALAS1 mRNA towards normal. This leads to reduced circulating levels of neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), the key causal factors of attacks and other disease manifestations of acute hepatic porphyria (AHP).
Dosage regimen	2.5 mg/kg once monthly
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Treatment of AHP in adults and adolescents aged 12 years and older.
Other approved therapeutic indications	No

Overview of the pharmaceutical	
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	One vial pack size
Orphan drug designation	Yes

2. Abbreviations

Abbreviation	Definition
AAR	Annualised attack rate
ADP	ALA dehydratase deficient porphyria
AE	Adverse event
AHP	Acute hepatic porphyria
AIP	Acute intermittent porphyria
ALA	Delta aminolevulinic acid
ALAS1	Delta aminolevulinic acid synthase 1
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BSC	Best supportive care
CEA	Cost-effectiveness analysis
CI	Confidence interval
CKD	Chronic kidney disease
DB	Double blind
DMC	Danish Medicines Council
eGFR	Estimated glomerular filtration rate
EPNET	European Porphyria Network
EQ-5D-3L	EuroQol 5-dimensions questionnaire (3-level version)
EQ-5D-5L	EuroQol 5-dimensions questionnaire (5-level version)

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Abbreviation	Definition
FAS	Full analysis set
HCC	Hepatocellular carcinoma
HCP	Hereditary coproporphyria
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ITT	Intent to treat
IV	Intravenous
LS	Least square
LY	Life year
LYG	Life-years gained
MAD	Multiple-ascending dose
MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric rating scale
OLE	Open-label extension
OWSA	One-way sensitivity analysis
PBG	Porphobilinogen
PCS	Physical Component Summary
PGIC	Patient Global Impression of Change questionnaire
PPEQ	Porphyria Patient Experience Questionnaire
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
RDI	Relative dose intensity

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

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3. Tables and Figures

3.1 Table of tables

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3.2 Table of figures

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4. Current dossier – in context to the previous assessment process for givosiran

Alnylam initially submitted GIVLAARI (givosiran) for assessment by the DMC in February 2020 within the framework of the 'old' method process (enforced prior to January 2021). In accordance with the process that was in effect before January 2021, Alnylam was provided with an assessment protocol on January 22nd, 2021. However, in January 2021 the DMC introduced a new assessment process based on a QALY-framework. After assessing the benefits of the new QALY-framework that was in effect in January 2021, Alnylam decided to withdraw its initial submission under the previous process on March 21st, 2021 to initiate a submission under the new procedure.

This decision was based on Alnylam's assessment that an application assessed via the new process with a QALY-framework would provide a more transparent and complete evaluation of the entire therapeutic value of GIVLAARI; including all clinical benefit over time and all costs using the same time horizon for both aspects. This is reflected in the DMC's annual report in 2020 in which it was reasoned that the new QALY-based framework would provide a more transparent, better standardised, and international recognized assessment framework, that would allow for easier defining cost-effective treatments and make consistent assessments across different therapies. Alnylam recognizes that the previous framework's disconnected evaluation of cost in relation to effect did not suitably evaluate questions of cost-effectiveness. Alnylam acknowledges and appreciates the contribution and efforts made by the DMC in providing the assessment protocol under the previous process (1). Therefore, the information and analysis requested by the DMC in the old assessment protocol, has been supplied in this dossier, if available and appropriate.

There is only one important element in the previous assessment protocol that Alnylam has not been able to address due to technical and clinical infeasibility. Specifically, the old assessment protocol defined the population in scope as **patients who require hospitalisation two or more times within six months**.

As Alnylam has noted previously during DMC protocol dialogue meetings, our concern is related to the defined limitation of the treatment setting i.e., **patients who require hospitalisation**. We understand the rationale behind the DMC's decision to include this as an inclusion criterion in the protocol, since the conventional management strategy in Denmark is to manage AHP-related attacks in hospital. However, we believe that the site of care is not a relevant consideration for evaluating the efficacy of givosiran.

The primary endpoint in Alnylam's global pivotal phase 3 ENVISION study was the annualized attack rate (AAR), which is intended to measure whether givosiran was more effective than placebo in preventing or halting the occurrence of AHP-related attacks. ENVISION is a multi-national clinical trial, and it is understood that there are variation in treatment practices worldwide in terms of whether AHP-related attacks are managed in hospital, outpatient, or other settings. Therefore, the AAR composite collected all these attacks regardless of how they were managed in local practice. However, whether the site of care of an attack was in the hospital instead of the outpatient setting should not be used to infer efficacy – instead, this should be considered as a health system characteristic of a given country.

We should note that this follows a convention that has been used in clinical trials in other disease states, such as cardiology. Increasingly, patient care in different disease states is shifting toward the outpatient setting, rather than just the inpatient setting – so endpoints in clinical trials capture management of patients in urgent care and outpatient settings, rather than just inpatient settings. In this context, we believe that the more important consideration for a product is whether it is effective at preventing the incident of an event – whether it's an AHP-related attack or a heart failure related event (2). Whether the management of this attack happens in a hospital or in the outpatient setting is irrelevant and should not be judged as a limitation of the treatment.

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We believe that limiting evaluation of the givosiran Phase 3 ENVISION data by the treatment setting wo uld be illogical based on the fundamental design of the study and a clinical understanding of the primary endpoint and the lack of connection between treatment setting and attack severity.

Alnylam would again like to fully address this to avoid any misconceptions concerning the contents of this dossier by describing:

1. The primary endpoint in ENVISION, how it is defined, why it was defined as it is, and how it is used to define the eligible population for givosiran
2. The target population and its relation to the ENVISION study population

Context of primary endpoint and target population

The fundamental takeaway should be that the treatment location/management strategies for handling porphyria attacks are different across countries, regions, and ER-departments. This necessitates the use of a composite endpoint in a global study. However, how severe-recurrent attacks are registered as one of the three individual components of the composite endpoint, should not be confused with attack severity.

The primary endpoint in ENVISION (the pivotal phase 3 global study for GIVLAARI) was the annualized rate of composite porphyria attacks (AAR), defined to capture attacks treated 1) at a hospital, 2) at an urgent health care visit or 3) with intravenous administration of haemin at home.

In ENVISION, the efficacy of givosiran was investigated in patients who were required to **have documentation of at least two composite porphyria attacks** within 6 months before baseline. These severity criteria were used to define the population with recurrent AHP.

This composite endpoint was carefully selected based on our EXPLORE study (a natural history study in an ENVISION-like patient population) and observed differences in the management strategies for porphyria attacks.

In EXPLORE it was demonstrated that the treatment setting for administering IV-haemin for recurrent attacks varied based on country- and local-practice. Based on these observations, it was determined that parameterisation using the three components (*1) hospitalisation, 2) urgent health care visit or 3) intravenous administration of haemin at home*) for the composite endpoint, would allow the study to capture most recurrent attacks, irrespective of differences in management setting for receiving IV-haemin.

As a reminder, the ENVISION study was conducted as a global trial across 18 countries due to the rarity of the disease. Thus, the primary endpoint needed to capture all recurrent attacks irrespective of the management setting across countries. If the endpoint had been defined as only one of the three components of the composite endpoint (i.e., attacks resulting in hospitalisation), the endpoint would not have provided an adequate estimate of disease severity or treatment effect, as depending on the locality, some attacks would not be captured solely based on the management setting.

Alnylam has provided some examples (not exhaustive) of country and local-specific treatment practices, necessitating use of the composite endpoint to capture all recurrent attacks.

1) Patients in the US may receive rescue haemin infusions in outpatient infusion centres, as it is the cheaper option for US insurers as no hospitalisation is needed (3). The outpatient treatment practice is also commonly observed in the U.S. for chemotherapy and has been adopted by porphyria treaters in the U.S., which is also driven by haematologists. Attacks managed by an outpatient visit in infusion centre would be registered as an urgent care visit.
2) In Germany, the treatment options can depend on the treating ER-department. Some patients can be treated as out-patients, i.e., out-patient admission in the ER-department for rescue IV haemin before returning home. This would be registered as an urgent care visit.
3) UK patients who are treated at National Acute Porphyria Service (NAPS) Centres may be eligible for rescue IV haemin at home, which is especially relevant for patients with central venous catheters. This

would be registered as intravenous administration of haemin at home. In support of this is the study by Gill et all. of patient and caregiver experiences of living with acute hepatic porphyria in the UK, which demonstrated high treatment at home in the UK (4).

From these examples, it should be clear that the same hypothetical patient who suffers from two recurrent attacks every 6 month, would have their attacks managed in different treatment settings based on the country in which the patient is situated. For example, in the UK the attacks could be registered as "intravenous administration of haemin at home", whilst in Germany and the US these attacks could be registered as "urgent health care visit".

In Denmark, the same hypothetical patient with the same attacks would be hospitalised for every recurrent attack. This is due to the management strategies in Denmark where patients with recurrent symptomatic porphyria are strictly handled by hospitalisation at the Porphyria center in Odense (KOL-interviews); patients are neither allowed to go home immediately after or between IV-haemin administrations, nor have IV haemin administration at home.

For the cost-effectiveness model, we assume that all AHP-related attacks are managed in hospital because patients need IV haemin as a rescue therapy for the management of attacks. IV haemin is not available outside of the hospital setting. This assumption was validated in consultation with Danish clinical experts in the management of this condition.

Conclusion

In the previous DMC protocol, the population in scope was defined as **patients who require hospitalisation two or more times within six months**. However, as explained for the reasons above it is neither technical and clinical feasible to conduct analysis using ENVISION data with a limitation on the treatment setting to hospitalisation-only nor is it available as a subgroup analysis.

As clearly explained above, ENVISION was designed to capture if recurrent attacks occurred and to which extent givosiran is effective and preventing these attacks from happening. To measure this, the composite endpoint was designed to capture all clinically relevant recurrent attacks considering the global scale of the trial and the different treatment practices for IV-haemin across countries. As clearly demonstrated by the examples above, the site of care is not an indicator of severity of attacks but of national and local management practices. The point is therefore to clearly demonstrate, that givosiran is effective in addressing the attacks or not, and this is best demonstrated by accounting for all recurrent attacks independent of treatment location.

5. Summary

5.1 Population, intervention, outcomes, and comparator (PICO)

This single technology assessment relates to givosiran as a treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older. AHP is characterised by severely painful acute attacks that are potentially life-threatening if not treated, and, for some patients, chronic debilitating symptoms that negatively impact daily functioning and health-related quality of life (HRQoL) (5–9).

Most patients with AHP have only one or a few acute porphyria attacks in their lifetime, with 3-5 % experiencing recurrent attacks (10), defined by the European Porphyria Network as ≥4 attacks per year (11,12). Based on this prevalence estimate, [redacted] patients in Denmark would be estimated to have recurrent attacks. This is aligned with reports from clinical experts from the Porphyria centre in Odense who confirmed that [redacted] patients are known to experience recurrent attacks.

Patients experience an extensive burden of disease in connection with attacks, in particular, due to the extreme pain experienced during attacks. However, HRQoL may also be significantly affected between attacks, e.g. due

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to the constant restrictions in order not to trigger acute attacks and the concerns/worries about new attacks. HRQoL may also be reduced due to chronic pain, anxiety and depression, and the reduced ability to perform daily activities. In addition, patients with AHP suffer long-term complications including chronic kidney disease (CKD), hypertension, hepatocellular carcinoma (HCC), and anaemia, and their occurrence increases with higher rates of acute attacks.

Givosiran received EU marketing authorisation on the 2nd of March 2020 for the treatment of AHP. Givlaari was reviewed under EMA's accelerated assessment programme(13).

Population: Adult and adolescent patients aged 12 years and older with AHP with recurrent attacks. Currently, treatment options are very limited for these patients, and no prophylactic treatments are available in Denmark, and consequently, prophylactic options are needed for these patients to reduce the risk of acute attacks and the ongoing accumulation of clinical and HRQoL burden.

Intervention: Givosiran is a double-stranded small interfering ribonucleic acid (siRNA) that causes degradation of aminolevulinate acid synthase 1 (ALAS1) messenger ribonucleic acid (mRNA) in hepatocytes through RNA interference, resulting in a reduction of induced liver ALAS1 mRNA towards normal. This leads to reduced circulating levels of neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), the key causal factors of attacks and other disease manifestations of AHP.

The recommended dose of Givlaari is 2.5 mg/kg once monthly, administered via subcutaneous (SC) injection. Based on average body weight of the European patients in ENVISION, the largest prospective study in AHP patients, the best estimation for body weight of Danish AHP patients is 65.3 kg.

Comparator: Best supportive care (BSC), consisting of standard treatments (such as rescue haemin, which is indicated for treating acute attacks of AHP) that are used in clinical practice to speed the resolution of symptoms and reduce the hospital length of stay during acute attacks.

When patients experience attacks, glucose infusion (300-400 g/day) is the first treatment. If the attacks are of a more severe character, the patients are treated with haemin infusion. Haemin infusion results in a negative feedback enzyme inhibition of haem synthesis and thereby slows down haem synthesis and excessive porphyria production. Haemin is infused daily for up to 4 days according to the summary of product characteristics in Denmark (14). However, in clinical practice IV rescue haemin treatment is often extended for longer in severely ill patients (15,16).

Outcomes: All outcomes considered in this dossier were assessed in the ENVISION study. The outcome measures considered in this dossier include:

Efficacy endpoints - Porphyria attacks

- Mean change in annualised attack rate (AAR) measured from baseline (primary endpoint)
- Proportion of patients who are free of attacks

Other secondary efficacy endpoints:

- Median changes from baseline in ALA (delta-aminolevulinic acid) and PBG (Urinary porphobilinogen)
- Annualised no. of days of haemin use
- Mean change from baseline in weekly average of worst daily pain measured using the numeric rating scale (NRS) of the Brief Pain Inventory (BPI-SF)
- Mean change from baseline in weekly average of worst daily fatigue measured using a NRS of the BFI
- Mean change from baseline in physical component score (PCS) of the 12-Item Short Form Survey (SF-12)
- Mean change from baseline in mental component score (MCS) of the SF-12

Safety endpoints

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- Proportion of patients who experience adverse events (AE)
- Proportion of patients who experience serious adverse events (SAE)
- Proportion of patients who discontinue treatment due to AE
- Proportion of patients who experience adverse reactions
- Qualitative review of the adverse reaction profile for givosiran

5.2 Evidence supporting the application

Studies supporting the efficacy and safety of givosiran.

ENVISION (Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria) is a Phase 3 randomised, double-blind, placebo-controlled, multicentre study with an open-label extension (OLE). All patients completing the 6-month double-blind treatment period were eligible to continue on OLE study in which they received treatment with givosiran for up to 30 months. ENVISION had the objective to evaluate the effect of SC givosiran (ALN-AS1), compared to placebo, on the rate of porphyria attacks in patients with AHP. Results were reported by Balwani et al. 2020 (17).

Criteria for participation in the ENVISION trial were:
Inclusion Criteria:

- ≥ 12 years of age
- Diagnosed with AHP (acute intermittent porphyria, hereditary coproporphyria, variegate porphyria, ALA dehydratase deficient porphyria)
- Elevated urinary or plasma PBG or ALA values within the past year
- Have active disease, with at least 2 documented porphyria attacks within the last 6 months
- Willing to discontinue or not initiate the use of prophylactic haemin throughout the study
- Women of childbearing potential must have a negative serum pregnancy test, not be nursing, and use acceptable contraception

Exclusion Criteria:

- Clinically significant abnormal laboratory results
- Anticipated liver transplantation
- History of multiple drug allergies or intolerance to SC injections
- Active HIV, hepatitis C virus, or hepatitis B virus infection(s)
- History of recurrent pancreatitis

5.3 Comparative efficacy

The design of the phase 3 ENVISION RCT reflects the current management of AHP. Supportive therapy with analgesics and rescue therapy with haemin for the treatment of acute attacks was permitted in both treatment arms.

- In the phase 3 ENVISION study, treatment with once-monthly givosiran resulted in a statistically significant and clinically meaningful reduction in the composite annualized attack rate, compared to placebo, of 74% ($p<0.001$) and 73% ($p<0.001$) in patients with AIP and AHP, respectively.
- In addition to reducing the number of attacks, once-monthly givosiran treatment led to fewer days of haemin use compared to placebo.
- The proportion of patients with AIP/AHP who were attack-free (i.e., did not experience an event that met pre-defined criteria for a composite attack) during the 6-month double-blind period was approximately 3-fold higher with once-monthly givosiran than with placebo (50.0%/50.0% vs. 16.3%/17.4 respectively).

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- In the phase 3 OLE, sustained reduction in composite porphyria attack rates in patients who continued to receive once-monthly givosiran and in those who crossed over to once-monthly givosiran from placebo have been observed.

5.4 Comparative safety

The main safety outcomes included in this application are:

- Proportion of patients who experience AEs compared to placebo
- Proportion of patients who experience SAEs compared to placebo
- Proportion of patients who discontinue treatment due to AEs compared to placebo
- Proportion of patients who experience adverse reactions
- Qualitative review of the adverse reaction profile for givosiran (narrative comparison)

In the phase 3 trial ENVISION, all reported safety analyses were performed on the safety population (i.e., patients who received at least one dose of the study drug; n=94). At least one AE was reported in 89.6% (n=43/48) of patients in the givosiran arm and in 80.4% (n=37/46) of patients in the placebo arm. SAEs were reported in 20.8% (n=10/48) of patients in the givosiran arm and in 8.7% (n=4/46) of patients in the placebo arm. The difference in serious adverse events was not driven by any particular event. There were no deaths in either treatment group over the course of the 6-month double-blind phase of the study or by the 18-month follow-up of the OLE phase (17). Givosiran has a well-characterised safety profile in patients with AHP and is generally well-tolerated by patients over the long term. Most AEs seen in ENVISION were of mild-to-moderate severity and/or resolved or stabilised within 6 months of therapy. The long-term safety of givosiran is being evaluated in the ENVISION OLE. 18-month data from the ENVISION OLE indicated that the longer-term safety profile of givosiran is consistent with that observed in the RCT.

5.5 Clinical conclusion

In conclusion, givosiran is the first therapeutic option that achieved sustained reductions in levels of ALA and PBG, toxic factors driving attacks and other disease manifestations of AHP. In phase 3, double-blind, placebo-controlled ENVISION trial, once-monthly SC administration of givosiran yielded statistically and clinically significant reductions in the rate of acute attacks and multiple other measures of disease burden.

The clinical benefits observed in ENVISION represents a breakthrough in the management of AHP patients. In summary, givosiran resulted in a significant and clinically meaningful reduction in the composite annualized attack rate, compared to best supportive care, of 74% ($p<0.001$) and 73% ($p<0.001$) in patients with AIP and AHP, respectively (17). This was accompanied by a significant reduction in the number of days with haemin use compared to best supportive care. Importantly, approx. a 3-fold higher proportion of patients with AIP/AHP were attack free at 6-months when treated with givosiran compared with best supportive care (17).

Notably in the phase 3 OLE phase, long-term efficacy was proven by consistent reductions in the composite porphyria attack rates, which were sustained in patients who continued to receive once-monthly givosiran and in those who crossed over to once-monthly givosiran from best supportive care (18).

The additional benefit was proven by secondary outcomes demonstrating patients had improvements in symptoms, which translated into improved HRQoL. Importantly givosiran leads to pain reduction while reducing the need for opioid treatment and further improved the ability of AHP patients to function physically and socially (SF-12-PCS) (17).

Givosiran transforms the standard of care for AHP as the only treatment with robust evidence showing prevention of acute attacks as well as a holistic treatment of the condition. There are no comparators that occupy the same place in therapy as givosiran, a disease-modifying, preventative treatment for AHP.

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5.6 Health economic analysis

A cost-effectiveness analysis was developed following the DMC guidelines to assess the cost-effectiveness of givosiran compared with BSC for the treatment of AHP in Denmark. AHP health-state transitions and associated costs were compared between givosiran and BSC. The model incorporated key clinical data from ENVISION and the literature—notably, the EXPLORE natural history study and the real-world data of Neeleman et al. 2018—and was developed to be representative of the Danish healthcare setting by using unit costs and health care resource utilization from Denmark (or adapted from other sources to the Danish context). Key model parameters were validated by a panel of clinical experts and/or a Danish clinical expert, Prof. Jan Frystyk (head of Department and head of Research Department of Endocrinology, Odense University Hospital & Institute of Clinical Research, Faculty of Health Sciences, University of Southern Denmark in Odense).

Over the CEA time horizon (lifetime), this model projects a substantial gain of [redacted] QALYs (discounted) for patients who received givosiran compared with those who received BSC. This was attributable to patients spending fewer years in more advanced AHP health states, and thus experiencing fewer acute attacks and a lower burden of chronic conditions. As a consequence of these benefits to patients, givosiran also reduced the impact of AHP on caregivers. The benefit of this QALY gain to patients should be viewed in context of the loss of QALYs patients with AHP experience compared with the general population.

In the base-case analysis, the total lifetime cost for a patient treated with givosiran was DKK [redacted] (discounted), which is DKK [redacted] more than the lifetime costs incurred by a patient treated with BSC (DKK [redacted]). The resulting ICER for givosiran compared with BSC was DKK [redacted] /QALY. The model takes a very conservative assumption that BSC cohort does not worsen over time. Notably, the ICER decreased by 28% to DKK [redacted] /QALY once a probability of disease worsening reflective of observed increase in AAR by time from diagnosis is applied for the first 5 years of the analysis.

Based on the base case settings, the estimated budget impact of recommending givosiran as standard treatment in Denmark at PPP was DKK [redacted] in year 1 and DKK [redacted] in year 5.

5.7 Unmet medical need

As givosiran is the first disease-modifying treatment for treating AHP, there remains a high unmet medical need for a safe and effective therapy to durably decrease the frequency of debilitating attacks, diminish chronic symptoms, and improve patients' physical functioning and quality of life. Current AHP treatment options focus on the control and symptomatic relief of acute attacks, while the management of repeated attacks is essentially limited to identifying and eliminating lifestyle triggers and use of symptomatic therapies for pain, hypertension, tachycardia, nausea, vomiting, and convulsions. The only specific treatment for acute attacks is infusion of rescue haemin, which can improve the acute symptoms of an AHP attack within a few days, although it is quite common for patient to have attacks lingering for longer and further to develop chronic symptoms and complications as described in section 6.1.3 (19).

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6. The patient population, the intervention and choice of comparator

6.1 The medical condition and patient population

6.1.1 Overview of the disease: Acute Hepatic Porphyria

Porphyria comprises a family of rare, serious, and sometimes life-threatening metabolic disorders predominantly caused by a genetic mutation leading to a partial deficiency in the activity of one of the eight enzymes responsible for haem synthesis (8).

Porphyria is typically classified as erythropoietic or hepatic, depending on the major site of overproduction of haem precursor, or as acute (neurologic) or cutaneous depending on the cardinal clinical manifestations. This is illustrated in Table 1.

Table 1: Classification of porphyria

Place in body	Acute/cutaneous	Type of porphyria
Hepatic	**Acute**	**Acute intermittent porphyria (AIP)**
		ALAD porphyria (ADP)
	Acute and cutaneous	**Hereditary coproporphyria (HCP)**
		Variegate porphyria (VP)
	Cutaneous	Porphyria cutanea tarda (PCT)
		Hepatoerythropoietic porphyria (HEP)
Erythropoietic	**Cutaneous**	Congenital erythropoietic porphyria (CEP)
		Erythropoietic protoporphyria (EPP)
		X-linked protoporphyria (XLP)

Note: The four acute hepatic porphyria types that are the focus of this submission are indicated with bold typeface and green shading (8)

AHP comprises a group of porphyrias in which the major site of excess production of haem precursors is the liver. There are four types of AHP: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and delta-aminolevulinic acid dehydratase (ALAD)-deficiency porphyria (ADP), which are in scope for this application. Acute intermittent porphyria is the most common subtype of this disorder and accounts for approximately 80% of all symptomatic cases (11,20,21). Each type results from a genetic defect leading to deficiency in one of the enzymes of the hepatic haem biosynthesis pathway. These defects cause the accumulation of toxic haem intermediates ALA and PBG in the liver. Acute attacks are accompanied by high excretion of the porphyrin precursors aminolevulinic acid (ALA) and porphobilinogen (PBG) in the urine (22–24). ALA is a cytotoxic molecule that promotes oxidative stress and is a potent vasoconstrictor that can promote injury in target organs(25). Neurotoxic effects of ALA may be exerted via oxidant or genotoxicity properties (26,27). Thus, ALA seems to be directly responsible for the symptoms of acute porphyria as illustrated in Figure 1 (5,25). Decreasing ALA and PBG levels would be predicted to reduce not only the frequency of acute attacks and the impact of the irreversible and cumulative damage they may cause, but also the burden of chronic conditions.

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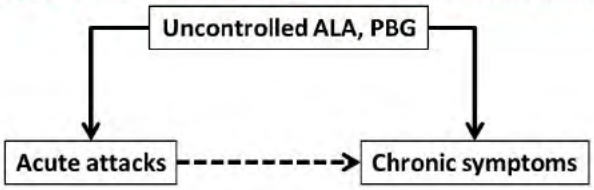
Figure 1: Role of toxic haeme precursors in acute and chronic conditions of AHP



ALA, aminolevulinic acid; PBG, porphobilinogen.

AHP is characterised by potentially life-threatening acute attacks associated with widespread dysfunction across the autonomic, central, and peripheral nervous systems. The majority of patients who experience acute attacks also experience chronic debilitating symptoms as described in section 6.1.3 (7). Chronic symptoms may be present even among patients that do not experience acute attacks. Several long-term complications are also associated with AHP as discussed in section 6.1.3 (22).

AHP is characterised by potentially life-threatening attacks and, for many patients, chronic debilitating symptoms that negatively impact daily functioning and HRQoL (5–9). The main clinical manifestations of AHP are summarised in Table 2

Table 2: AHP - core disease characteristics

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

6.1.2 Pathophysiology of AHP

In AHP, toxic haem intermediates accumulate in the liver due to increased liver ALAS1 gene transcription, increased haem consumption, and mechanisms related to hormonal fluctuation during menstruation and pregnancy (6,9,27). In the past, there was uncertainty regarding the pathogenic mechanism of acute attacks. It was thought that acute neurovisceral attacks could arise due to either neurotoxic effects of aminolevulinic acid (ALA) and/or porphobilinogen (PBG) accumulation or haem deficiency in neuronal tissue. With the support of experimental and clinical data, it is now accepted that the haem intermediate ALA is directly toxic, playing a major role in the pathophysiology of the disease (5,27,28).

As shown in Table 1, there are four types of AHP: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and delta-aminolevulinic acid dehydratase (ALAD)-deficiency porphyria (ADP) (10). Each type results from a genetic defect leading to deficiency in one of the enzymes of the hepatic haem biosynthesis pathway. These defects cause the accumulation of toxic haem intermediates ALA and PBG in the liver, with ALA believed to be the primary toxic intermediate responsible for causing both acute attacks and chronic symptoms (5). An overview of the pathophysiology is provided in Figure 2.

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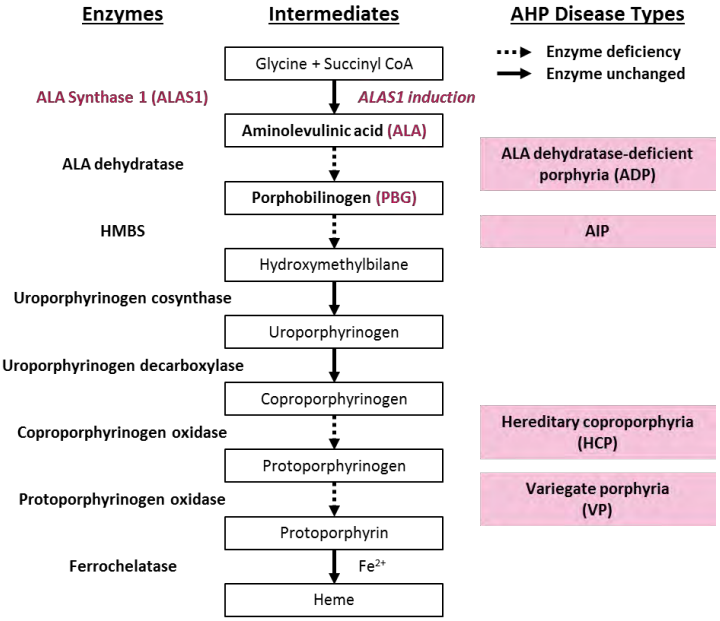
Figure 2: Pathophysiology of AHP



AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; HMBS, hydroxymethylbilane synthase. Source: Adapted from Bissell et al., 2017(5).

Depending on the type of AHP, the disease manifests in the form of acute neurovisceral attacks alone (AIP, ADP) or as acute attacks with cutaneous phototoxicity that occurs apart from or along with attacks (HCP, VP). AIP and ADP are the only types of porphyria that are not generally associated with cutaneous phototoxicity due to the causative enzyme deficiencies occurring prior to porphyrin formation in the haem biosynthetic pathway (8). However, cutaneous symptoms may occur in patients with AIP if the disease is complicated by advanced renal disease (8).

6.1.3 Clinical features of Acute Hepatic Porphyria

AHP disease severity

There is currently no standard classification to define disease severity in AHP. A study by Neeleman et al., 2018(22) proposed a classification of AHP based on the frequency of occurrence of attacks as follows:

- Recurrent: >4 attacks per year
- Symptomatic: ≥1 attack in any year but did not meet the criteria for a recurrent case
- Asymptomatic: mutation carriers who did not experience attacks

The classification of AHP severity described in Neeleman et al. was subsequently used as a basis for the development of the health states in the economic model, as described in section 9.1. However, based on findings from the ENVISION phase 3 study of givosiran, categorising all patients with more than four attacks per year as part of one singular health state is an overly broad and crude consideration of patients' disease severity. The ENVISION study revealed a high variation in the number of attacks patients could experience in a given year, ranging from 0 to 52.(18) The addition of a "Severe" disease health state for patients with more than 24 attacks per year allows for a more granular estimation of patients' disease severity. Danish expert clinicians considered a four-level categorisation of AHP health states to be appropriate, so this categorisation is used to define health states in this submission. (29)

Acute Attacks

AHP attacks manifest as episodes of potentially extreme incapacitation characterised by a combination of non-specific symptoms and if left untreated, AHP attacks are known to be potentially life-threatening (30). Attacks start with intense and usually diffuse abdominal pain and muscle weakness, followed by nausea and vomiting, constipation or diarrhoea, hypertension, tachycardia, limb, head, neck or chest pain, mental symptoms (including confusion and hallucinations), convulsions, and seizures (5,9,10). neurovisceral symptoms are generally indistinguishable between the different types of AHP; however, symptoms may vary substantially between patients (27,31).

Recurrent acute attack

The proposed categorisation by Neeleman et al. aligns with the definition of recurrent acute attacks in the European Porphyria Network (EPNET) guidelines as >4 attacks per year, and the majority of studies align with this definition (7,22,32,33). Only 3%–5% of symptomatic patients experience recurrent acute attacks (defined as ≥4 attacks per year) (11)..(10) Extreme cases of 50 to 100 attacks per year were reported in the UK survey of patients with AIP have been reported (34).

Chronic disease manifestations

Chronic, ongoing signs and symptoms, outside of those found in attacks, occur frequently in AHP. Neeleman et al., 2018, reported the prevalence of porphyria symptoms in recurrent patients (>4 attacks per year), symptomatic patients (1–4 attacks per year), and asymptomatic individuals (0 attacks) with AIP (22). The data showed high rates of pain, neurological, and psychiatric symptoms in all three groups, with the prevalence of symptoms generally increasing with higher frequency of attack (22) Between-group differences in the major categories of pain, neurological, and psychiatric symptoms were statistically significant (22). Significant differences in the majority of subcategories of symptoms were also reported when comparing recurrent or symptomatic cases to asymptomatic cases alone (0 attacks) with AIP (22). The data showed high rates of pain, neurological, and psychiatric symptoms in all three groups, with the prevalence of symptoms generally increasing with higher frequency of attack (22). Between-group differences in the major categories of pain, neurological, and psychiatric symptoms were statistically significant (22). Significant differences in the majority of subcategories of symptoms were also reported when comparing recurrent or symptomatic cases to asymptomatic cases alone (22).

All recurrent cases and 91.7% of symptomatic cases reported pain, the cardinal symptom of AHP. Abdominal pain was the most reported chronic symptom in all categories of acute attack frequency. Chronic neurological symptoms were also highly prevalent among recurrent attack patients (81.8%), with motor weakness and paraesthesias being the most common manifestations.

Advanced neuropathy, coma, or respiratory failure occurred only in patients who experienced attacks. Chronic psychiatric illness was reported in 81.8% of patients with recurrent attacks, who had the highest rates of anxiety, depression, psychosis/hallucinations, insomnia, and suicidality among the three groups.(22) These data demonstrate the heavy burden of chronic manifestations in AHP, the strong association between the prevalence of chronic symptoms and acute attack frequency, and the ongoing presence of chronic AHP symptoms even in some patients with no history of acute attacks. Chronic psychiatric illness was reported in 81.8% of patients with recurrent attacks, who had the highest rates of anxiety, depression, psychosis/hallucinations, insomnia, and suicidality among the three groups.(22) These data demonstrate the significant impact heavy burden of chronic manifestations in AHP, the differences strong association betweenin the prevalence of chronic symptoms as they relate to and acute attack frequency, and the ongoing presence of chronic AHP symptoms, even in the complete absence of some patients with no history of acute attacks.

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Table 3: Chronic symptoms

Symptom	Recurrent (n=11) (%)	Symptomatic (n=24) (%)	Asymptomatic (n=53) (%)	Linear-by-linear Chi² association test, p-value
Pain	100.0	91.7	30.2	<0.001
Neurological	81.8	45.8	17.3	<0.001
Psychiatric	81.8	33.3	18.9	<0.001

Note: Recurrent patients were defined as having >4 attacks per year, Symptomatic patients had at least one attack in any year that they were followed but did not meet that criterion for a Recurrent patient, and Asymptomatic individuals were mutation carriers who did not experience attacks. Source: Neeleman et al. ((22))

Long-term complications

Long-term complications associated with AHP include chronic kidney disease (CKD), hypertension, hepatocellular carcinoma (HCC), and anaemia, and their occurrence increases with higher rates of acute attack (Table 4) (22,35–37). Although the findings from the ENVISION phase 3 study of givosiran showed dramatic lowering of reduction in attack rates, no assumptions on lowering of long-term complications have been made in the HE-model for this submission, since it is currently unknown whether an intervention targeting the underlying disease process leads to reversal of long-term complications.

Table 4: Long-term complications in AIP

Long-term complication	Recurrent (n=11) (%)	Symptomatic (n=24) (%)	Asymptomatic (n=53) (%)	Linear-by-linear Chi² association test, p-value
CKD	63.6	45.8	13.2	<0.001
Hypertension	72.7	70.8	26.4	<0.001
HCC	9.1	8.3	1.9	0.15
Anaemia	63.6	16.7	5.7	<0.001

Note: Recurrent cases were defined as having >4 attacks per year, Symptomatic cases had at least one attack in any year that they were followed but did not meet the criteria for a Recurrent case, and Symptomatic controls were mutation carriers who did not experience attacks. AIP: acute intermittent porphyria; CKD: chronic kidney disease; HCC: hepatocellular carcinoma. *p-value is for Chi-squared or Fisher's exact test comparisons of Recurrent vs Asymptomatic, and Symptomatic vs Asymptomatic. Note: Recurrent cases were defined as having >4 attacks per year, Symptomatic cases had at least one attack in any year that they were followed but did not meet the criteria for a Recurrent case, and Symptomatic controls were mutation carriers who did not experience attacks. AIP: acute intermittent porphyria; CKD: chronic kidney disease; HCC: hepatocellular carcinoma. Source: Neeleman et al. (2018)(22)

Chronic kidney disease

CKD and renal impairment are potential long-term complications of AHP (27,35,37,38). High levels of the toxic metabolite ALA induce vascular injury, and repeated attacks may cause acute kidney injury and progression to irreversible CKD (35). Although no data are available on the increase in mortality due to CKD in patients with AHP specifically, CKD Stage 3 or 4 is associated with mortality hazard rate 7.6 times higher than in the general population (39).

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Anaemia

Anaemia increases with increasing frequency of acute attacks (22). Although no data are available on the increase in mortality due to anaemia in patients with AHP specifically, it has been associated with a 70% increase in 8-year mortality (40).

Hypertension

AHP may lead to an increased long-term risk of chronic sustained hypertension, (35,37,41,42) and deaths due to complications of hypertension in AIP patients have been reported (37).

HCC

An estimated 10% of patients with AHP die from cancer of the liver,(36,43) and HCC has been reported as a long-term complication of AHP, occurring in approximately 1.5% of AHP patients (36,37,44–48). HCC may occur in AHP patients who do not experience attacks or show signs of cirrhosis,(27,37) and may be due to direct carcinogenicity of ALA, reduction in free radical scavenging due to reduced haem-containing antioxidant enzymes, or tumour suppressor genes being directly or indirectly affected by mutations in the HMBS gene (26,37).

Survival

In recent years, improvements in disease recognition and the prompt treatment of acute attacks with haemin have dramatically reduced attack-related mortality, making it a relatively rare event (41,49). Although there has been a decline in attack-related mortality, the overall mortality risk of patients with AHP is still increased compared to the general population. A recently published retrospective, population-based, cohort study by Baravelli et al., based on data from 33 patients with AHP in the Norwegian Porphyria Registry collected from 1992 to 2017, found an overall mortality HR for AHP patients of 1.3 (95% CI 1.0, 1.8) compared with the general population (50). The increase in mortality risk may be attributed to several long-term complications (i.e. CKD, hypertension, HCC, anaemia, and epilepsy) that are associated with reductions in survival. Additionally, a high rate of suicide is reported in AHP compared with that seen in the general population (3.7% vs 0.01%) (51). Suicidality is more common among patients that experience recurrent attacks (22). These findings are compatible with reports from the literature that suicidality among young adults with chronic disease is more than 70 times that of the general population (52).

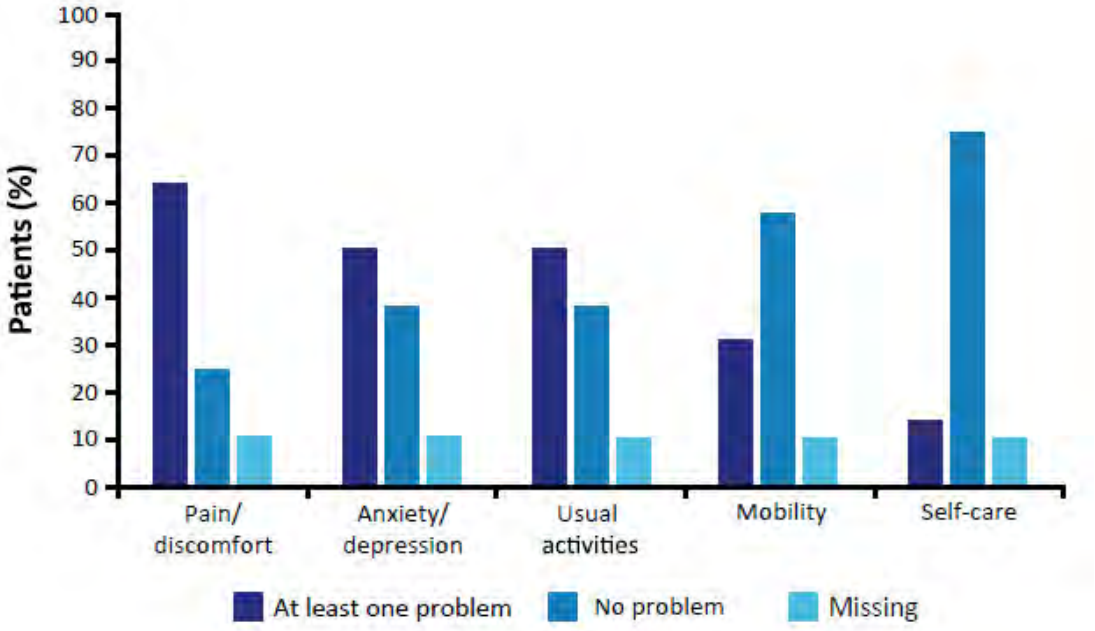
6.1.4 Diagnosis

For most patients with AIP, symptom onset is between the second and fourth decades of life, with a median age at diagnosis of 33 years (11,20). This is also the case for those with VP and HCP.
Diagnosis is often challenging due to the non-specific symptoms and the rare nature of the disease. AHP is often initially overlooked or misdiagnosed. For 61% of patients included in the EXPLORE natural history study, the first international natural history study in patients with hepatic porphyria characterised by recurrent attacks (defined in this study as ≥3 attacks per year or on prophylactic treatment to prevent attacks), accurate diagnosis took over 5 years and further a U.S. study demonstrated that diagnosis of AHP is delayed on average by up to 15 years (20). A recent survey of 38 patients conducted in collaboration with the British Porphyria Association (Gill et al., 2019) found that the time between first symptoms and AHP diagnosis averaged 4.2 (SD=5.9) years (34,53). This same survey reported that 17 of the 38 patients (45%) were initially misdiagnosed before being diagnosed with AHP (53).

6.1.5 Burden of illness – Quality of Life - Impact on the quality of life of patients, their families and carers

Patients with AHP experience debilitating attacks and disabling chronic symptoms between attacks resulting in a reduced HRQoL, particularly with regard to pain/discomfort, anxiety/depression, and the ability to function normally (7). Patients in the EXPLORE study reported experiencing substantial problems with pain, anxiety/depression, everyday activities, and mobility, and 25% of AHP patients required assistance in activities of daily living (Figure 3) (54).

Figure 3: Symptomatic patients with AHP reporting at least some problem in specific domains of the EQ-5D-5L



AHP: acute hepatic porphyria; EQ-5D-5L: 5-level version of the EuroQol five-dimensional health status questionnaire. Source: EXPLORE study, Gouya et al. (2020)(7)

For AHP patients, quality of life is negatively affected not only during attacks but also between attacks. AHP patients who have experienced acute attacks report high rates of anxiety and depression (22,55,56). AHP patients describe feelings of isolation, not only due to a lack of understanding about the disease by friends, family, and healthcare professionals, but also due to the intensity of the pain they experience (32).

The extent of the debilitation that AHP patients suffer during acute attacks is extreme, as is revealed by patients' testimonials. Patients characterize the pain of acute attacks as "not compatible with life"(30) and "not of this world" (57). One patient described the terror associated with recurrent attacks as follows: "The overwhelming feeling was always utter fear, that this was it. That this one was going to get worse…the fear that my body would sort of break from the pain, because I couldn't, in my head I'm thinking there is only so much I can deal with, at some point you're going to snap."(53). Other patient descriptions of AHP attacks are presented in Table 5.

Table 5: AHP patients' descriptions of their experience of acute attacks

Pain
"So, porphyria attacks for me start with pain. Just constant stabbing, whipping, burning pain across my ribs and my abdomen. It will then spread up to my lungs. So, it feels like I can't breathe properly. Spreads down into my lower abdomen, my legs. And the intensity of the pain is anywhere from 8 to 10 out of 10. It doesn't really matter at that stage what pain killers I take, because the pain is just so overwhelming [...] it would feel like someone was pouring acid on my intestines and then ripping them open. And then around my ribs and my lungs particularly, it would feel like someone was scraping my ribs with knives. And then in my spine I would feel like a hot poker, pressing into my spinal cord and sending shooting pains up and down my body."
"It's like sharp burning - it's like hot rods digging, that is how I would describe it. In a barbed wire, like wrapped around my back and stomach when it gets really bad down there."
"It's a real hot feeling like it feels like there's hot coals packed in there. And it feels like someone's like poking in more of them, and there's all this pressure, you know, like stretching and burning ... And then that like carries on. And then whenever, oh, and then sometimes also I'll feel like hot knives stabbing me."
"... and then the worst days is like being disemboweled, having a hot pan shoved into your intestines or into your abdomen while having your ribs filleted."
"The shooting pains, well they are literally that – it will be in my limbs and it will kind of start around the top of my neck and the pain will kind of shoot down to my hands and I'm holding something, my hands will just kind of release. It's almost like an electric shock, actually that's a good way to describe it: an electric shock to the limbs... if it's in my legs – [...] it's a similar thing, it will be just like someone stabbing you with an electric current and it can shoot up and down and up and down."
"If you said to me the only way to get rid of this pain is to shoot you, I would do it. I threatened to jump out of a window, I have threatened to do all sorts of things because it hurts so much that it's not worth living through it's so bad."
Nausea
"You're like throwing up to the point where like you want to die, and you're spitting up bile, and even though your stomach is completely empty and you're like, 'where is this coming from? I haven't eaten in hours. I've been throwing up for half a day'. I'm vomiting foam at that point."
"I have terrible nausea; I can't even keep water down at that point, so I had to be hydrated on a drip in hospital."
Neurological symptoms
"I had like paralysis also in my legs, and I couldn't walk. I mean like I was dragging a leg. And also I had difficulty breathing. I almost got put on the ventilator."
"And then in June I got really poorly again and ended up paralysed, and I could not walk for a year."
"I suffer with hallucinations, confusion, I don't really know what's going on, I don't really know where I am, I'm not safe to be alone."
"... headaches so bad that they've caused me to lose my sight on numerous occasions."
"It's re-occurred several times now. In my 20 attacks, it's happened more recently in my last five, where I've ended up waking up one morning and I can't move my leg or I can't, or I get out of bed to go to the toilet and I fall. And that's just where the nerves have been attacked obviously, during the porphyria attack."

Furthermore, patients with AIP in particular experience serious life consequences, such as limitation in family size (56). Some AHP patients have even reported that the excruciating porphyria-related pain and concerns regarding receiving appropriate diagnosis and care have led to the loss of spouses and the custody of their children (58).

With a peak occurrence in the third decade of life (59) AHP disproportionately impacts patients in their prime productive years, and negatively impacts self-sufficiency and employment prospects (56,60). The EXPLORE study reported that 67% of AHP patients were not able to work full time, and that 85% of AHP patients in employment had lost on average 54 workdays in the past year due to AHP (54).

The reduced functional status of AHP patients also constitutes a substantial caregiver burden, with employed AHP caregivers reporting an average of 17 workdays lost in order to care for AHP patients (54,61).

A UK survey of AHP patients revealed that the acute and chronic nature of AHP combined with a lack of effective treatments result in feelings of frustration, fear, anxiety, and depression that affect both patients and their caregivers. Frequently mentioned concerns among patients and carers included coping with pain, a range of

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other symptoms experienced (e.g., nausea, fatigue, and seizures), and the cognitive and psychiatric symptoms that often accompany this disease (53,62).

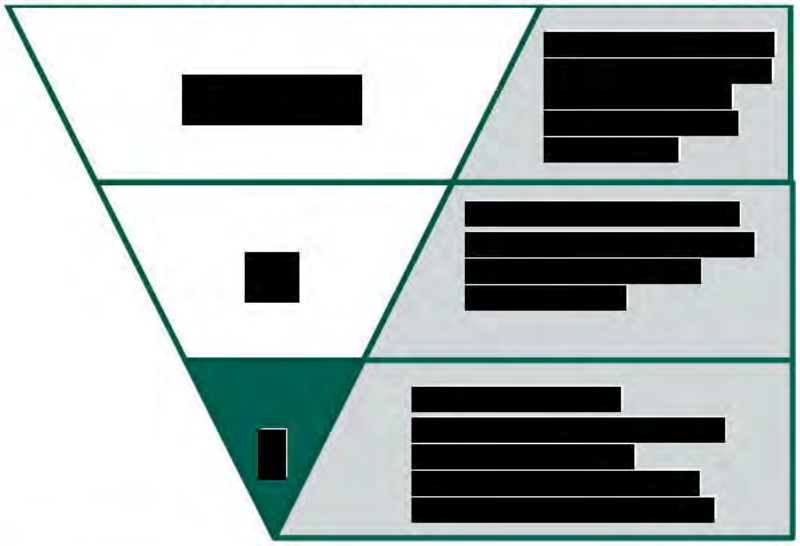
Unmet medical need

Prior to givosiran there were no therapies for the prevention of recurrent AHP attacks available in Denmark (See section 5.3 for overview). In Denmark AHP-related attacks are managed by hospital admission and prompt treatment as discussed in section 0. Following recovery from an acute attack, chronic symptoms and long-term complications can continue to cause significant morbidity and mortality. There remains a high unmet medical need for a safe and effective therapy that addresses the underlying cause of AHP and improves the HRQoL of patients with this condition. Since givosiran is the only disease-modifying therapy that treats the underlying AHP disease process, thereby preventing the occurrence of attacks and addressing ongoing chronic pain, it meets an important unmet need for patients with a history of recurrent attacks in Denmark (17).

6.1.6 Epidemiology - Incidence and prevalence in Denmark

The incidence of symptomatic AHP in Denmark is unknown (63), but the incidence for Europe is estimated to 0.13 per million, with the exception of specific regions where the incident might be higher due to a founder effect (11). [redacted]

Figure 4: Funnel diagram describing the number of patients who will be eligible for givosiran treatment



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[redacted]

[redacted]

6.1.7 Patient populations relevant for this application

The eligible population will be patients with AHP with recurrent attacks. The eligibility criteria for treatment should be the same as the key inclusion criteria of the ENVISION trial (NCT03338816).

- ≥ 12 years of age
- Diagnosed with Acute Hepatic Porphyria
- Have active disease, with at least 2 documented porphyria attacks within the last 6 months

6.2 Current treatment options and choice of comparator(s)

6.2.1 Current treatment options

There are no comparator treatments for givosiran in Denmark—until givosiran, patients afflicted with AHP have lacked any treatment options to prevent AHP-related acute attacks and have had to rely on supportive therapy to manage the chronic pain that occurs as part of this condition (17). The management of patients with recurrent acute attacks is challenging (64). Options currently available for preventing acute attacks include lifestyle modifications and avoidance of medications that are known to precipitate attacks (3,64).

Givosiran, a disease-modifying, preventative treatment for AHP, is intended for use as a long-term therapy, with rescue therapy as an adjunctive measure for patients who experience a breakthrough acute attack. While attacks are reduced by almost 75% in patients who receive givosiran, there remains a need for a treatment that can ameliorate breakthrough acute attacks when they do occur (18).

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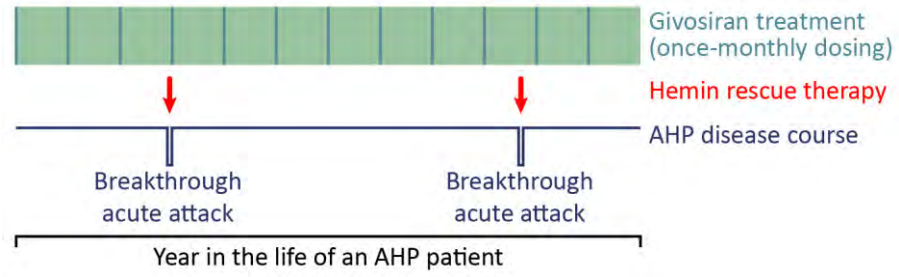
Thus, even with the availability of givosiran, rescue therapy retains an important role in the treatment of AHP. Once an acute attack occurs, rescue therapy may be instituted (64). Use of haemin as a rescue therapy is aligned with the Danish summary of product characteristics (14).

Carbohydrate loading is another rescue therapy option for patients experiencing an acute attack, but experts agree that it should be limited to mild attacks or as a stop-gap measure until haemin can be administered since the effects of treatment are weak and there is no reliable evidence on its efficacy (27,64). As there are no definitive data supporting carbohydrate loading for the prophylaxis of acute attacks, the use of carbohydrate loading as prophylaxis is not recommended (1,3).

The place in therapy of haemin and carbohydrate loading are completely different from that of givosiran—they are rescue therapies that are generally used on a short-term basis and for which efficacy is measured by the resolution of the acute attack (Figure 5) (64). The posology of Normosang (haemin), as detailed in the SmPC, confirms the short-term intended use of this product, with a maximum recommended dosing regimen of 4 days (14). However, in clinical practice IV rescue haemin treatment is often extended for longer in severely ill patients (15,16).

Figure 5: Rescue therapies are administered as short-term treatment for breakthrough attacks



AHP: Acute hepatic porphyria

In addition to the short-term treatment targeting the resolution of the attack (haemin and carbohydrate loading), symptomatic therapy including treatment for pain, hypertension, tachycardia, nausea, vomiting, and convulsions can mitigate the symptoms of AHP, both during an attack as well as in between attacks.

6.2.2 Choice of comparator(s)

As agreed in consultation with the DMC, the comparator in this submission conducted for Denmark is BSC, constituting the standard treatments, such as rescue haemin, that are used in clinical practice to speed the resolution of symptoms and reduce the hospital length of stay hospital stays during acute attacks.(3,64) BSC was determined to be the appropriate comparator for the submission because givosiran is the only disease-modifying therapy that treats the underlying AHP disease process, thereby preventing the occurrence of attacks and addressing ongoing chronic pain (7).

6.2.3 Description of the comparator(s)

There is no accepted standard of care for treating recurrent AHP, beyond merely managing acute attacks after they occur. Patients are therefore offered BSC constituted by treatment at the hospital with glucose infusion (300-400 g/day), and if glucose infusion lacks effect, haemin treatment is initiated (63). Haemin is infused daily for up to 4 days according to the SmPC (14). However, in clinical practice IV rescue haemin treatment is often extended for longer in severely ill patients (15,16). The effect on pain and visceral symptoms occurs after 1-2 days, while the effect on any paralysis is poorer. Management and treatment of symptoms like pain, hypertension, tachycardia, nausea, vomiting, and convulsions should be provided in order to mitigate the symptoms.

6.3 The intervention

Givosiran, manufactured by Alnylam Pharmaceuticals, Inc., is the only disease-modifying therapy that treats the underlying AHP disease process, thereby preventing the occurrence of attacks and addressing ongoing chronic pain (17). Givosiran is a small interfering ribonucleic acid (siRNA) therapeutic targeting delta aminolaevulinic acid synthase 1 (ALAS1) (65). Administration of givosiran significantly lowers induced liver ALAS1 levels in a sustained manner and thereby decreases levels of the toxic heme intermediates ALA and PBG to near-normal levels (17,65). By reducing accumulation of these intermediates, givosiran significantly reduces or prevents the occurrence of porphyria-related attacks and also decreases other aspects of disease burden (17). While attacks are reduced by almost 75% in patients who receive givosiran, there remains a need for best supportive care treatment that can ameliorate breakthrough acute attacks when they do occur (17). Patients will therefore receive BCS as describe above when such breakthrough acute attacks occur (see section 6.2.3)

Posology

The dosing is 2.5 mg/kg once monthly by SC injection, no co-medication needed, and givosiran treatment is expected to continue throughout the patient's lifetime.

Monitoring

Liver function tests should be performed prior to initiating treatment with givosiran, and these tests should be repeated monthly during the first 6 months of treatment, and as clinically indicated thereafter. Notably, monthly liver function tests after the first 6 months of treatment are not a standard requirement for givosiran (19).

Increases in serum creatinine levels and decreases in estimated glomerular filtration rate (eGFR) were reported during treatment with givosiran. In the ENVISION study, the median increase in creatinine at month 3 was 6.5 µmol/L (0.07 mg/dL) and resolved or stabilised by month 6 with continued monthly treatment with 2.5 mg/kg givosiran. Progression of renal impairment has been observed in some patients with pre-existing renal disease and these events were by biopsy deemed to be consistent with the patients' underlying disease(17,66). Careful monitoring of renal function during treatment is required in such cases of patients with pre-existing renal disease (66), however regardless of givosiran treatment renal monitoring is always encouraged for all AHP patients due to long-term disease related complications (3).

Treatment discontinuation

Interrupting or discontinuing treatment should be considered for clinically relevant transaminase elevations. In case of subsequent improvement in transaminase levels, resumption of treatment at a 1.25 mg/kg dose after interruption could be considered (17,66). In the ENVISON study 5 patients treated with givosiran the transaminase elevations resolved with ongoing dosing at 2.5 mg/kg. Per protocol, one patient with ALT more than 8 times the upper limit of normal (ULN) (defined as stopping rule) discontinued treatment and one patient with ALT more than 5 times the ULN interrupted treatment and resumed dosing at 1.25 mg/kg. ALT elevations in both patients resolved (17,66).

7. Literature search and identification of efficacy and safety studies

7.1 Identification and selection of relevant studies

Based on the new DMC method guideline the DMC can accept that systematic literature review is not carried out if one or several studies have already directly compared the new pharmaceutical with the relevant comparator.

The pivotal phase-3 ENVISION trial provides head-to-head data with the relevant comparator used as the current standard treatment in Denmark, and since no further comparative studies with givosiran have been conducted by Alnylam, a literature search will not contribute any additional relevant information.

Alnylam has discussed this with the DMC prior to the submission, and the DMC acknowledged that the systematic literature review would not be necessary for the present application.

7.2 List of relevant studies

Table 8: Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	ClinicalTrials.gov number	Dates of study (start and expected completion date)	Used in comparison of*
1. Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria. Balwani et al., N Engl J Med 2020 (17).	ENVISION	NCT03338816	January 31, 2019 - August 2021*	Givosiran vs. placebo for patients with Acute Hepatic Porphyrias (AHP)
2. Data on file: CLINICAL STUDY REPORT 2 INTERIM ANALYSIS FOR ALN-AS1-003 (GIVOSIRAN, Alnylam Pharmaceuticals, 2021 (18).	ENVISON + ENVISON-OLE	NCT03338816	January 31, 2019 - August 2021*	Givosiran vs. placebo for patients with Acute Hepatic Porphyrias (AHP) Givosiran long-term safety and efficacy (18-month extended phase)
3. Eighteen-Month Interim Analysis of Efficacy and Safety of Givosiran, an RNAi Therapeutic for Acute Hepatic Porphyria, in the Envision Open Label Extension, Kuter et al.,. Blood (poster presentation, abstract), 2020 (67).	ENVISON-OLE	NCT03338816	June 27, 2018 - August 2021.	Givosiran long-term safety and efficacy (18-month extended phase)

*The randomized phase of ENVISION was finished on June 27, 2018, which was then extended into the open-label period of the trial. The open-label extension phase is expected to be completed in August 2021.

For detailed information about ENVISION and the OLE phase, refer to **Appendix B**. ENVISION OLE 24-month data are expected to be presented at the United European Gastroenterology congress (UEG) 2021 and American College of Gastroenterology (ACG) 2021 in October, but are unavailable as of now.

8. Efficacy and safety

8.1 Efficacy and safety of givosiran compared to placebo for patients with acute hepatic porphyria with recurrent attacks

8.1.1 Relevant studies

The phase 3 trial ENVISION (Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria) had the objective to evaluate the effect of SC givosiran (ALN-AS1), compared to placebo, on the rate of porphyria attacks in patients with AHP. Results were reported by Balwani et al. 2020 (17).

ENVISION is a phase 3 randomised, double-blind (DB), placebo-controlled multicentre study with an OLE. All patients completing the 6-month treatment period, with either givosiran or placebo, may be eligible to continue

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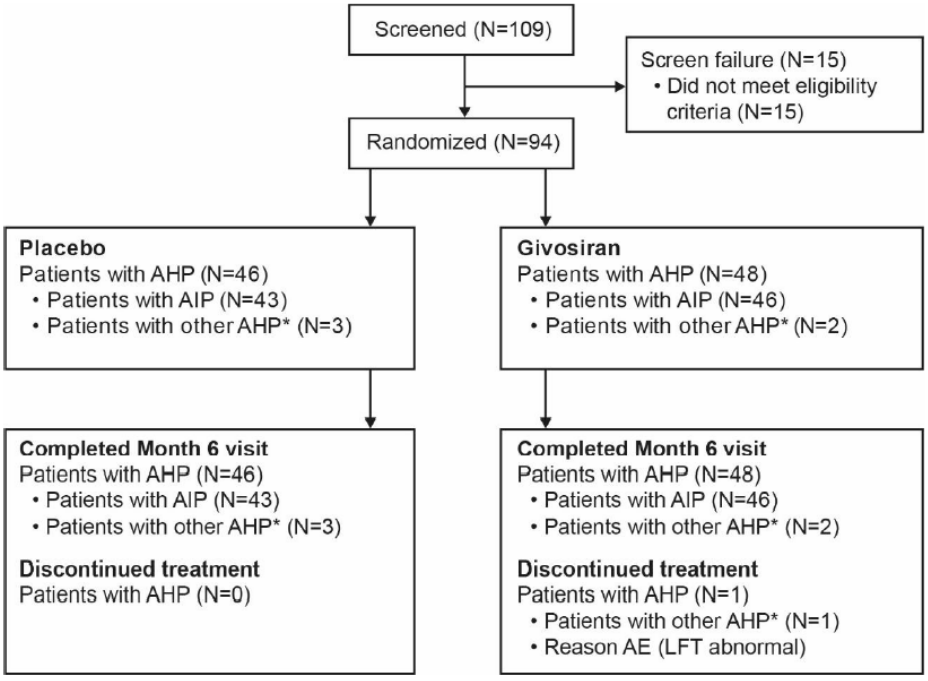
on OLE study in which they will receive treatment with givosiran for up to 30 months. In this dossier, data is presented for 6-month DB phase of ENVISION and the 18-month data-cut of the OLE study.

The main inclusion criteria in the ENVISION trial were age ≥12 years, documented AHP, and at least two porphyria attacks in the last 6 months. Patients had to be willing to discontinue and/or not initiate haemin prophylaxis. Patients were randomised 1:1 to study drug (Givosiran 2.5 mg/kg by SC injection monthly; n=48) or placebo (sodium chloride 0.9% weight/volume for SC administration monthly; n=46) in a double-blind manner. Patients with significant ALT elevations were allowed to be resumed in the DB RCT phase at a lower dose (1.25 mg per kilogram). Further in the OLE phase of the study two doses were assessed during the OLE period: 2.5 and 1.25 mg/kg givosiran once monthly. The 1.25 mg/kg dose was introduced as an a rechallenge dose in response to patients experiencing liver transaminase elevations.

Figure 6: CONSORT flow diagram for the ENVISION RCT



*Patients with other AHP includes patients with HCP, VP, or without an identified AHP mutation.
AE: adverse event; AHP: acute hepatic porphyria; AIP: acute intermittent porphyria; ALT: alanine aminotransferase; HCP: hereditary coproporphyria; LFT: liver function test; N: number; RCT: randomised controlled trial; QM: monthly; VP: variegate porphyria. Source: Balwani et al. (2020) (17).

Because the vast majority of patients with AHP have the AIP subtype of the disease, the primary endpoint and most secondary efficacy endpoints were set up to be assessed in patients with AIP subtype with an identified mutation to allow for a more homogeneous population for an assessment of efficacy. Alnylam have chosen to present the results from both the primary AIP efficacy population as well as the overall AHP population to demonstrate consistency of the results. As the AIP subtype represented ≈ 95% of the patients in the ENVISION trial, the AIP analysis is a very close approximation of the ITT population, which was used for reporting all safety outcomes. Because givosiran acts upstream of the genetic defects in the heam-synthesis pathway that differentiate the AHP subtypes (see Figure 2), no difference in effect can be expected. Efficacy results presented in section 8.1.2 clearly demonstrate consistent reductions in the primary endpoint across the AHP and AIP populations of the trial.

The primary endpoint of the study was the composite AAR requiring 1) hospitalisation, 2) an urgent healthcare visit, 3) or IV haemin administration at home, in patients with AIP over a 6-month double-blind treatment period. Details of the definition and parameterisation of the endpoints provided in this application are available in **Appendix D**. The AAR is presented for both the AHP and AIP cohort and in additional to this subset analysis is

provided to demonstrate consistent results across all major stratifications of patients, which provides the rationale for the results being representative and generalizable across all AHP patients. The full study characteristics are presented in **Appendix B**. Baseline characteristics for the patients included in the ENVISION trial are provided in **Appendix C**.

8.1.2 Efficacy and safety – results per study

8.1.2.1 Efficacy: ENVISION and ENVISION-OLE

The 6-month efficacy results of the primary endpoint of ENVISION is presented in Table 9. The primary endpoint from the trial was the AAR with three components: attacks requiring 1) hospitalisation, 2) an urgent healthcare visit, or 3) IV haemin administration at home. The primary endpoint was analysed in the AIP population and in the AHP population as a secondary endpoint (both shown in Table 9).

All other secondary endpoints from the AIP population that were available also for the AHP population are presented in Table 10. The results for the AIP population are published in both Balwani et al., 2020 (17) and the European Public Assessment Report for Givosiran (19). Where data on file is used for the 6-month efficacy analysis this is clearly stated; however, all AHP analyses other than the mean AAR are based on data on file from the clinical study report of ENVISION (18). Additional data are provided from the ENVISON-OLE, the extension phase of the ENVISION trial to support long-term efficacy and safety, which are all data-on file from the clinical study report (18).

Table 9: Primary endpoint – AAR porphyria attack composite endpoint in AIP/AHP patients - ENVISION trial

	AHP			AIP		
Primary endpoint **6 month follow-up**	**Placebo (n=46)**	**Givosiran (n=48)**	**Difference (95 % CI), p-value**	**Placebo (n=43)**	**Givosiran (n=46)**	**Difference (95 % CI), p-value**
Mean AAR (95% CI)*	12.26 (9.22, 16.29)	3.35 (2.37, 4.74)	RR: 0.27 (0.17, 0.43) p=0.001	12.52 (9.35, 16.76)	3.22 (2.25, 4.59)	RR: 0.26 (0.16, 0.41) p=0.001
Median AAR (Q1, Q3)*	10.65 (2.24, 16.29)	1.04 (2.37, 4.74)	9.61, NT	10.68 (2.24, 26.09)	1.04 (0.00, 6.23)	9.64, NT

*The AAR analysed in the AHP population was a prespecified secondary endpoint, which met statistical significance according to hierarchical testing procedure. The median AAR was a secondary endpoints, and the between-group difference in the median values in this category was not calculated with the use of statistical models (simple subtraction).
AAR: annualised attack rate; AHP: acute hepatic porphyria; CI: confidence interval; RR: rate ratio; NT: not tested; Q: quartile.

Table 10: Key secondary and exploratory endpoints - 6-month double-blinded phase – ENVISION trial

	AHP			AIP		
6-month follow-up	**Placebo (n=46)**	**Givosiran (n=48)**	**Difference*, p-value***	**Placebo (n=43)**	**Givosiran (n=46)**	**Difference*, p-value***
Secondary endpoints*						
Urinary ALA mmol/mole of creatinine*						
Mean level at baseline (95%CI)	[redacted]	[redacted]	[redacted]	17.5 (NR)	20.0 (NR)	NR

6-month follow-up	AHP			AIP		
	Placebo (n=46)	Givosiran (n=48)	Difference*, p-value*	Placebo (n=43)	Givosiran (n=46)	Difference*, p-value*
ALA Least-squares mean (95%CI) at 6 months				23.2 (18.1, 28.2)	4.0 (-0.7, 8.7)	–19.1 (-26.0, -12.2) p<0.001
ALA median (IQR) at 6 months				16.2 (8.0, 23.0)	1.3 (0.9 to 4.6)	-12.8 (95CI: -16.1, -7.8) p<0.001
Urinary PBG mmol/mole of creatinine*						
Mean PBG level at baseline (95%CI)				46.8 (NR)	50.4 (NR)	NR
PBG Least-squares mean (95%CI) at 6 months				49.1 (39.3, 59.0)	12.9 (3.7, 22.1)	–36.2 (-49.7, -22.7) p<0.001
PBG Median (IQR) at 6 months				35.1 (25.6, 50.0)	4.4 (1.6, 15.3)	-27.5 (-34.0, -21.0) p<0.001
Annualized no. of days of haemin use*						
Mean (95% CI)				29.71 (18.41, 47.94)	6.77 (4.20, 10.92)	0.23 (0.11-0.45), p=0.001***
Median (Q1 – Q3)**				27.61 (2.14, 47.55)	0.0 (0.00, 10.81)	27.61 (2.14, 36.74)
Daily worst score for pain*						
‡Median of change in AUC from baseline (IQR)				-5.3 (-23.0, 11.1)	-11,5 (-29.2, 3.0)	10.1 (–22.8 to 0.9), p=0.046‡
‡Median average change from baseline (IQR)				-0.010 (-0.42, 0.40)	–0.570 (-0.97, -0.18)	–0.4 (–1.0 to 0.1), p=0.049‡
Daily worst score for fatigue*						
Least-squares mean (95% CI) of change in AUC from baseline				-4.208 (-13.53, 5.12)	-11.148 (-20.10, -2.20)	-6.940 (-19.84, 5.96) p=0.2876

6-month follow-up	AHP			AIP		
	Placebo (n=46)	Givosiran (n=48)	Difference*, p-value*	Placebo (n=43)	Givosiran (n=46)	Difference*, p-value*
Least-squares mean (95% CI) of average change from baseline				-0.182 (-0.60, 0.23)	–0.502 (-0.90, -0.10)	-0.321 (-0.90, 0.25) p=0.2698
Daily worst score for nausea*						
Least-squares mean (95% CI) of change in AUC from baseline				-4.011 (-10.88, 2.86)	1.481 (-5.10, 8.06)	5.492 (-4.00, 14.98) p=0.2532
Least-squares mean (95% CI) of average change from baseline				–0.181 (-0.49, 0.12)	0.067 (-0.23, 0.36)	0.248 (-0.17, 0.67) p=0.2459
SF-12*						
PCS Mean (95% CI) at baseline				38.420 (35.56, 41.28)	39.427 (36.65, 42.20)	-1.007 (-5.03, 3.01) p=0.6197
PCS Least-squares mean (95% CI) of change from baseline at 6 months				1.431 (-0.10, 3.86)	5.369 (3.05, 7.69)	3.939 (0.59, 7.29) p=0.0216
MCS Mean (95% CI) at baseline				41.036 (38.02, 44.05)	40.408 (38.07, 42.75)	0.628 , NR
MCS Mean (95% CI) change from baseline at 6 months				1.299 (-1.25, 3.85)	3.655 (0.74, 6.57)	2.37, NR
Exploratory endpoints						
Proportion of Patients with 0 Attacks (%)				7 (16.3%)	23 (50%)	34.7%, NT
Mean proportion of days with opioid use over 6 months	NR			38%	23%	15 %, NT
PGIC at 6 months* **	NR			18.4%	59.4%	41 %, NT
PPEQ at 6 months (Givosiran vs Placebo, % patients)* **	NR			Refer to section with exploratory endpoints		

Note: Scores for pain, fatigue, and nausea were measured on a numerical rating scale ranging from 0 to 10, with higher scores indicating more severe symptoms. Scores on the Physical Component Summary of the 12-Item Short-Form Health Survey, version 2 (SF-12), range from 0 (worst functioning) to 100 (best functioning), with published literature in other chronic diseases suggesting that a change of 2 to 5 points represents a clinically meaningful difference.

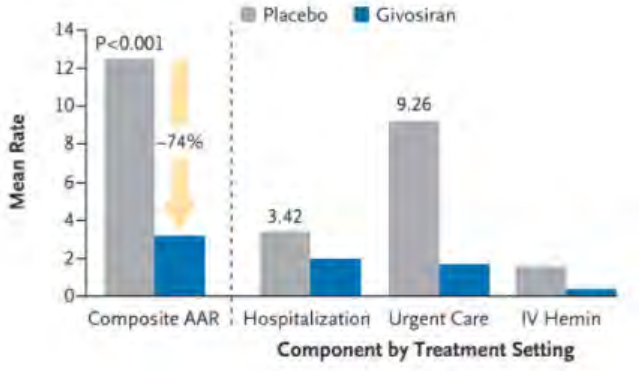
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

*Secondary endpoints were analysed using a prespecified hierarchical order in the AIP population at 6-month intervention period unless otherwise stated. p-values of other outcomes are reported as nominal, as the endpoint did not meet the conditions of the prespecified hierarchical order.
**The between-group difference in the median values in this category was not calculated with the use of statistical models.
*** This value is a rate ratio (95% CI) for the comparison between givosiran and placebo.
****PGIC: Proportion of patients reporting "much improved" or "very much improved". None of the placebo patients reported that their condition was "very much improved". PPEQ: Results are given in the section with exploratory endpoints below.
‡Because of a significant deviation from normal distribution, the planned methods of a mixed model for repeated measures or analysis of covariance were not valid. A nonparametric stratified Wilcoxon signed-rank test was therefore conducted. The median of the between-group difference was estimated with the use of the Hodges–Lehmann method.
AUC: area under curve; CI: confidence interval; MCS: SF-12 Mental Component Summary Score; NR: not reported; NT: not tested; PCS: SF-12 Physical Component Summary score; PGIC: Patient Global Impression of Change Questionnaire; PPEQ: Porphyria Patient Experience Questionnaire.

Composite annualized attack rate (AAR) – primary endpoint

In patients with AIP, the mean AAR over 6 months was 3.2 (95% confidence interval [CI], 2.3 to 4.6) in the givosiran group and 12.5 (95% CI, 9.4 to 16.8) in the placebo group, representing a 74% lower rate in the givosiran group (P<0.001). Efficacy data from the AHP group were consisted with these findings (Table 9). For each of the three components of the composite attacks, there was a greater reduction in the givosiran group than in the placebo group, illustrated in Figure 7 (AIP group).

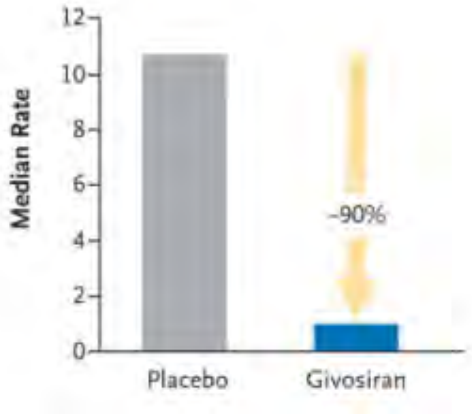
Figure 7: Reduction in composite AAR, and the three components of AAR (AIP group) – ENVISION trial



AAR: annualised attack rate; IV: intravenous.
Note: All components of the AAR-composite endpoint were significantly reduced in the givosiran group compared to the placebo group

The median annualized attack rate was 1.0 (interquartile range, 0.0 to 6.2) in the givosiran group and 10.7 (interquartile range, 2.2 to 26.1) in the placebo group, a relative difference of 90% (AIP group), illustrated in Figure 8 (17).

Figure 8: Median AAR for Givosiran vs. placebo group – ENVISION trial

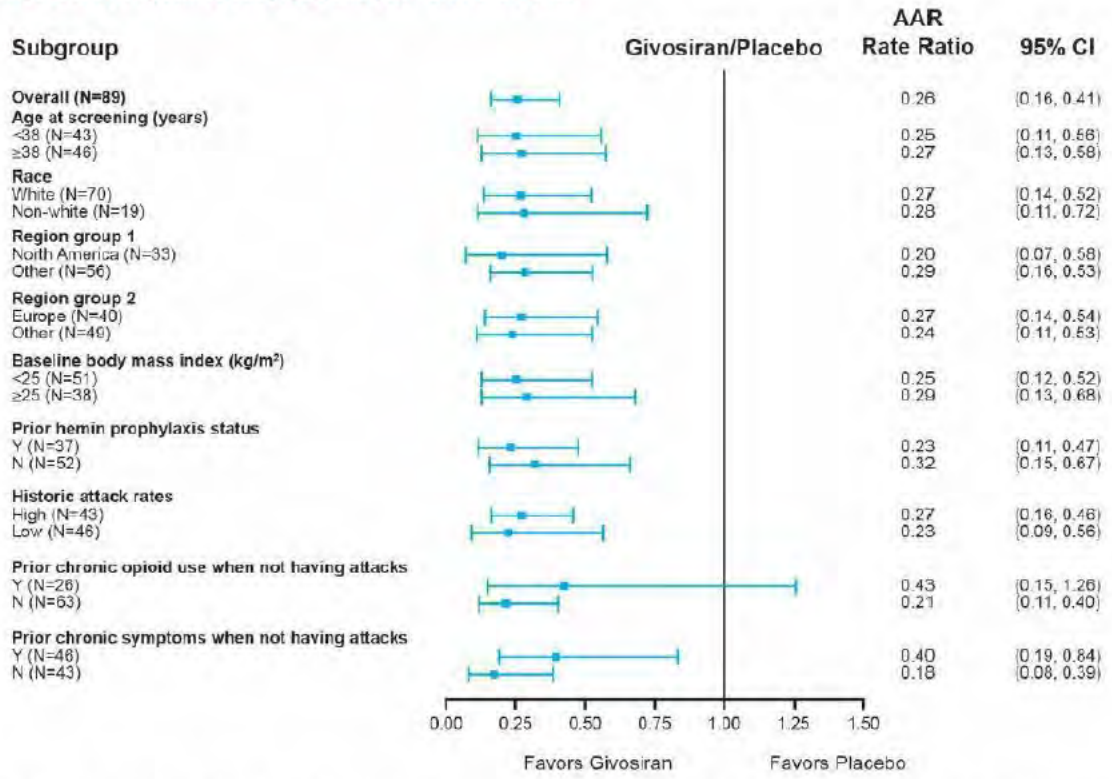


This decrease was evident within the first month and was sustained throughout the 18-month OLE-phase (see Figure 10). Fifty percent of the patients in the givosiran group had no porphyria attacks during the intervention period, as compared with 16.3% of those in the placebo group (AIP group).

AAR subgroup analysis

In a pre-specified subgroup analysis of AAR in AIP patients, the significant treatment benefit of givosiran compared to placebo was consistent across all subgroups except prior opioid use when not having attack. Although the 95% CI for this subgroup crossed 1.0, the point estimate lay within the 95% CIs in the other subgroups, and the result simply represents variation in response and small sample size not powered for demonstrating superiority in subgroups. EMA in their assessment report also considered gender as a specific subgroup, and demonstrated that this factor did not have any influence on givosiran efficacy or safety (18).

Figure 9: Pre-specified subgroup analysis - ENVISION trial



Note: AAR in AIP group stratified by key baseline characteristics. AAR: annualised attack rate. Source: Balwani et al. (2020)(17)

Sustained and long-term reduction in porphyria attacks – results from ENVISION-OLE (AHP population)

In the OLE phase, the reduction in the composite AAR was sustained for patients previously treated with givosiran in the DB phase (givosiran/givosiran) and was reduced to a similar level for patients switching from placebo in the DB phase to givosiran in the OLE phase (placebo/givosiran), as illustrated in Figure 10.

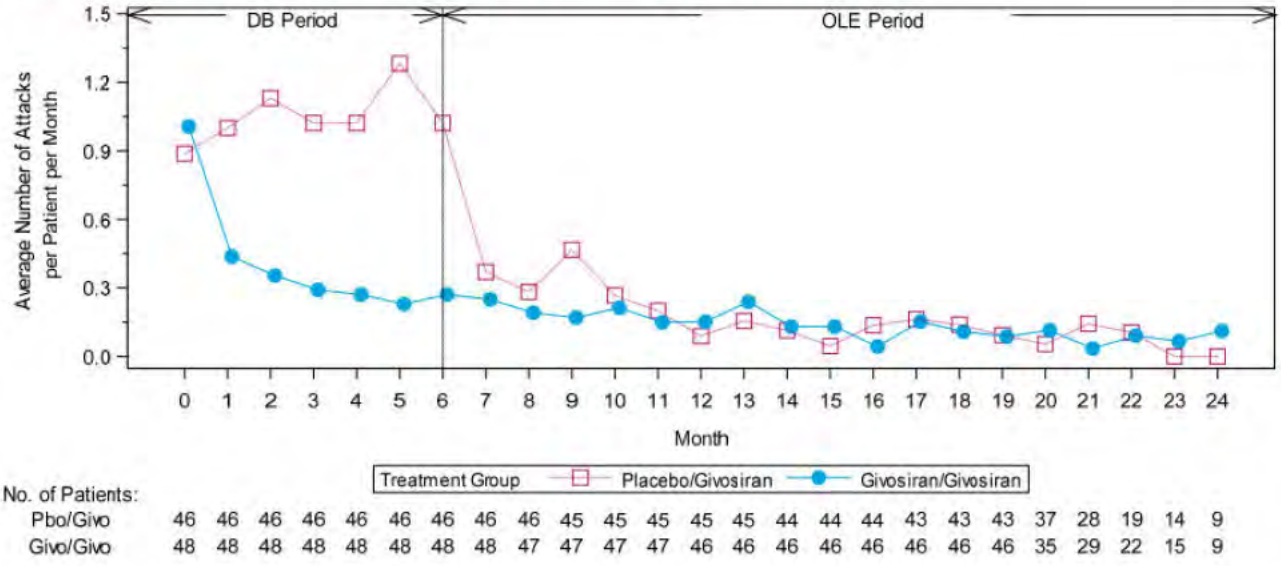
[redacted]

Table 11: Comparison of AAR at DB- and OLE-phase in the ENVISION trial compared to baseline AAR – AHP population

Parameter	Placebo/Givosiran, n = 46	Givosiran/Givosiran (n = 48
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

AHP=acute hepatic porphyria; DB=double-blind; OLE: open-label extension

Figure 10: Average number of attacks per patient per month during the DB and OLE periods



AHP: acute hepatic porphyria; DB: double-blind; IV: intravenous; Givo/Givo, Givosiran/Givosiran; OLE=open-label extension; Pbo/Givo, Placebo/Givosiran.
Note: Month 0 represents the average rate per month from the 6 months prior to randomization, and the estimate was calculated as total number of attacks/total duration in months. Month 1 and beyond were categorized relative to the first dose of study drug, and the estimate was calculated as total number of attacks/total number of patients reached that month. One month=28 days was used in categorization.

Summary of Secondary Endpoints (6 month – ENVISION, AIP population)

The key secondary endpoints are shown in Table 10.

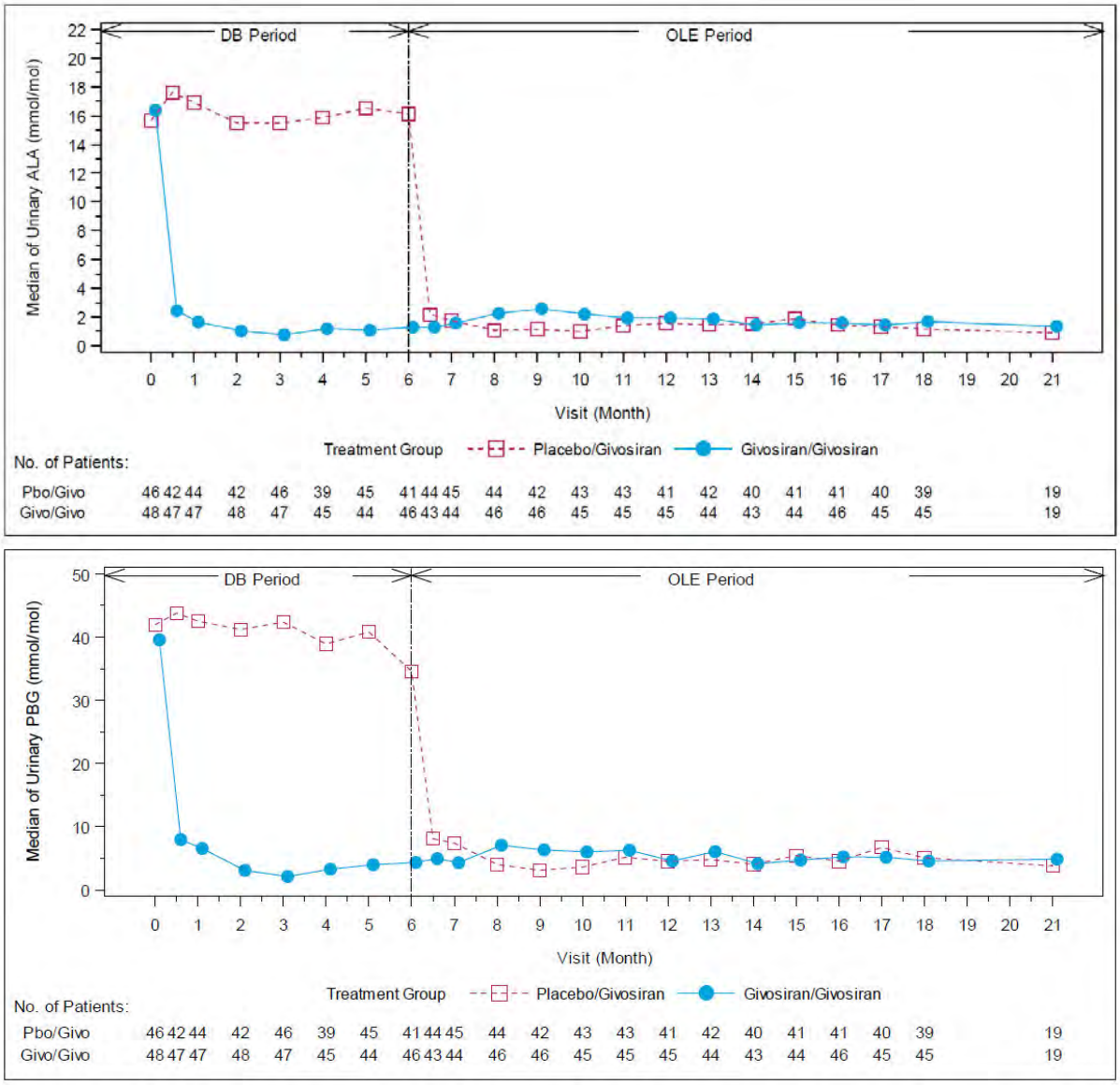
Urinary ALA and PBG reductions

Among the patients with AIP, levels of urinary ALA (at 6 months) and PBG (at 6 months) were significantly lower in the givosiran group than in the placebo group (P<0.001). Reductions were sustained throughout the intervention period (Figure 11); in the givosiran group, the median percent reduction from baseline at 6 months was 86% for urinary ALA levels and 91% for PBG levels. In the OLE-phase (AHP-population) sustained reductions were also achieved throughout the observation period as shown in Figure 11.

In the OLE-phase sustained reduction of urinary ALA levels was observed in the givosiran/givosiran group through 18 months of givosiran treatment with median reductions from baseline in ALA levels ranging from 82.0% to 93.8% through 18 months of treatment. Patients in the placebo/givosiran group had rapid and sustained reductions in ALA levels with a time course similar to that observed in givosiran patients in the DB period (Figure 4). Near maximal reduction in ALA was achieved within 2 weeks of crossing over to givosiran treatment.

Urinary PBG levels was observed in patients in the givosiran/givosiran group through 18 months (Figure 11, bottom panel) of givosiran treatment with median reductions from baseline in PBG levels ranging from 75.6% to 94.5% through 18 months of treatment. Patients in the placebo/givosiran group had rapid and sustained reductions in PBG levels with a time course similar to that observed in givosiran patients in the DB period (Figure 5). Near maximal reduction in PBG was achieved within 2 weeks of crossing over to givosiran treatment.

Figure 11: Median urinary ALA (top panel) /PBG (bottom panel) levels by visit during givosiran treatment over time (AHP-population)



DB: double-blind; Givo: givosiran; OLE:open-label extension; PBG: porphobilinogen; Pbo:placebo

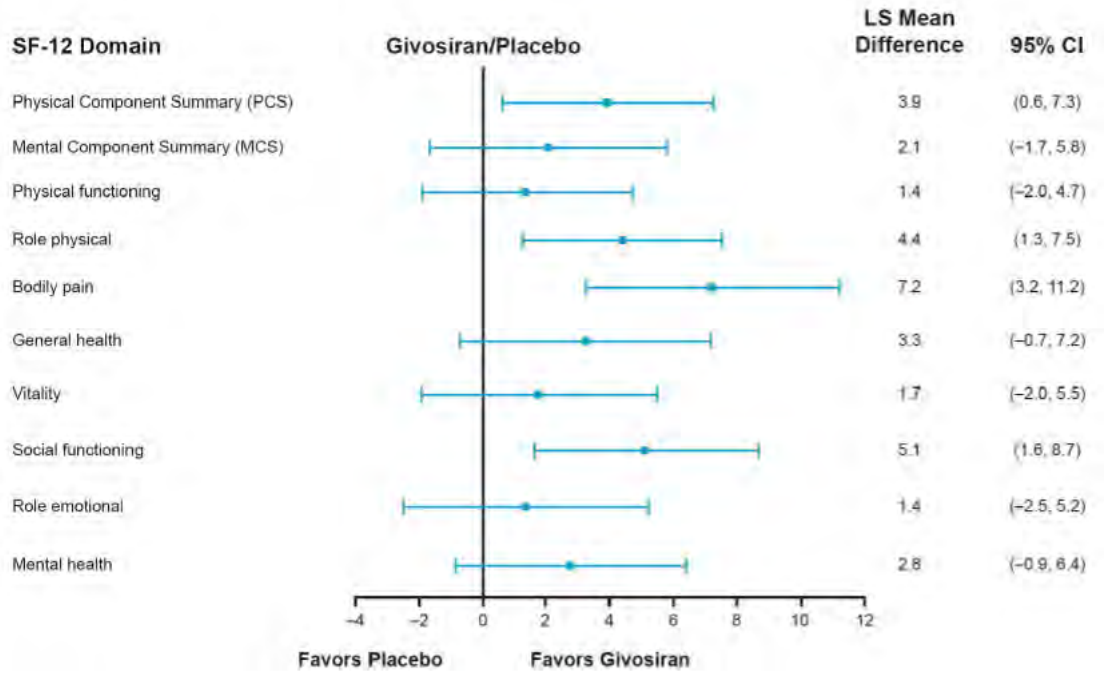
Other secondary endpoints

In patients with AIP, the mean annualized number of days of haemin use was significantly lower in the givosiran group than in the placebo group at 6 months (6.8 days vs. 29.7 days, representing a 77% lower number in the givosiran group) (P<0.001). Overall, 54% of the patients in the givosiran group had no days of haemin use, as compared with 23% of those in the placebo group. Reduction in haemin use may be beneficial, since haemin is potentially associated with both acute side effects (e.g., headache, fever, and phlebitis) and chronic side effects (e.g., iron overload, venous obliteration, and complications with indwelling central venous catheters) (68,69).

Among the patients with AIP, the worst daily pain score was significantly lower in the givosiran group than in the placebo group (P=0.046). There were no significant between-group differences in the worst daily scores for fatigue or nausea, although trends numerically did favour givosiran.

Among the patients with AIP, the mean (95 % CI, p-value) change from baseline in the Physical Component Summary of the SF-12 was 3.9 (0.6, 7.3, p=0.028) points higher (indicating improvement) in the givosiran group than in the placebo group at 6 months. Improvements in SF-12 PCS were clinically meaningful, based on published literature in other chronic diseases suggesting that a change of 2 to 5 points represents a meaningful change (70,71). Results across SF-12 domains showed a consistent effect favouring givosiran over placebo, with the largest effects observed for the domains bodily pain, social functioning, and role limitations due to physical problems.

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



AIP: acute intermittent porphyria; LS: least square; SF-12: 12-Item Short Form Health Survey. Source: Balwani et al. (2020)(17)

Exploratory Endpoints (6 months – ENVISION, AIP population)

No statistical testing was performed for exploratory endpoints, but they are reported here to supplement the findings of the primary and secondary efficacy analysis. In summary, givosiran resulted in improvements in the need for opioid usage, consistent with a reduction in AAR necessitating less analgesic usage to treat attacks. Also associated with the reductions in the AAR, patients treated with givosiran reported large improvements in their condition using the PGIC instrument and much higher overall satisfaction with porphyria treatment than patients treated with placebo.

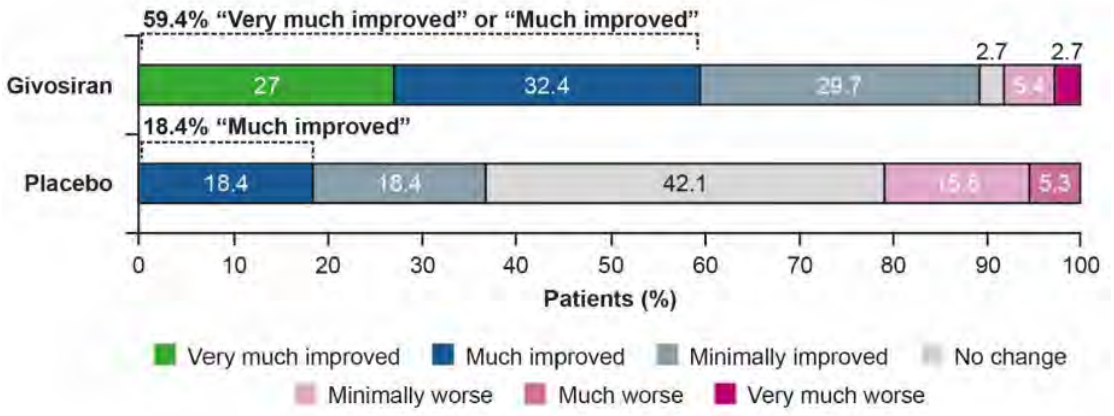
Analgesic Usage: Givosiran treatment led to a lower proportion of days with opioid use over the 6-month DB period compared with placebo in the AIP population (Givosiran: 23% vs Placebo: 38%) (72). This is an important finding, as can be assumed to reduce the likelihood of developing opioid dependence and reduce the adverse reactions associated with opioid treatments.

Quality of life:

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

that their condition was 'Much improved', while no placebo-treated patients reported that their condition was 'Very much improved' (Figure 13) (72).

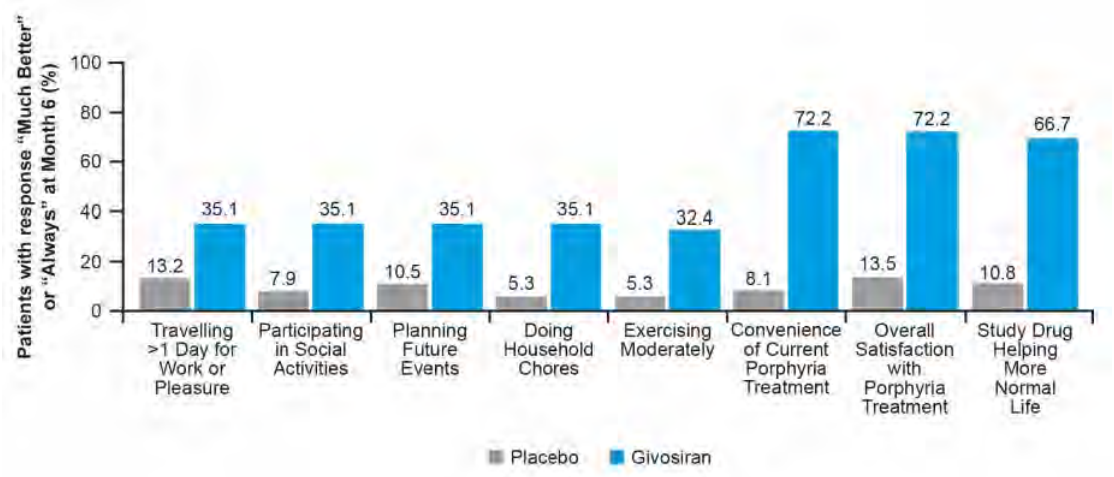
Figure 13: ENVISION: PGIC in AHP at 6 months.



The figure presents the proportion of patients with response 'Much Better' (other options were "Minimally Better", "No Change", "Minimally Worse", "Much Worse"). AHP: acute hepatic porphyria; PGIC: Patient Global Impression of Change. Source: Balwani et al., 2020.(17)

Similarly, the PPEQ instrument demonstrated a more than 5-fold improvement in the overall satisfaction with porphyria treatment in patients treated with givosiran compared with patients receiving placebo (72.2% vs 13.5%) (Figure 14) (72).

Figure 14: ENVISION: PPEQ in AHP at 6 months.



AHP: acute hepatic porphyria; PPEQ: Porphyria Patient Experience Questionnaire. Source: Balwani et al., 2020.(17).

Conclusion on Clinical Benefit of Givosiran

In conclusion, givosiran is the first therapeutic option that achieved sustained reductions in levels of ALA and PBG, toxic factors driving attacks and other disease manifestations of AHP (17,65). In the phase 3, double-blind, placebo-controlled ENVISION clinical study, once-monthly SC administration of givosiran yielded statistically and clinically significant reductions in the rate of acute attacks and multiple other measures of disease burden (17).

The clinical benefits observed in ENVISION represents a breakthrough in the management for AHP patients. In summary givosiran resulted in significant and clinically meaningful reduction in the composite annualized attack rate, compared to best supportive care, of 74% ($p<0.001$) and 73% ($p<0.001$) in patients with AIP and AHP, respectively. This was accompanied by a significant reduction in the number of days with haemin use compared to best supportive care. Importantly, approx. a 3-fold higher proportion of patients with AIP/AHP were attack free at 6-months when treated with givosiran compared with best supportive care (17).

- Notably in the phase 3 OLE, long-term efficacy was proven by consistent reductions in the in composite porphyria attack rates, which were sustained in patients who continued to receive once-monthly givosiran and in those who crossed over to once-monthly givosiran from best supportive care (18).

Addition benefit was proven by secondary outcomes demonstrating patients had improvements in symptoms, which translated into improved HRQoL. Importantly givosiran leads to pain reduction with reduce need for opioid treatment and an further improved the ability of AHP patients to function physically and socially (SF-12-PCS + MCS) (17).

Givosiran transforms the standard of care for AHP as the only treatment for prophylaxis of acute attacks that is supported by robust RCT evidence(17,65). There are no comparators that occupy the same place in therapy as givosiran, a disease-modifying, preventative treatment for AHP.

8.1.2.2 Safety: ENVISION and ENVISION-OLE

The primary outcomes for AEs are listed in Table 12, while events with high frequency and events of interest are listed in Table 13. All reported safety analyses were performed on the safety population, which include patients who received at least one dose of the study drug (n=94, ITT AHP-population). Overall, the proportion of patients experiencing any AEs were reported by 90% of the patients in the givosiran group and 80% of those in the placebo group. AE that were reported more frequently in the givosiran group than in the placebo group were injection-site reactions, nausea, chronic kidney disease, decreased eGFR, rash, increased alanine aminotransferase (ALT) levels, and fatigue (17).

The percentage of serious AEs was higher in the givosiran group than in the placebo group (21% vs. 9%). The difference in serious AEs was not driven by any particular event. Serious AEs that were reported in at least 2 patients were worsening of chronic kidney disease (in 2 patients in the givosiran group) and events consistent with central venous catheter infection (in 1 patient in the givosiran group and 2 patients in the placebo group). For the two CKD events these are addressed in detail in the section below concerning renal events, but were not considered treatment-related. One patient in the givosiran group discontinued treatment because of abnormal results on liver-function testing; this occurrence was reported as a serious AE. There were no deaths (17).

Table 12: Primary outcomes for adverse events in Safety Population (AHP)

Adverse events	Placebo (n=46), (%)	Givosiran (n=48), (%)	Risk Ratio (95 %CI), p-value
Any AE	37 (80)	43 (90)	1.11 (0.94, 1.32), p = 0.221
Any SAE	4 (9)	10 (21)	2.40 (0.81, 7.10), p = 0.115
Any AE leading to discontinuation of the trial regimen	0*	1 (2)*	2.88 (0.12, 68.89), p = 0.525
Any adverse reaction	12 (46)	22 (26)	1.76 (0.99-3.12), p = **0.055**
Death	0	0	-

AE: adverse event, SAE: serious adverse event. Serious adverse events were defined as adverse events that resulted in death, were life-threatening, required *in-patient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, were a congenital anomaly or birth defect, or were important medical events as determined by the investigators. All adverse events (including serious adverse events) were graded for severity. Severe events were adverse events for which more than minimal, local, or non-invasive intervention was indicated; had a more severe effect on limiting self-care activities of daily living; or had potential for life-threatening consequences or death. NT = no statistical testing. *As there were 0 events in the reference arm, 0.5 events were added to each cell to make statistical calculations. There were no difference in discontinuations due to AE and discontinuations irrespective of reason.*

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 13: Specific outcomes for adverse events in all trial patients

Adverse events	Placebo (n=46), (%)	Givosiran (n=48), (%)
Adverse events with higher frequency (≥5 percentage points) in the givosiran group	n (%)	n (%)
Injection-site reaction	0	12 (25)
Nausea	5 (11)	13 (27)
Chronic kidney disease	0	5 (10)
Decreased eGFR	0	3 (6)
Rash	0	3 (6)
Increased alanine aminotransferase	1 (2)	4 (8)
Fatigue	2 (4)	5 (10)
Adverse events with higher frequency (≥5 percentage points) in the placebo group		
Pyrexia	6 (13)	1 (2)
Hypoesthesia	4 (9)	0
Dyspepsia	4 (9)	0
Vomiting	5 (11)	2 (4)
Urinary tract infection	6 (13)	3 (6)
Back pain	4 (9)	1 (2)
Adverse events of interest		
Hepatic	1 (2)	6 (13)
Renal		
Any event	3 (7)	7 (15)
Increased serum creatinine or decreased eGFR	2 (4)	7 (15)

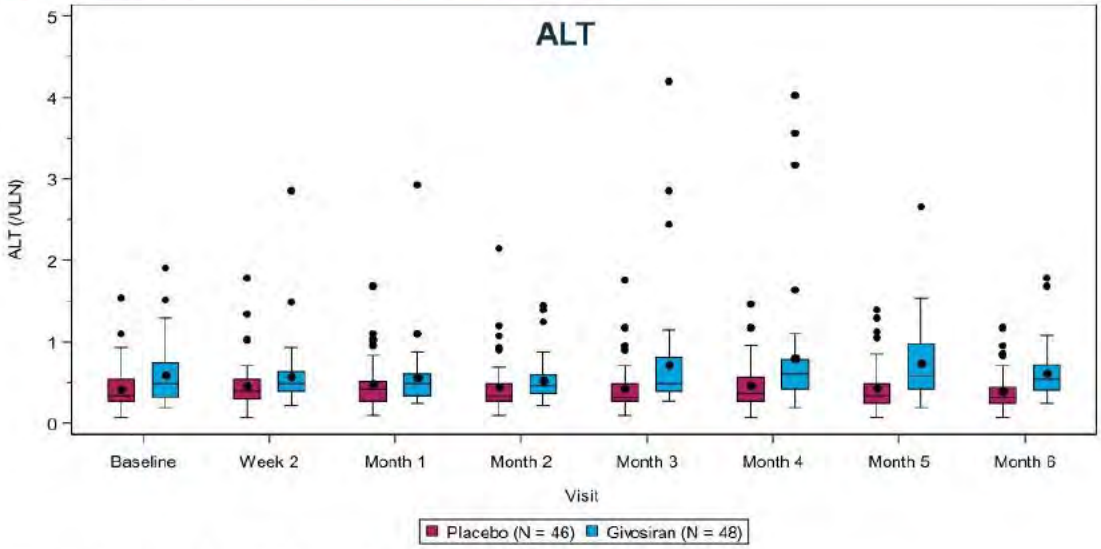
Injection-*site reactions include all adverse events that are included under the term of high-level injection-site reactions in the Medical Dictionary for Regulatory Activities (MedDRA). Hepatic adverse events included elevated aminotransferase levels, which occurred in each of the 7 patients in the givosiran group and were selected according to MedDRA terms for drug-related hepatic disorders. Renal adverse events included all events selected according to MedDRA terms for chronic kidney disease. This category includes a subgroup of patients who had changes in the serum creatinine level or estimated glomerular filtration rate (eGFR) that were reported as an increased blood creatinine level, a decreased eGFR, chronic kidney disease, or nephropathy.*

Hepatic adverse events:

Hepatic AEs, as characterized by elevations in serum alanine aminotransferase (ALT) levels, were more frequent in the givosiran group than in the placebo group. While there was considerable variability in ALT levels, most ALT elevations were mild to moderate in severity. An ALT level of more than 3 times the ULN was reported in 7 patients (15%) in the givosiran group and in 1 (2%) in the placebo group. These increases occurred primarily 3 to 5 months after the initiation of givosiran and placebo, illustrated in Figure 15 (17). All the events were reported as hepatic AEs except for one in a patient in the givosiran group who had a history of non-alcoholic steatohepatitis, in whom the investigator considered that the elevated ALT level was consistent with previous

values. Illustrated in Figure 15 and [redacted], the increase in ALT levels were reversible in most cases.

Figure 15: ENVISION results of intervention impact on ALT (18)



ALT, alanine aminotransferase; ULN, upper limit of normal.

[redacted]

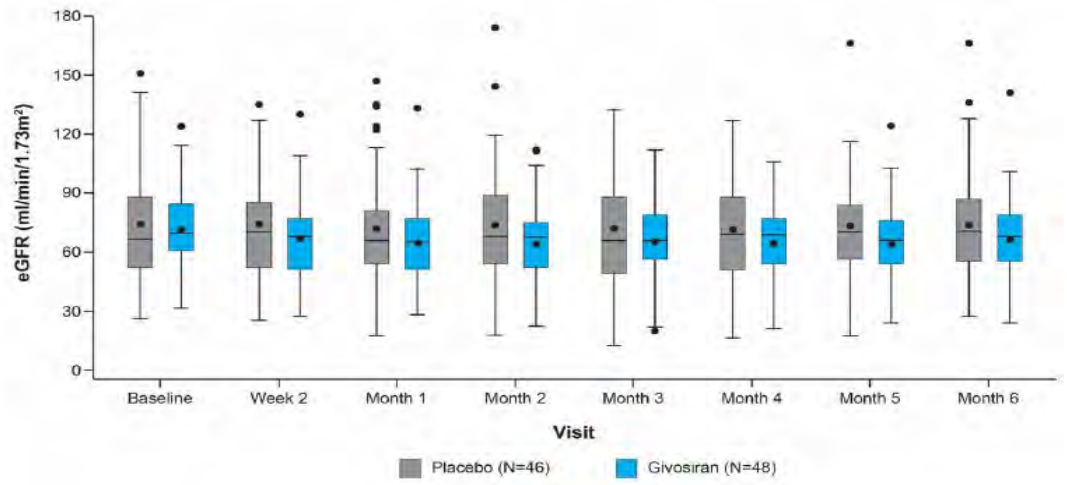
In the givosiran group, for 1 patient who had an ALT elevation of 9.9 times the ULN, the abnormal results on liver-function testing were reported as a serious AE; in this case, the patient permanently discontinued treatment with givosiran, in accordance with the stopping rules prespecified in the protocol (ALT increased by 5.4xULN and aspartate transaminase (AST) increased by 3.6xULN). The elevation resolved with normal ALT values at 6 months. In 1 patient with an ALT elevation of 5.4 times the ULN, the administration of givosiran was temporarily interrupted, in accordance with the protocol-specified dosing rule, and was resumed at a lower dose (1.25 mg per kilogram) after resolution, without recurrence of the ALT elevation. No other AEs led to treatment

discontinuation or withdrawal from the trial, and the other 5 patients who had an ALT level of more than 3 times the ULN had resolution of the ALT elevations with continued dosing (at 2.5 mg per kilogram). Elevations of ALT were seen at similar frequencies and degrees in patients with or without elevated ALT at baseline. However, it should be noted that at baseline abnormally elevated ALT concentrations were observed in 20.8% of patients in the givosiran group and 4.3% in the placebo arm (17).

Renal adverse events:

Renal AEs were reported in 15% (n=7) of the patients in the givosiran group and in 7% (n=3) of those in the placebo group; the majority of these events were an increase in the serum creatinine level or a reduction in eGFR (17). The results of eGFR are illustrated in Figure 17.

Figure 17: ENVISION results of intervention impact on eGFR (17)



eGFR: Estimated Glomerular Filtration Rate.

Of these events, 5 patients in the givosiran group had either the onset or worsening of chronic kidney disease, and 1 patient in the placebo group had worsening nephropathy, all of which were associated with an increased creatinine level and a decreased eGFR. Two patients in the givosiran group who had worsening of chronic kidney disease were considered to be serious due to elective hospitalisation for diagnostic evaluation. Renal biopsies in both patients were consistent with underlying disease (hypertension and porphyria-associated nephropathy), and there were no signs of immune complex or primary glomerular renal disorders (17).

Most of the renal AEs were mild to moderate in severity and resolved or stabilised by Month 6 without treatment interruption. No patients discontinued either givosiran or placebo because of a renal AE (17). Overall, an analysis of renal measures showed minor increases in the serum creatinine level (median increase at 3 months, 0.07 mg per deciliter [6.2 µmol per liter]) and corresponding decreases in the eGFR were noted early during givosiran treatment; both findings were mainly reversible over time without any dose modifications (17). Stratification of patients according to the baseline category of eGFR did not show an increased percentage of renal impairment (as assessed by the eGFR) in any group (17).

Other AEs of interest

Injection-site reactions occurred in 25% of the patients in the givosiran group and were associated with 7% of 279 givosiran doses. All the reactions were mild or moderate in severity, and none led to discontinuation. There were no clinically significant elevations in amylase or lipase levels and no development of antidrug antibodies (17).

Nausea was reported in 13 patients taking givosiran (27.1%) and in five patients taking placebo (10.9%). No nausea SAEs were reported, and most were mild in severity. One severe AE of nausea in a patient that was treated with givosiran was assessed as being unlikely due to the study drug. Vomiting was reported in two (4.2%)

patients taking givosiran and in five (10.9%) patients taking placebo. Most events were mild or moderate in severity. A severe AE of vomiting occurred in the same givosiran patient who had experienced severe nausea. This event was also assessed as being unlikely due to the study drug and resolved within 1 day of onset with no change in dosing. No events of vomiting led to study drug interruption or discontinuation (17).

All reported AEs of rash (3 patients in the givosiran group; 6.3%) were mild in severity. Two of the AEs were considered to be possibly related to the study drug. All rashes resolved without change in dose to the study drug. Pyrexia was reported in one givosiran patient (2.1%) and in six patients taking placebo (13.0%). The givosiran patient experienced three events, all of which were mild or moderate in severity. Fatigue was reported in five patients taking givosiran (10.4%) and in two patients taking placebo (4.3%). Two AEs in two givosiran-treated patients were considered possibly related to study drug. All AEs of fatigue were mild in severity. Acute Pancreatitis was reported in one givosiran-treated patient (2.1%) and in three placebo-treated patients (6.5%). No cases of anaphylactic reaction or severe hypersensitivity that were considered related to givosiran were reported in the placebo-controlled DB period. The safety analysis was consistent across the subgroups of AHP that were tested (17).

There were deaths and no reports of hepatocellular carcinoma in the ENVISION and ENVISION-OLE study. As patients with AHP are at increased risk of hepatocellular carcinoma, this risk is also continuously monitored in the ongoing safety studies as described below.

Ongoing-studies examining long-term safety and efficacy

The ENVISION-OLE study will continue as planned with a total of 30 months of extended follow-up. In addition, Alnylam is committed to monitoring safety in a company-sponsored AHP registry which will provide long-term safety and effectiveness data in a real-world cohort of AHP patients taking givosiran (73).

The proposed registry, named ELEVATE, is expected to evaluate approximately 150 patients with an aim of at least 900 patient-years of givosiran exposure (i.e., average observation period of at least 6 years). Patients will be enrolled from sites in Europe and North America (other regions may be considered as needed). ELEVATE initiated its first site in April 2021.

Furthermore, safety is continuously monitored from post-marketing surveillance with frequent reporting to the EMA/FDA. Any new safety concerns will be reported, and the product summary updated accordingly. All studies and post-marketing surveillance will continue to monitor the risk of hepatic and renal effects and carcinogenicity. To date no associated carcinogenicity has been observed in the clinical studies, and based on the preclinical carcinogenicity profile, there is no evidence to suggest givosiran has any carcinogenic potential (66).

Conclusion on the safety of givosiran

The safety profile of givosiran in patients with AHP has been well characterised in the placebo controlled ENVISION trial and the associated OLE phase. The cumulative safety data to date show that givosiran is generally well-tolerated and has a safety profile that is clinically manageable. In the ENVISION trial, the frequencies of AEs and SAEs were comparable between the givosiran and placebo arms (17). The main safety concerns were the potential effects of treatment on the liver and the kidney, which are addressed adequately through appropriate routine risk minimisation measures as demonstrated in ENVISION by monitoring hepatic and renal function. Renal and hepatic AEs in ENVISION were mostly reversible and were also consistent with the underlying pathology of AHP (17). The majority of ALT elevations observed in patients taking givosiran were mild to moderate, occurred approximately 3–5 months after givosiran was started, and resolved or stabilised by Month 6 (2). Observed increases in serum creatinine among patients taking givosiran were generally small (median change of 0.07 mg/dL at Month 3) and resolved or stabilised by Month 6. Observed deceases in eGFR also resolved or stabilised by the final assessment at 6 months. Eighteen-month data from

the OLE phase of ENVISION indicate that the long-term safety profile of givosiran is consistent with that seen in the randomised trial phase (18,67).

Given the clear clinical benefit of givosiran in terms of attacks averted, symptom improvement, and improvements in physical functioning and HRQoL (see section 8.1.2), the benefit-to-risk profile of givosiran is favourable.

8.1.3 Comparative analyses of efficacy and safety

Results from the comparative analysis

This section is not applicable as the ENVISION trial is the only study of interest and results have already been provided above.

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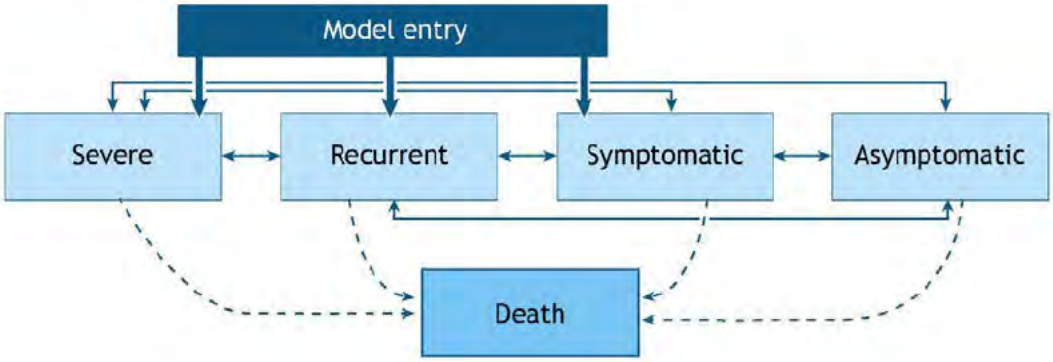
9. Health economic analysis

9.1 Model

No economic models for givosiran or for other technologies used in clinical practice in the indicated population had been published at the time of the model development. We therefore developed a *de novo* CE model in conformity with requirements of the latest Danish Medicines Council's methods guideline for assessment of new medicines (74).

This standard Markov model was developed using Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) to assess costs and effects, life-years (LYs) and quality-adjusted life-years (QALYs) of givosiran and BSC in a simulated cohort of AHP patients. The cohort transitioned across five health states corresponding to the four mutually exclusive categories of AHP disease severity based on the frequency of acute attack, plus death. Figure 18 shows the design of the *de novo* Markov model for the CEA for givosiran.

Figure 18. AHP Markov model structure



AHP: Acute hepatic porphyria

Findings from the systematic literature review (SLR) yielded no widely accepted, standardised system for classifying patients' disease severity of AHP. The search did yield one relevant framework for staging this condition using mutually exclusive categories, which was proposed by Neeleman et al. (2018) (22). Furthermore, the relevance of this framework in staging the condition for the use of the present economic model was affirmed by expert clinicians with experience in treating patients with AHP(75). The definitions of the model health states are summarised in Table 14.

Table 14: Definitions of model health states

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

*The existence of a clinically distinct severe health state was supported by the HRQoL data from the ENVISION trial and validated by expert clinicians who indicated that the definitions of model health states were clinically sound and were consistent with the experience of AHP patients that they see in clinical practice (see Section 10.1.11 and 12.1.4). Sources: Balwani et al. (2020)(17); Neeleman et al. (2018)(22)

According to the ENVISION inclusion criteria, all patients were required to have experienced repeated acute attacks, corresponding to ≥2 attacks in the 6 months prior to study entry. To align with this study population, all patients in the cohort enter the model sorted into the Symptomatic, Recurrent or Severe health states as defined in Table 14, based on the distribution of baseline severity of patients enrolled in ENVISION(33). The proportion of the cohort entering the model in each health state was obtained by pooling data on the baseline distribution of givosiran and placebo patients in ENVISION.

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

9.1.1 Justification of the chosen structure in line with the clinical pathway of care

Basing the model on levels of attack frequency (defined by the AAR) is relevant in the context of a disease that is characterised by recurrent acute attacks, each of which have a debilitating impact on patient wellbeing and HRQoL. An increase in the frequency of acute attacks is also associated with higher rates of chronic conditions (Section 9.2.1.3).

The staging system (Table 14) in the present CEA reflects the number of attacks a patient experiences per year, rather than considering the number of attacks that patients experience in any year of their life (i.e., distinguishing between >4 attacks per year vs >4 attacks in any one year over a lifetime). An additional disease category (Severe disease; defined as >24 attacks per year) was also added to the staging system in the economic model to refine the 'recurrent disease' definition proposed by Neeleman et al. (2018)(22). Based on findings from the ENVISION study, it was considered that categorising all patients with more than four attacks per year to be part of one singular health state was an overly broad and crude consideration of patients' disease severity. ENVISION demonstrated a high variation in AAR, ranging from 0 to 53. The addition of the 'Severe disease' health state allows for a more granular estimation of the severity of AHP disease and aligns with the understanding of AHP by global clinical AHP experts, as mentioned in the paragraph above.

Furthermore, HRQoL data from ENVISION affirms that there is a clinically meaningful separation in how patients experience 'Recurrent' vs 'Severe' disease. Patients with a high AAR (i.e., >24 attacks per year) experience clinically meaningfully worse disease than patients who have >4 to ≤24 attacks per year, thus demonstrating that the 'Severe' health state is distinct from the 'Recurrent' disease state. Structured interviews with expert clinicians confirmed that the definitions of the model health states were clinically sound(75).

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

Table 15 summarises the assumptions in the CE model for givosiran.

Table 15: Givosiran CE model assumptions

Assumptions	Justification
Disease severity is based on the frequency of acute attacks and presence of chronic symptoms.	A framework proposed by Neeleman et al. (2018)(22) stages AHP according to frequency of acute attacks. The frequency of symptoms, comorbidities and late complications were shown to be correlated with three levels of attack frequency.
	Evidence on HRQoL from ENVISION demonstrate the existence of a fourth level of disease severity (>24 attacks per year), which has been validated independently by the expert clinicians Dr. Eliane Sardh, Dr. Janneke Langendonk and Prof. Laurent Gouya.
	The relevance of this framework in staging the condition for the use in the economic model was affirmed by expert clinicians with experience treating patients with AHP (75)
Mortality rate due to an AHP attack is assumed to be 0%.	Due to improved AHP diagnosis and management and broader use of haemin to treat acute attacks (per its indication), attack-related mortality has decreased to low levels over the past decades (27,41,49).
	No deaths due to attacks were observed in the phase 1 study of givosiran, the phase 3 study (ENVISION double-blind period + OLE), or the EXPLORE natural history study(7).
Disutility associated with acute attacks is distinct from the ongoing disutilities associated with chronic health states.	Definitive identification of EQ-5D utilities related to attacks directly observed in the EXPLORE study(7).
	EQ-5D data from EXPLORE analysed to derive mean disutility 'on attack' of -0.235 (applying Danish EQ-5D tariffs(76))
The average duration of an acute attack is 7.3 days.	Directly observed in the EXPLORE study and validated by expert clinicians (7,75).
100% of acute attacks are treated in hospital	The proportion of patients treated in the hospital is in line with clinical practice in Denmark where haemin cannot be administered at home and attacks are not treatment in urgent outpatient settings.
The transition probabilities relating to the effectiveness of givosiran that were observed in the ENVISION OLE continue over time beyond the duration of the OLE period. A 5-year time point selected for extrapolation limit After 5 years, the cohort is assumed to remain stable	Directly observed in the ENVISION OLE (18 months of follow-up) and in the OLE period of the phase 1 Part C study (up to 3 years at the latest data-cut (16 October 2019).
	The cumulative evidence from these separate studies supports the assumption of continuing benefits of givosiran treatment.
	No indication that there is any diminishing effect of givosiran treatment with ongoing use even over increasingly long periods of follow-up.
After 6 months double-blinded data, patients in the BSC arm are assumed to be stable unless they die.	All patients in the placebo arm of the ENVISION trial transitioned to givosiran in the OLE period and as such, no data were available for these patients beyond 6 months. A conservative assumption was implemented for transitions in the BSC arm in the base case.

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Assumptions	Justification
	A scenario analysis will explore the possibility of BSC cohort getting worse overtime by applying a probability of disease worsening obtained by the observed relationship between AAR and time from diagnosis.
Following treatment interruption, the BSC transitions are applied	This assumption was adopted in the absence of data. Data on rates of treatment discontinuation due to any reason in patients receiving givosiran were obtained from the ENVISION double-blind (6 months) and OLE periods (12 months).
AHP cohort mortality HRs for all health states versus the general population were set to 1.3.	These assumptions are based on AHP cohort mortality versus the general population by Baravelli (2020)(50). A scenario analysis will explore a mortality HR of 1.0 for the Asymptomatic health state.
BSC is assumed to have no price associated with pharmacologic therapy or treatment administration.	Patients receiving BSC would not receive a comparable pharmacologic treatment and therefore, no related (treatment or administration) costs would be incurred.

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

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

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

- The risk of attacks and related acute symptoms (including AEs of acute haemin treatment). Acute porphyria attacks are included in the model as events that may occur at every cycle in any of the health states, over the entire time horizon of the model. One-off utility decrements and costs associated with acute attacks are considered in the model.
- The presence of chronic conditions found to be correlated with the frequency of attacks, as described in Section 9.2.1.3. The model includes the ongoing impact of chronic conditions on HRQoL, mortality and costs.

In line with current treatment practice and the best evidence available to model mortality in AHP, the CEA does not incorporate death due to acute attacks. If untreated, AHP attacks are known to be potentially life-threatening(3) but due to improved AHP diagnosis and management and broader use of haemin to treat acute attacks (per its indication), attack-related mortality has decreased to low levels over the past decades (27). No deaths due to attacks were observed in the phase 1 study of givosiran (double-blind period + OLE), the phase 3 study (ENVISION double-blind period + OLE) or the EXPLORE natural history study. On the basis of this evidence, the model assumes a 0% mortality rate due to acute attacks.

9.1.4 Key features of the model not previously reported

Table 16 summarises the additional key features of the model.

Table 16: Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime horizon	The lifetime horizon is the appropriate time scale for the CEA, given that AHP is a chronic and incurable hereditary disease requiring long-term specialist	The DMC's Method Guide for Assessment of New Medicines Version 1.0 (2021)(74)

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Factor	Chosen values	Justification	Reference
		management across a patient's lifetime. In model simulation the time limit is set to approximately 60 years, corresponding to 122 model cycles.	
Discount rate	Both costs and outcomes (LYs and QALYs) were discounted at 3.5% annually up to year 35 in the model, 2.5% up to year 70 in the model and 1.5% thereafter.	The chosen discount rate for costs and outcomes is in line with the DMC guide to the methods of assessment of technologies and the recommended reference document published by the Ministry of Finance in Denmark.	The DMC's Method Guide for Assessment of New Medicines Version 1.0 (2021); Dokumentationsnotat – den samfundsøkonomiske diskonteringsrente 7/1/2021(74,77)
Perspective	Restricted societal perspective	In the base-case setting the restricted societal perspective is considered, including direct medical costs, transportation cost and the value of use of time.	The DMC's Method Guide for Assessment of New Medicines Version 1.0 (2021)(74)
Cycle length	The simulation is conducted in cycles of 6 months.	The cycle duration was selected to match the duration of the double-blind period of the ENVISION study, which is the key source of data for the model. In addition the cycle duration matches the intervals between routine clinic visits for these patients, as set out in the AHP management recommendations from Balwani et al. 2017. In the schedule for follow-up assessments, most assessments occur at 6-12 months intervals. Monitoring can be considered as a good approximation for frequency of clinically important events, since intervals in follow-up visits/examinations are set to prevent that disease worsening goes unidentified. Routine monitoring is done at intervals which allow to timely detect clinically meaningful events/changes in disease status. Thus 6 months can be considered as the minimum amount of time to observe clinically meaningful events and therefore for the cohort to transition from one health state to another.	ENVISION Trial and evidence on monitoring patterns (3)

CEA: cost-effectiveness analysis; DMC: Danish Medicine Council; LY: life-years; QALY: quality-adjusted life-years.

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9.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

9.2.1 Presentation of input data used in the model and how they were obtained

The patient characteristics and clinical variables used in the CE model are summarised in Table 17. The HRQoL inputs to the CE model are summarised in Section 9.4.2 (Table 35).

Table 17: Summary of clinical variables applied in the model

Variable	Value	Lower value	Upper value	PSA distribution	Source
Initial age (y)	41.64	37.90	45.39	Gamma	ENVISION(33)
Weight (kg)	65.3	61.55	69.04	Gamma	ENVISION(33)
Proportion of females	85.7%	65.9%	97.5%	Beta	ENVISION(33)
Average age at menopause	51	40	57	Normal	Rahman et al. 2015(78)
Menopause onset	Normal distribution				Fitting average age and SD reported by Rahman et al. 2014
Initial cohort distribution					ENVISION(33)
Asymptomatic	0.00	–	–	–	
Symptomatic	0.27	0.22	0.33	Dirichlet	
Recurrent	0.63	0.51	0.75	Dirichlet	
Severe	0.10	0.08	0.12	Dirichlet	
Extrapolation of givosiran from cycle 4 - number of cycles	7	6	8	Gamma	ENVISION(33)
AAR by health state					ENVISION(33)
Asymptomatic	[redacted]	[redacted]	[redacted]	–	
Symptomatic	[redacted]	[redacted]	[redacted]	Gamma	
Recurrent	[redacted]	[redacted]	[redacted]	Gamma	
Severe	[redacted]	[redacted]	[redacted]	Gamma	
Severe treatment-related AE per-cycle incidence					ENVISION(33)
Givosiran					

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Variable	Value	Lower value	Upper value	PSA distribution	Source
Asthaenia	0.021	0.017	0.025	Gamma	
Lipase increased	0.000	0.000	0.000	Gamma	
Iron overload	0.021	0.017	0.025	Gamma	
Headache	0.021	0.017	0.025	Gamma	
Placebo					
Asthaenia	0.000	0.000	0.000	Gamma	
Lipase increased	0.022	0.017	0.026	Gamma	
Iron overload	0.000	0.000	0.000	Gamma	
Headache	0.000	0.000	0.000	Gamma	

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

9.2.1.1 Data sources

Data on porphyria-related clinical variables needed to populate the model is presented in section 8. Where required, values for clinical variables were also obtained from Alnylam data on file for relevant studies.

In addition, three targeted literature searches were conducted in PubMed and Google search engines in March 2021 to identify studies reporting mortality, HRQoL, and cost data associated with AHP and the chronic symptoms/comorbidities identified by Neeleman et al. (2018) (22) and included in the CEA. The targeted searches for HRQoL and costs were not restricted to porphyria-related studies. These searches were performed using several terms, combined with the name of each chronic condition, as shown in Table 18. The cost search prioritized studies conducted in Denmark and the Nordics; when Denmark-specific studies or studies conducted in the Nordics were not available, studies conducted in the UK were used. For all searches, studies reporting primary research and the most recent studies were prioritized for retrieval. Please consult section 9.2.1.10 for the outcome of the mortality search, section 9.4.2.3.1 for outcome of the HRQoL search, and section 9.5 for the outcome of the HCRU and costs search.

Table 18: Search strategy for targeted literature search

Search	Terms
Mortality	("Mortality" OR "Death" OR "Survival") AND ("acute hepatic porphyria" OR "AHP")
HRQoL	("Health State Utility Values" OR "EQ5D Values" OR "EQ-5D Values" OR "Health-related quality of life" AND "chronic pain" OR "neurologic symptoms" OR "psychiatric symptoms" OR "chronic conditions")
HCRU and costs	("cost" OR "economic burden" OR "cost study" OR "resource use" AND name of each chronic condition* AND ("Denmark" OR "Nordics" OR "England" OR "UK" OR "United Kingdom")

HCRU: healthcare resource utilization; HRQoL: health-related quality of life
*Back pain, abdominal pain, upper extremities pain, lower extremities pain, paralysis, advanced neuropathy

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9.2.1.2 Health states

As previously described, the health states for the model were based on a framework for staging AHP reported by Neeleman et al. (2018) (22), as well as on analyses of HRQoL data from ENVISION, which affirmed the presence of a clinically 'Severe' health state (>24 attacks per year). The definitions of the model health states are summarised in Table 14 and in Section 9.1.

Patients were categorised into each of the model health states by pooling across the givosiran and placebo treatment arms in the ENVISION trial, and calculating patients' respective AAR in the double-blind (0–6 months) and OLE periods (Table 19). The mean AAR for each health state was calculated as the average of these two AAR values (i.e., the average of the AAR in the double-blind period and the AAR in the OLE).

Table 19: Mean AAR by health state from ENVISION

Health state	Mean AAR (95% CI)*
Asymptomatic	[redacted]
Symptomatic	[redacted]
Recurrent	[redacted]
Severe	[redacted]

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

In the current analysis, AAR estimates are consistent with the definition of attacks used in the primary endpoint of the ENVISION study. For the purposes of assigning healthcare resource use and associated costs to these attacks, and in line with clinical practice in the Denmark, the model considers that 100% of acute attack treatment occurs in hospital. This assumption was confirmed by Prof. Jan Frystyk (Head of Department and Head of Research Department of Endocrinology, Odense University Hospital & Institute of Clinical Research, Faculty of Health Sciences, University of Southern Denmark in Odense).

Each attack is assigned a one-off disutility weighted by the average attack duration, as well as a one-off cost. The description of the disutility associated with an acute attack and its estimation is described in Section 9.4.2.2.

In addition to the one-off impact of acute attacks, each health state is attributed an ongoing utility value, mortality probability, and cost per cycle. These are estimated based on the presence of chronic symptoms/comorbidities for Severe, Recurrent, Symptomatic and Asymptomatic cohort of patients defined based on the study by Neeleman et al. (2018) (22) and assuming the Severe health-state has equal prevalence to the Recurrent health-state. Thus, in the model, the disutility associated with acute attacks (applied only over the duration of attacks) is distinct from the ongoing utility decrements associated with the chronic conditions and applied by health states, as shown in Figure 19. A description of the utility decrements assigned to the chronic conditions included in the health states is provided in Section 9.4.2.3.

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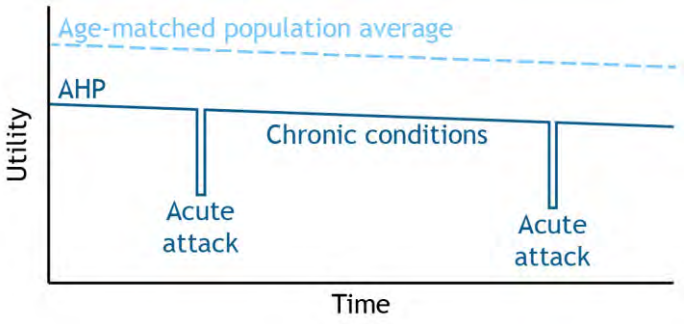
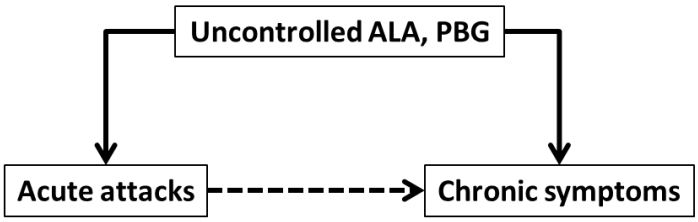
Figure 19: Conceptual schematic of utilities in the model



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

Uncontrolled ALA and PBG levels impact both the acute and chronic aspects of AHP (Figure 20). Decreasing levels of these toxic precursors would be predicted to reduce not only the frequency of acute attacks and the impact of the irreversible and cumulative damage they may cause, but also the burden of chronic conditions. In the CEA, long-term complications such as CKD and HCC are not considered as incidence data are poor or not available. These conditions can also not be included as prevalence conditions by health state, since they are not known to be reversible (i.e., there is no evidence that the conditions will improve with improvements in AHP health states). On the other hand, the CEA does consider chronic conditions which can be reverted with lower AHP attack frequency, such as pain, neurologic symptoms, and psychiatric conditions.

Figure 20: Role of toxic haem precursors in acute and chronic conditions of AHP



AHP: acute hepatic porphyria; ALA: aminolevulinic acid; PBG: porphobilinogen. Sources: Anderson et al. 2005, Pischik and Kauppinen 2015, Peoc'h et al. 2018, and Wang 2019. (26,27,41)

9.2.1.3 Chronic conditions

There are no published long-term studies that comprehensively record the prevalence of chronic conditions among patients with AHP in Denmark. Clinical experts in AHP have agreed with Alnylam that the most appropriate source for chronic condition prevalence in this disease is the long-term natural history study conducted by Neeleman et al. (2018)(22). This rich dataset provides a half-century of follow-up for 88 patients in the Netherlands. A key focus of Neeleman et al. was to assess the prevalence of symptoms and long-term complications(22). In contrast, the ENVISION trial had the primary objective of assessing the efficacy and safety of givosiran, and the EXPLORE study focused on the natural history and current clinical management of AHP over a relatively short time period (6 months with an optional 12-month visit). Consequently, neither ENVISION nor EXPLORE capture long-term data on chronic conditions, and neither provided as comprehensive an assessment of chronic symptom burden in patients with AHP as did Neeleman et al. (22). Therefore, the study by Neeleman et al. (22) represents the long-term disease experience of AHP patients more accurately and comprehensively than either ENVISION or EXPLORE—or indeed any other study.

Furthermore, whereas Neeleman et al. (22) studied patients with a wide range of AAR, including Asymptomatic patients, both ENVISION and EXPLORE enrolled only patients with repeated attacks. Indeed,

Neeleman et al. (2018) (22) is unique in the literature for reporting the prevalence of chronic conditions stratified by attack frequency, making it the only data source available to capture this critically important aspect of the disease burden of AHP in the model.

Patients in the Neeleman et al. cohort had been exposed to AHP for a much longer time than patients in ENVISION or EXPLORE, and therefore offer a more accurate representation of the full extent of chronic conditions that typically occur in this disease(22). The 88 patients described by Neeleman et al. had a median age at AHP onset of 30 years, and the reported median age at the end of study follow-up was 54 years(22). This indicates that the average duration of disease in the Neeleman et al. cohort was approximately 24 years at the end of follow-up(22). In contrast, the mean duration of AHP in the overall ENVISION trial population was only 9.7 years, and the median time since first attack in EXPLORE was even shorter, at 8 years. Thus, it was more appropriate to populate the model with rates of AHP chronic symptoms reported by Neeleman et al., because this long-term study is more representative of the relevant timescale of disability accrual in this chronic disease(22).

Finally, the eligibility criteria in ENVISION and EXPLORE specifically excluded patients with any condition that could interfere with their participation in these studies. Thus, these studies inherently underestimate the true burden of comorbidities and complications in AHP patients encountered in clinical practice. For the CEM, therefore, it was more clinically realistic to use the real-world cohort described by Neeleman et al. (22) as the source of prevalence data on chronic conditions when estimating the impact of AHP chronic symptoms.

The model incorporates only those chronic conditions that are reversible, as shown in Table 20, and does not include the long-term complications reported in the same study. As previously mentioned, this is a simplification of the model which can be considered conservative since BSC cohort is expected to develop more complication over time by remaining in the symptomatic/recurrent/severe health-states.

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Table 20: AHP chronic conditions

	Severe*	Recurrent	Symptomatic	Asymptomatic
Pain	100%	100%	92%	30%
Headaches	36.4%	36.4%	29.2%	13.2%
Chest	9.1%	9.1%	4.2%	1.9%
Back	45.5%	45.5%	33.3%	7.5%
Abdomen	90.9%	90.9%	79.2%	28.3%
Upper extremities	36.4%	36.4%	25.0%	3.8%
Lower extremities	45.5%	45.5%	25.0%	5.7%
Genitalia	0.0%	0.0%	8.3%	0.0%
Neurological	82%	82%	46%	17%
Paraesthesias	81.8%	81.8%	81.8%	8.3%
Motor weakness	45.5%	45.5%	45.5%	20.8%
Paralysis	9.1%	9.1%	9.1%	20.8%
Urinary incontinence	0.0%	0.0%	0.0%	4.2%
Advanced neuropathy/coma/respiratory failure	27.3%	27.3%	27.3%	20.8%
Psychiatric	82%	82%	33%	19%
Anxiety	45.5%	45.5%	20.8%	5.7%
Depression	36.4%	36.4%	12.5%	9.4%
Psychosis/Hallucinations	36.4%	36.4%	4.2%	9.4%
Insomnia	27.3%	27.3%	20.8%	11.3%
Suicidality	18.2%	18.2%	0.0%	1.9%

Source: Neeleman et al. 2018(22); AHP: acute hepatic porphyria *Assumed equal to Recurrent since Neeleman et al. does not split between recurrent and severe.

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9.2.1.4 Impact of menopause on disease natural history

The analysis assumes that all female patients with AHP in the Asymptomatic health state at the time of menopause will remain asymptomatic over their lifetime and therefore can discontinue givosiran treatment with no risk of further AHP-related attacks. This model assumption was validated with expert clinicians. The model applies this assumption:

- Only to female patients
- Only to patients who achieve the Asymptomatic health state before menopause
- Regardless of whether the patient is in the givosiran or BSC arm
- Based on a probability distribution of age at menopause onset

Notably, this menopause assumption is applied consistently to patients in the givosiran and BSC arms of the cost-effectiveness model—i.e., it reflects the disease natural history, not a treatment-specific effect. Evidence on the natural history of AHP demonstrates that at menopause many women experience a reduction in attacks due to changes in hormonal levels(5,59,79). This reflects the fact that sex hormones have the capacity to influence the rate of haem biosynthesis by inducing the first enzyme in the haem pathway, ALAS1, thereby precipitating clinical expression of the underlying AHP mutation (80) (Figure 1).

Multiple expert clinicians were consulted regarding our health-economic analysis, including Prof. Laurent Gouya, who is the coordinator of the Porphyria Rare Diseases Reference Centre in Paris (which is the only center in France to manage all aspects of AHP) and the senior investigator in the ENVISION trial. Agreement with this assumption was also provided by another ENVISION investigator who is an author on the publication in *New England Journal of Medicine* (7). These experts have noted that, in their experience, attacks and symptoms are unlikely to resolve after menopause in patients still experiencing frequent AHP-related attacks by menopause onset, whereas well-controlled patients have a high likelihood of remaining asymptomatic after menopause. These clinicians confirmed that it would therefore be appropriate for the model to assume that patients who are well-controlled and attack-free (i.e., in the Asymptomatic health state) by menopause onset would no longer require therapy to prevent attacks. This aligns with the natural history of AHP; namely, women are more likely to have AHP attacks, with the majority aged between 20 and 40 years (10) and this has been linked to changes in ovarian physiology(21,80).

This phenomenon is also common for other conditions influenced by sex hormones and has been reflected in the health-economic assessment of drugs for other medical conditions in which the rate of discrete events like attacks is influenced by female sex hormones. For example, in the Single Technology Appraisal of fremanezumab for migraine prophylaxis, the NICE Evidence Review Group highlighted the importance of accounting for the natural history of migraine, in which many female patients experience spontaneous remission of migraine attacks after menopause, and thus the need for the fremanezumab CEA to incorporate a treatment stopping rule upon menopause onset (81).

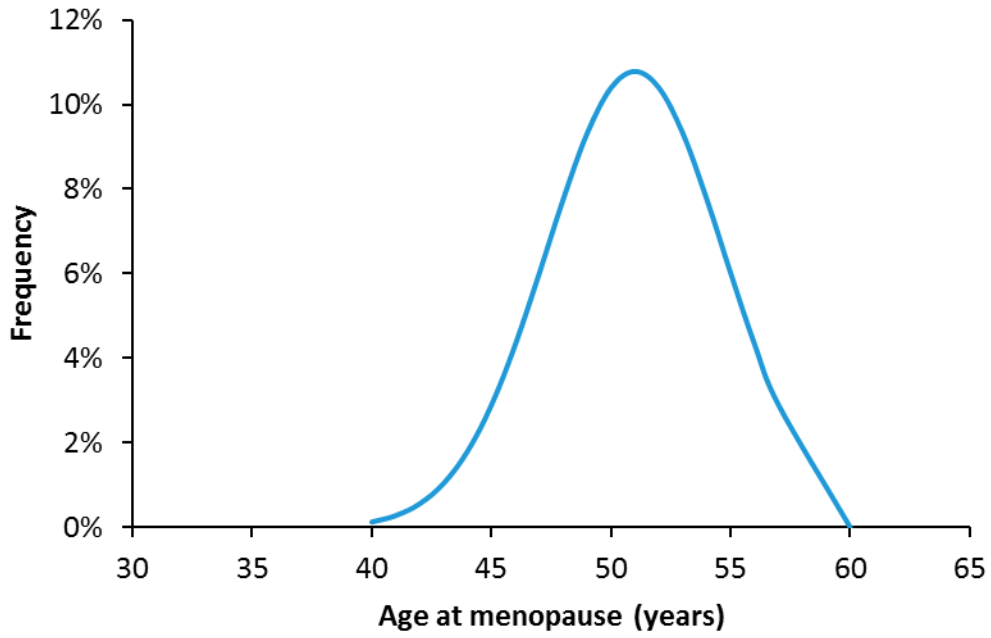
There is a solid pathophysiological rationale for linking a treatment-stopping rule for well-controlled AHP patients to female sex hormone levels. Sex hormones have the capacity to influence the rate of heam biosynthesis by inducing the first enzyme in the heam pathway, ALAS1, thereby precipitating clinical expression of the underlying AHP mutation(80). Clinical experts emphasized that female sex hormones play an important role in the manifestation of the disease (8). It is established in the literature that acute attacks are associated with the menstrual cycle in a number of women with AHP (3,82) and pregnancy can exacerbate attacks(80). A population-based study by Andersson et al. (2003) in the North of Sweden found that in 25% of symptomatic women oral contraceptive hormone therapy precipitated acute attacks, and in most of these cases, oral contraceptives triggered the patients' first-ever attacks(83). Sex hormone-binding globulin is commonly increased during attacks(80). Gonadotropin-releasing hormone (GnRH) analogs mimic menopause by creating a hypoestrogenic state, and GnRH analogues have been effective at reducing attack frequency in

some women with AHP, though their potential role in clinical practice is limited by serious side effects with long-term use, including osteoporosis and endometrial dysplasia (3,84). Thus, the onset of menopause would be expected to halt the need for treatment in well-controlled patients.

Based on these considerations, our analysis assumes that women who are in the Asymptomatic health state by the time they reach menopause will remain asymptomatic over their lifetime and therefore can discontinue treatment with no risk of further AHP-related attacks. Consistent with expert-clinician opinion that women with poorly controlled AHP (i.e., those still having attacks) are unlikely to experience resolution of attacks and symptoms after menopause, the model considers that women in the Symptomatic, Recurrent, and Severe health states remain at risk after menopause and therefore need to stay on treatment.

The timing of menopause onset in the base case analysis is modelled using a continuous probabilistic function based on the normal distribution fit to the mean and standard deviation (SD) of menopause onset in a Swedish cohort comprising more than 22,000 postmenopausal women followed from 1997 through 2011 (78). It is believed that the mean and SD of menopause onset in Sweden can be applicable to Denmark. This probabilistic function is shown in Figure 21, based on a mean (SD) age at menopause of 51 (3.7) years.

Figure 21: Probability distribution for age at menopause



Source: Rahman et al. 2015(78)

A crucial aspect of this new menopause-onset function in the revised model is that it results in the vast majority of the cohort entering menopause many years after model entry. All patients in the model cohort start at age 41.6 years, and within approximately 2 years (i.e., by age 43 years) only 1% of the female population would have entered menopause.

9.2.1.5 Treatment effectiveness

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

The effectiveness of treatment was obtained from the ENVISION study, considering both the 6-month double-blind and the OLE periods at the latest data cut-off, at which time all patients who had not discontinued had

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complete 18-month efficacy data. All patients randomised to double-blind treatment enrolled in the OLE except one patient in the placebo arm.

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

9.2.1.6 Distribution of the cohort at baseline

The proportion of the cohort entering the model in each health state was obtained by pooling data on the baseline distribution of givosiran and placebo patients in ENVISION (Table 21). The distribution of the cohort at baseline in ENVISION was derived based on the historical AAR of patients in each study arm. [redacted]

Table 21: Distribution of the cohort at baseline in ENVISION

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

9.2.1.7 Transition probabilities – Givosiran

Transition probabilities in the givosiran arm of the model are estimated from observations at 6 months during the double-blind period of ENVISION and at 12 months during the OLE period. By 6 months, the majority of patients had improved to the Asymptomatic or Symptomatic categories (Table 22). Of the Severe patients at study start, all showed AAR reductions. Similar trends in AAR were observed in the OLE period (6–12 months (Table 23); 12-18 months (Table 24)).

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Table 22: Number of givosiran patients transitioning between health states from baseline to month 6, ENVISION double-blind period

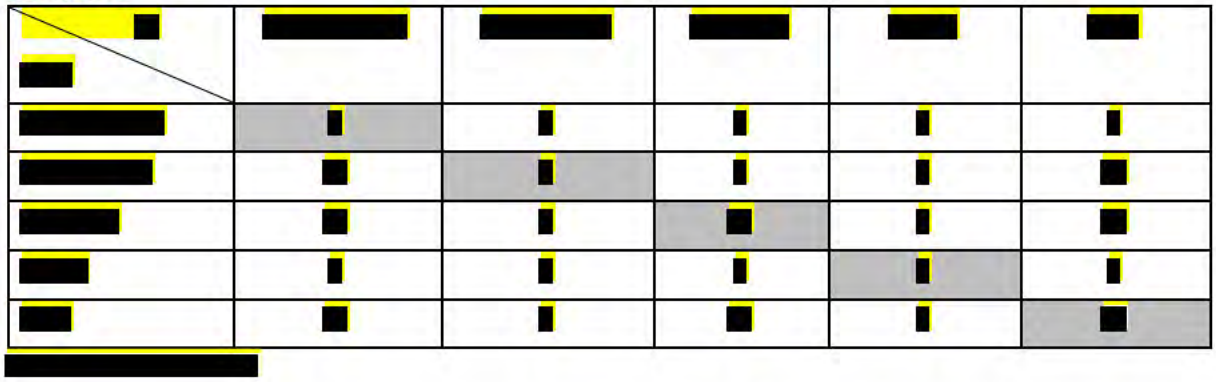


Table 23: Number of givosiran patients transitioning between health states from month 6 to month 12, ENVISION OLE period.

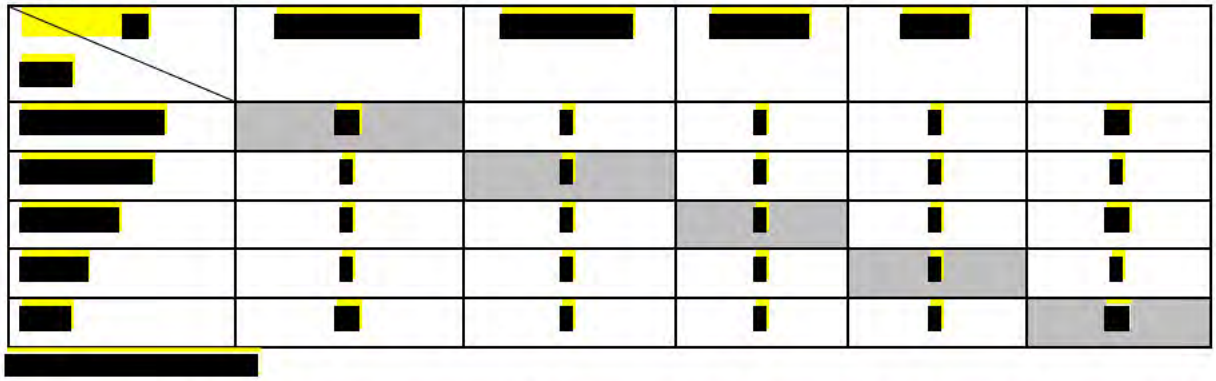
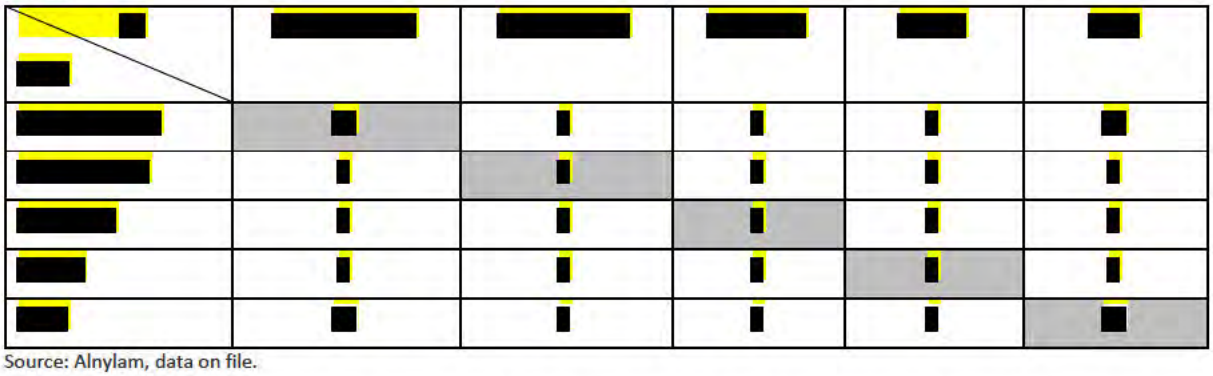


Table 24: Number of givosiran patients transitioning between health states from month 12 to month 18, ENVISION OLE period.



Source: Alnylam, data on file.

Data from the ENVISION double-blind period (Table 22) and OLE (Table 23 and Table 24) were used to estimate givosiran transition probabilities in the first and second cycles, respectively (Table 25 and Table 26) and in cycles 3–10 (Table 27). Patients in the ENVISION OLE period maintained or further improved the health state amelioration achieved in the double-blind period. This finding was consistent with the observation from the OLE period of the phase 1/2 Part C study that patients on givosiran showed maintenance of attack reduction for up to 30 months in the most recently presented results, and for up to 3 years at the latest data-cut of 16 October 2019 (Alnylam, data on file). The concordance of evidence from these separate studies supports the assumption of continuing benefits of givosiran treatment, with no indication from increasingly long periods of follow-up that there is any diminishing effect of givosiran treatment with ongoing use. Therefore, the model assumes that the transition probabilities observed in the ENVISION OLE period continue over time beyond the duration of the OLE period. A 5-year time point was selected as a reasonable extrapolation limit for this trend.

After that point, the cohort is assumed to remain stable (i.e., no further transitions between alive AHP severity health states, though transitions to death occur).

Table 25: Givosiran health-state transition probabilities in cycle 1, based on ENVISION double-blind month 6 data

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 26: Givosiran health-state transition probabilities in cycle 2, based on ENVISION OLE month 6 to month 12 data

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 27: Givosiran health-state transition probabilities in cycles 3 to 10, based on ENVISION OLE month 12 to month 18 data

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

9.2.1.8 Transition probabilities - BSC

Transition probabilities in the BSC arm of the model are estimated from observations at 6 months in the double-blind period of ENVISION. No data for BSC are available beyond Month 6 because at this point patients transitioned to givosiran in the OLE. Among the Recurrent patients, nine patients showed worsening and four showed improvement in frequency of attacks (Table 28).

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Table 28: Number of placebo patients transitioning between health states from baseline to month 6, ENVISION double-blind period

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

[redacted]

Observations in the ENVISION double-blind period (Table 28) were used to estimate BSC transition probabilities in the first cycle (Table 29). Because no data are available beyond 6 months, a simplifying assumption was implemented where we assumed that in the BSC arm patients remain stable (i.e., no improvement or worsening) after the end of the 6-month DB period.

Table 29: BSC health-state transition probabilities, based on ENVISION double-blind month 6 data

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

[redacted]

This is believed to be a highly conservative extrapolation assumption, given that worsening health status is expected in AHP patients in the absence of disease-modifying therapy, so the freezing of health states in BSC patients after 6 months does not reflect the reality that AHP is a chronic disease. On the contrary, data from the placebo arm of ENVISION reveal a strong positive relationship between time from diagnosis and AAR at 6 months (Figure 22; regression coefficient 0.62; P=0.007), demonstrating disease worsening over time in the absence of effective treatment.

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[redacted]

[redacted]

To address the uncertainty about the conservative assumption that health-state transitions in the BSC arm occur only in the first model cycle, a scenario analysis was performed in which BSC efficacy was based on the placebo group in ENVISION for the first cycle, and thereafter a per-cycle probability of disease worsening was applied to define transition to a health state one level worse (i.e., from Asymptomatic to Symptomatic, from Symptomatic to Recurrent, and from Recurrent to Severe). The probability of disease worsening was estimated based on data on time from diagnosis and AAR at 6 months in the placebo arm of the ENVISION double-blind trial. The estimated 13% per-cycle probability of disease worsening was applied in the placebo arm from the second cycle up to cycle 10 (year 5). This probability was also applied post-treatment discontinuation in the givosiran arm.

9.2.1.9 General population mortality

General population mortality is defined as age- and gender-specific all-cause mortality and has been included in the model based on country-specific mortality tables for Denmark, HISB8(85). The general mortality rate used in the model corresponds to the age of the cohort at each given cycle and has been adjusted based on the proportion of females in the analysis.

9.2.1.10 AHP mortality

A recently published retrospective, population-based, cohort study by Baravelli et al.(50), based on data from 333 patients with AHP in the Norwegian Porphyria Registry collected from 1992–2017, found an overall mortality hazard ratio (HR) for AHP patients of 1.3 (95% CI 1.0, 1.8) compared with the general population. The study found no statistically significant difference in mortality risk between hospitalised AHP patients, non-hospitalised AHP patients, or asymptomatic AHP patients. A survival benefit could be expected for a disease-modifying treatment with demonstrated clinical efficacy; however, since currently available data do not enable us to address the question of whether givosiran conveys a survival benefit, a conservative assumption was made that the mortality rate would be the same in all health states, yielding the same survival between

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givosiran and BSC treatment arms. Thus, the base-case analysis considers a mortality HR of 1.3 vs the general population in all model health states.

Applying the same HR in the Asymptomatic health state, which more patients in the givosiran arm achieve, as in the other health states should be considered a conservative approach for the base case, since an increased burden of chronic conditions and thus mortality is expected in patients with greater disease severity. In fact, despite overlapping 95% CIs, the mortality HR point estimate for AHP gene mutation carriers without porphyria symptoms in the Baravelli et al. study did differ from those in other patient subgroups: 0.7 (95% CI 0.3, 1.4) versus 1.0 (95% CI 0.5, 2.5) in AHP patients who had been hospitalised for an acute attack and 1.0 (95% CI 0.6, 1.6) in patients with porphyria symptoms who had never been hospitalised for acute attacks. To reflect the lower point estimate for patients without symptoms compared with those hospitalised for acute attacks, a scenario analysis was performed in which the overall AHP mortality HR of 1.3 was applied only to patients in the Symptomatic, Recurrent, and Severe health states, while patients in the Asymptomatic health state were assumed to have a mortality HR of 1.0 (i.e., no increased mortality relative to the general population).

9.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

9.2.2.1 Patient population

The characteristics of the simulated patient cohort at model entry, based on the baseline characteristics of the European population of ENVISION. It is important to understand that the initial age at model entry does not correspond to age at diagnosis. There is a major distinction between incident patients (i.e., age at disease onset) and prevalent patients (i.e., age of the patient if they were to initiate treatment today). Our model represents the efficacy of givosiran in this prevalent population, as investigated in the ENVISION trial, corresponding to the cross-section of patients in Denmark who would initiate givosiran now, rather than at the moment in time of disease onset or diagnosis.

Table 30 : Patient population

Patient population Important baseline characteristics	Used in the model (number/value including source)
Initial age (years)	41.64 (Alnylam, data on file)
Weight (kg)	65.30 (Alnylam, data on file)
Percentage of females	85.7% (Alnylam, data on file)

9.2.2.2 Intervention

The intervention in the analysis is givosiran (189mg/vial), administered SC once a month. A positive CHMP opinion for givosiran was obtained on January 31, 2020 (73) and the European marketing authorization was issued on March 2, 2020. Use in the trial is aligned with use in clinical practice.

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Table 31: Intervention

Intervention	Used in the model (number/value including source)
Posology	2.5mg/kg
[redacted]	[redacted]
Criteria for discontinuation	• Discontinuation due to unplanned reasons • Discontinuation following menopause onset in asymptomatic cohort

9.2.2.2.1 Treatment discontinuation

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

Data on treatment discontinuation due to any reason in patients receiving givosiran were obtained from the ENVISION double-blind (6 months) and OLE periods (12 months). Beyond the trial period, ToT was extrapolated by fitting parametric models to observed time-to-event data. Akaike information criterion (AIC) and Bayesian information criterion (BIC) estimators were used to evaluate the relative quality (i.e., fit) of the parametric models considered, namely: Exponential, Weibull, Gompertz, Log-Normal, and Log-Logistic (Table 32).

Table 32: Fit statistics of parametric models to givosiran time-on-treatment data

	AIC	BIC
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Table 33 presents the parameters used to extrapolate ToT data over time with each of the tested parametric models. The CEA uses the Log-Logistic model.

Table 33: Model parameters for parametric functions to extrapolate givosiran time on treatment curves

	Exponential	Weibull	Gompertz	Log-Normal	Log-Logistic
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]

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9.2.2.3 Comparators

There are no comparator treatments in Denmark - until givosiran, patients afflicted with AHP have lacked any treatment options to prevent AHP-related acute attacks and have had to rely on supportive therapy to manage the chronic pain that occurs as part of this condition(7). Management strategies have focused on avoiding attack triggers, managing chronic pain, and using rescue therapy for patients experiencing acute attacks (3).

Normosang® (heam arginate) is available as a rescue therapy, with an indication for the treatment of acute attacks of AHP. Rescue therapies, including haemin and carbohydrate loading, are used in AHP to speed resolution of AHP-related attacks by helping to resolve symptoms and reduce the length of hospital stays once the patient has begun experiencing an attack (5,7,69). Thus, there is no current standard of medical care for treating AHP, beyond merely managing acute attacks after they occur.

The comparator in the analysis conducted for Denmark is BSC, constituting the standard treatments, such as rescue haemin, that are used in clinical practice to speed the resolution of symptoms and reduce the hospital length of stay (LOS) during acute attacks(3). BSC was determined to be the appropriate comparator in the analysis because givosiran is the only disease-modifying therapy that treats the underlying AHP disease process, thereby preventing the occurrence of attacks and addressing ongoing chronic pain(17). BSC in the model is therefore considered representative of BSC in the real practice in Denmark.

9.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes have been described in details in Section 9.2.1.7, Section 9.2.1.8 and Section 9.3.

9.2.2.5 Adverse reaction outcomes

The incidences of AEs associated with givosiran and BSC in the model were based on data from ENVISION (ENVISION CSR). The analysis included only severe treatment-related AEs during the 6-month double-blind period (Safety Analysis Set), with adjustments to incidence made to account for the 6-month cycle length (Table 34).

Table 34: Adverse reaction outcomes

Adverse reaction outcome	Used in the model (numerical value)	
	Givosiran (cycle incidence)	BSC/placebo (cycle incidence)
Asthenia	0.021	0.000
Lipase increased	0.000	0.022
Iron overload	0.021	0.000
Headache	0.021	0.000

BSC, best supportive care.

9.3 Extrapolation of relative efficacy

Patients in the ENVISION OLE period not only maintained the improvement achieved in the double-blind period but showed continual improvement beyond the initial beneficial effect of givosiran in the double-blind period for 2 years (Figure 23A). Furthermore, of 21 patients who were asymptomatic in the givosiran arm at 6 months, 89.5% remained continuously free of attacks by month 18 (2 developed attacks and 2 discontinued;

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Alnylam, data on file). These findings are consistent with the observation from the OLE period of the phase 1/2 Part C study that patients on givosiran showed maintenance of attack reduction for 3 years at the latest data-cut of 16 October 2019 (Figure 23B).

[redacted]

[redacted]

[redacted]

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

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As previously described in details, observations in the ENVISION double-blind period (Table 28) were used to estimate BSC transition probabilities in the first cycle (Table 29). No data for BSC are available from ENVISION beyond month 6 because at this point patients transitioned to givosiran in the OLE. Data from the EXPLORE natural history study also cannot be used to inform transition probabilities for BSC because the attack rate in the pre-study period may have issues with reliability, as it incorporates patient recall of past attacks, and the burdensome set of assessments required for each and every attack in EXPLORE led to patients under-reporting attacks during the study to avoid completing the assessments.

9.4 Documentation of health-related quality of life (HRQoL)

All information on HSUV are presented in Section 9.4.2.

9.4.1 Overview of health state utility values (HSUV)

All information on HSUV are presented in Section 9.4.2.

9.4.2 Health state utility values used in the health economic model

A summary of the HRQoL values for the CEA is provided in Table 35 and a detailed description of each value is provided further below.

Table 35: Summary of HRQoL values used in the model.

State	Utility decrement	SE	Reference in submission	Assumptions
Acute attack	-0.235	0.157	EXPLORE	Calculated from mean EQ-5D utility (DK tariff) during attack minus utility not on attack. It is applied for attack duration of 7.3 days.
Chronic symptoms/comorbidities				
Pain	-0.383	—	McDermott et al. (2006) (86)	Utility with the condition/disutility: the average between the utility values for mild, moderate, and severe pain. Utility without the condition: utility value for the general population with similar characteristic as in the study, i.e., 63 years of age and 50% females.
Neurological	-0.097	—	Sullivan et al. (2011) (87)	Utility with the condition/disutility: "Other hereditary and degenerative neuropathy". Utility without the condition: the general population utility with the same age as the cohort with the condition in the study, i.e., 56 years of age.
Psychiatric	-0.272	—	Ara and Brazier (2011) (88)	Utility with the condition/disutility: mental illness/anxiety/depression/nerves. Utility without the condition: HRQoL in patients without mental illness/anxiety/depression/nerves.
Asymptomatic	-0.173	0.017	McDermott et al. (2006), Sullivan et al. (2011), Ara and Brazier (2011),	Estimated based on multiplicative approach, which allows to estimate the overall utility decrement in function of the prevalence of pain, neurological and psychiatric conditions by health-state.
Symptomatic	-0.419	0.042		
Recurrent	-0.553	0.055		

State	Utility decrement	SE	Reference in submission	Assumptions
Severe	-0.553	0.055	Ara and Brazier (2017)(86–89)	

CEA, cost-effectiveness analysis; CKD, chronic kidney disease; EQ-5D, EuroQol Five-Dimension Questionnaire; HCC, hepatocellular carcinoma; MS, multiple sclerosis; HRQoL, health-related quality-of-life; SE, standard error

9.4.2.1 General population utility value

The gender- and age-specific utility of the general population is used as a base to subtract the utility decrements of AHP, considering both the temporary disutility associated with acute attacks and the long-term utility decrement associated with presence of chronic conditions. This approach allows AHP-related disutilities to be considered independently of the decreasing utility of the aging cohort, thus adjusting for age.

No study reporting the utility in the general population specifically in Denmark was identified. Therefore the model used the equation reported in the study by Ara and Brazier 2011(90) (estimated in the UK population), which allows to generate the utility in the general population as a function of age:

$$EQ\text{-}5D = 0.9508566 + 0.0212126*male - 0.0002587*age - 0.0000332*age^2$$

The equation by Ara and Brazier 2010 includes also a coefficient to account for gender in the estimation of general population utility value. The gender adjustment for utility is not requested in DMC guidelines, however this equation was still used in the model as the study by Ara and Brazier 2011(90) represent the gold standard for general population utility estimation. Moreover, the impact of gender on the utility value is minimal, for example at model start the utility value for males only would be 0.90 and the utility values for females only would be 0.88. Finally, but most importantly, the model does not use the utility of the general population as absolute value in the engine, but it uses it in relative terms to allow adjusting for reduction in quality of life as the cohort ages over time. Thus, the age part of the equation (changing over time) is what really is taken into consideration as per DMC guidelines.

9.4.2.2 Acute attack disutility

Each attack is associated with a temporary reduction in the HRQoL of patients in accordance with the duration of the attack. This is reflected in the analysis by including a disutility at the occurrence of each attack. The acute attack disutility is applied for each attack for an average attack duration of 7.3 days, as observed in the EXPLORE study and validated by expert clinicians. Both disutility value and attack duration are averaged across all attacks and therefore do not differ by attack treatment location or by health state.

The acute attack disutility and mean attack duration considered in the model were obtained from observations in the EXPLORE study. In EXPLORE, EQ-5D-5L data were collected at scheduled 6-month intervals. EQ-5D-5L records were transformed into utility values by applying the Danish EQ-5D-5L tariffs(76) at the patient level. When an attack occurred, lab tests as well as a patient symptom assessment were conducted. A "during attack" flag was recorded for all questionnaires completed in association with acute attacks, including the EQ-5D. This flag allowed definitive identification of EQ-5D utilities related to attacks. For the subgroup of patients with at least one EQ-5D questionnaire during an attack, disutility per attack was estimated by taking the difference between the mean utility index during attacks and when not having an attack (Table 36). This methodology avoided any possibility of double counting HRQoL impact attributable to acute attacks vs. the "background" disease state, as previously depicted in Section 9.1.3.

Table 36: Temporary HRQoL decrement per acute attack

	Value in the model	Source
Disutility of attack	-0.235	EXPLORE study Calculated from mean EQ-5D utility (DK tariff) during attack of minus utility not on attack
Average attack duration (days)	7.3	EXPLORE study Validated by expert clinicians

Source: Alynlam data on file

EXPLORE was determined to be the optimal source for estimating disutility per attack using EQ-5D because 10.1% of the EQ-5D questionnaires completed in EXPLORE were administered during an attack (Alnylam, data on file). In contrast, 0.4% of the EQ-5D assessments in the ENVISION trial were administered during an attack (Alnylam, data on file). Therefore, the data are insufficient to perform the same attack-disutility calculation using ENVISION EQ-5D results as was done for EXPLORE.

9.4.2.3 Chronic condition utility decrement

In addition to the temporary decrement of acute attacks, the model considers the ongoing health-state utilities based on long-term HRQoL decrements associated with chronic conditions.

Figure 25, the scatterplot of AAR vs. EQ-5D–derived utility data collected in the double-blind period of ENVISION shows that some patients with very high number of attacks have EQ-5D utility values close to 1 whereas many patients with very few attacks have very low utility values (Pearson correlation coefficient r=-0.0178, p=0.8656). It is possible that the ENVISION study is not of a sufficiently large sample size or long enough duration to reach a "steady state" estimation of the true underlying utility of these patients. In addition, patients in ENVISION had a relatively short average duration of disease, and thus may not yet have accrued the level of HRQoL impairment due to AHP chronic symptoms, comorbidities, and late complications that would be observed in patients with longer disease duration.

[redacted]

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In addition to the fundamental problem that EQ-5D scores did not correlate with AAR during ENVISION, there are numerous logistical obstacles to using data from this trial to set health-state utilities, including the following critical issues:

1. The EQ-5D assesses instantaneous health status on the day of questionnaire administration—i.e., it has no recall period of the past week, month, etc.—whereas health state based on AAR has to be calculated over some longer time period, which creates a mismatch whenever health state is not stable.
2. Health states in ENVISION are not stable for most patients, and indeed this fact underlies the transition probabilities in the model. Therefore, EQ-5D measurements averaged from different time points do not correspond cleanly to a given health state and are confounded by treatment.
3. Results in the double-blind period are confounded by treatment, considering that at 6 months 100% of Severe patients were in the placebo arm whereas 80% of Asymptomatic patients were in the givosiran arm.
4. Per the ENVISION eligibility criteria, no patients were in the Asymptomatic state at baseline, so it is impossible to use baseline EQ-5D measurements to populate all four model health states.
5. Considering attacks during the ENVISION OLE, no patients were in the Severe health state by Month 12 or Month 18 (i.e., when AAR was calculated between Month 6 and Month 12 or between Month 12 and Month 18), so it is impossible to use EQ-5D measurements from the OLE to populate all four health states.
6. The relatively low prevalence of chronic conditions among patients in ENVISION likely reflects the short disease duration relative to the timeframe over which these conditions accumulate, as seen in the long-term study by Neeleman et al. (2018) (22). Thus, ENVISION does not allow us to appropriately simulate the HRQoL burden of chronic conditions over the model time horizon.

Similarly, the 6–12-month follow-up in EXPLORE is insufficient to capture HRQoL changes associated with the occurrence of these conditions that are known to occur over a lifetime. In addition, the relatively small sample sizes in ENVISION and EXPLORE would yield few (and sometimes no) patients for each possible combination of chronic conditions, precluding rigorous calculation of HRQoL decrements for any given combination.

For these reasons, the long-term HRQoL decrements associated with pain, neurological and psychiatric symptoms were obtained from the literature and were then applied to the proportion of the cohort with these conditions in every health state based on prevalence data reported by Neeleman et al. 2018 (Table 20). This approach allowed us to leverage the unique, long-term dataset of Neeleman et al. (22), which reports data on the occurrence of chronic conditions of AHP over a 50-year period from 1960 to 2016), which is more accurate and representative of how patients may truly develop complications due to this disease over a lifetime.

9.4.2.3.1 Targeted literature search

The initial HRQoL SLR retrieved no studies in patients with AHP quantifying HRQoL for chronic conditions. A pragmatic search of the literature was therefore conducted in October 2020, targeting the search to HRQoL of chronic pain, neurological and psychiatric symptoms independently the presence of AHP.

As per NICE DSU recommendation (DSU technical support document 9) (91), inclusion/exclusion criteria defined based on PICOS were not used to define the scope of the HRQoL target search since they would unnecessarily restrict the search and would therefore not be useful in identifying appropriate utility values for modelling purposes. The scope of the research was limited to conditions for which HRQoL data were needed (i.e. chronic pain, neurologic symptoms, psychiatric symptoms) and to the type of HRQoL data required (i.e. EQ-5D data reported as utility values). In addition, we considered only studies including adults Danish/Nordics/EU patients (in order of preference) and which were published in English.

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The searches were conducted in PubMed and in Google.com. The searches were conducted by combining search terms referring to the conditions of interest and search terms referring to the type of HRQoL data required. The terms referring to the conditions which were used are:

- Chronic pain;
- Neurologic symptoms;
- Psychiatric symptoms.

The terms referring to the QoL data which were used are:

- Health State Utility Values;
- EQ5D Values;
- EQ-5D Values;
- Health-related quality of life.

Each term related to the conditions of interest was combined with one of the terms referring to HRQoL data in subsequent searches. The results were ordered in terms of relevance and only if the title appeared within scope was the study considered for further investigation. The full text was reviewed only if the study appears to meet fully the pre-defined scope defined as described above. All studies for which the full text was reviewed at first appeared to be within scope and relevant information from each study was extracted following recommendation from NICE DSU technical support document on HRQoL search (91).

A full list of identified studies initially considered for inclusion is provided in Table 37 with details of condition of reference and utility values described.

Table 37: Identified studies meeting inclusion criteria for chronic condition disutilities.

Study	Condition	Utility, mean (range or SD)	Population	Comments
Hoxer et al. (2019) (92)	Chronic pain in haemophilia	Moderate no chronic pain: 0.70 (0.21) Moderate + chronic pain: 0.51 (0.24)	Mean age: 35 y Proportion female: 62%	Utility in haemophilia without chronic pain is reported which allows estimation of utility decrement for chronic pain. It is unclear if chronic pain is similar in haemophilia and AHP.
Stafford et al. (2012) (93)	Migraine pain	No migraine: 0.87 (0.15) Mild pain: 0.66 (0.23) Moderate pain: 0.53 (0.27) Severe pain: -0.20 (0.29)	Mean age: 47 y Proportion female: 76.4%	Utility decrement potentially relevant to chronic pain in AHP could be estimated by subtracting the average of mild and moderate pain from the no-migraine utility (severe migraine pain is not considered relevant to chronic AHP pain since the most severe pain in AHP is expected to occur during acute attacks).
McDermott et al. (2006) (86)	Neuropathic pain	Mild: 0.67 Moderate: 0.46 Severe: 0.16	Mean age: 63 y Proportion female: 50%	Utility without the condition is not reported; utility decrement potentially relevant to chronic pain in AHP was estimated by subtracting the average of mild, moderate, and severe pain from the general population utility (= 0.813).

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Study	Condition	Utility, mean (range or SD)	Population	Comments
Hawton and Green (2016) (94)	MS (relapsing-remitting)	EDSS 0: 0.897 (0.132) EDSS 1: 0.763 (0.186) EDSS 2: 0.719 (0.229) EDSS 3: 0.523 (0.317) EDSS 4: 0.596 (0.274) EDSS 5: 0.438 (0.359) EDSS 6: 0.502 (0.275) All: 0.623 (0.294)	Mean age: 50.7 y Proportion female: 73.9%	The study also reports progressive disease, but relapsing-remitting was deemed more similar to AHP. Because neurologic symptoms in AHP vary it is unclear which EDSS levels should be averaged to yield a utility proxy for neurologic symptoms in AHP.
Sullivan et al. (2011) (87)	MS	With the condition: 0.495 (0.037) Utility decrement vs no condition: -0.2271 (0.034)	Mean age: 52.2 y Proportion female: NR	Utility decrement of the condition is reported directly. Disutility is averaged across all MS stages making it unclear if this is an appropriate utility proxy for neurologic symptoms in AHP.
	Paralysis	With the condition: 0.350 (0.058) Utility decrement vs no condition: -0.2466 (0.0994)	Mean age: 45.3 y Proportion female: NR	Utility decrement of the condition is reported directly but likely overestimates the utility decrement due to neurologic symptoms in AHP since paralysis is among the most severe of the different neurologic symptoms associated with AHP.
	Other hereditary and degenerative neuropathy	With the condition: 0.584 (0.030) Utility decrement vs no condition: -0.097 (0.0966)	Mean age: 56.0 y Proportion female: NR	Utility decrement of the condition is reported directly.
Kolovos et al. (2017) (95)	Depression	Remission: 0.70 (0.67–0.73) Minor depression: 0.62 (0.58–0.65) Mild depression: 0.57 (0.54–0.61) Moderate depression: 0.52 (0.49–0.56) Severe depression: 0.39 (0.35–0.43)	Mean age: 56 y Proportion female: 67%	EQ-5D is reported by stage of depression; it is unclear which stage represents the average utility due to psychiatric symptoms in AHP. Psychiatric symptoms in AHP include conditions other than depression, such as anxiety, psychosis and insomnia.
Ara and Brazier (2011) (88)	Mental illness/ anxiety/ depression/ nerves	Without the condition: 0.878 (0.861, 0.894) With the condition: 0.606 (0.585, 0.626)	Mean age: 45.5 y Proportion female: NR	Average utility for different types of psychiatric symptoms is reported, thus avoiding having to pick a single condition as a proxy for psychological symptoms in AHP. Utility without these conditions is reported which allows estimation of utility decrement.

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

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Among the studies for which the full text was reviewed and data extracted (Table 37), a list of the studies which were then not considered appropriate to inform utilities of the chronic conditions in the model is reported Table 38, along with the reason for exclusion.

Table 38. Identified studies which were not considered appropriate following full-text review

Study	Condition	Reason for exclusion
Hoxer et al. (2019) (92)	Chronic pain in haemophilia	It is unclear if chronic pain is similar in haemophilia and AHP, given that haemophilia is a very different condition.
Stafford et al. (2012) (93)	Migraine pain	Migraine pain is more likely to be acute rather than ongoing pain. Thus it would be more appropriate as a proxy of acute attack pain rather than AHP chronic pain.
Hawton and Green (2016) (94)	MS (relapsing-remitting)	It may be difficult to justify which EDSS stage corresponds to average HRQoL in patients with AHP and neurologic symptoms. Moreover, HRQoL impairment reported for MS is likely to include overall impact of the condition and may be overestimating the impact of a single neurologic symptom.
Sullivan et al. (2011) (87)	MS	Same as above
Sullivan et al. (2011) (87)	Paralysis	Paralysis represents a very extreme situation of neurological symptoms and in Neeleman et al. 2018, only a small proportion of patients with neurological symptoms had paralysis. Thus it may not be representative of the HRQoL in the average AHP patient with neurological symptoms.
Kolovos et al. (2017) (95)	Depression	It is unclear which stage represents the average utility due to psychiatric symptoms in AHP. Psychiatric symptoms in AHP include conditions other than depression, such as anxiety, psychosis and insomnia.

AHP: acute hepatic porphyria; EDSS: Expanded Disability Status Scale, **HRQoL: health-related quality of life,** MS: multiple sclerosis; NR: not reported, SD: standard deviation

Three studies in chronic pain in different indications met the inclusion criteria: Stafford et al. (2012) for migraine(93), Hoxer et al. (2019) for haemophilia(92), and McDermott et al. (2006) for neuropathic pain(86). McDermott et al. was considered the most relevant because neuropathic pain was deemed to be a better proxy for chronic pain in AHP than chronic pain in haemophilia, given the high prevalence of neurologic conditions in AHP, and given that the pain scores reported by Stafford et al. were specific to pain during migraine attacks, which are likely unrepresentative (i.e., more severe) than chronic pain between attacks. The average between the utility values reported by McDermott et al. for mild, moderate and severe neuropathic pain was subtracted from the utility of the general population with the same average age and proportion of females as in the study to obtain the utility decrement of chronic pain (-0.383) (86). This utility decrement is similar to the values from the other two studies (-0.19 and -0.275 per Hoxer et al. and Stafford et al., respectively)(92,93).

The targeted search on neurologic symptoms retrieved studies in multiple sclerosis, as well as a catalogue by Sullivan et al of EQ-5D scores for the UK in paralysis and other conditions. For neurologic symptoms, the utility decrement that appeared most relevant was reported by Sullivan et al. for "Other hereditary and degenerative neuropathy". Neurologic symptoms in AHP as reported by Neeleman et al. vary in severity from mild (e.g., paraesthesia) to moderate (e.g., motor weakness) and very severe (e.g., paralysis and advanced neuropathy)(22). Sullivan et al. provided utility decrements that can be applied in the model directly, and using the value for the broad category "Other hereditary and degenerative neuropathy" avoids restricting the disutility measure in the model to a specific neurological condition such as multiple sclerosis or paralysis that may not be fully representative of the entire range of neurologic symptoms in AHP. Moreover, this utility decrement (-0.097) is much lower than the values derived from the other identified studies for neurologic symptoms and is therefore a conservative choice(87).

As for neurologic symptoms, psychiatric symptoms in AHP include a range of different conditions such as depression, anxiety, insomnia and psychosis. For this reason, the study which appears most relevant was by Ara and Brazier(88), who reported the utility with and without aggregate psychiatric conditions defined as "Mental illness/anxiety/depression/nerves". The utility of the population with the condition was subtracted to the utility of the population without the condition to obtain the utility decrement of psychiatric symptoms in the model (0.27).

9.4.2.3.2 Calculation of health-state disutilities due to chronic conditions

To assign health-state utility decrements due to chronic pain, neurologic symptoms, and psychiatric symptoms, we estimated the proportion of the cohort with one, two, or three of these chronic conditions. Because the prevalence data reported by Neeleman et al. did not report the distribution of multiple concurrent chronic conditions, we applied the multiplicative approach developed by Ara and Brazier(89), which is recommended by the International Society for Pharmacoeconomics and Outcomes Research Good Practices for Outcome Research Task Force. We applied this method by multiplying the utility in the absence of a given condition by the product of the ratios of the utilities for individuals with the conditions to the utility of individuals in the general population.

A utility decrement on the general population utility was obtained from the literature for each higher order category among chronic symptoms/comorbidities (i.e., pain, neurological and psychiatric). The utility value for the two or more combined condition was estimated combining the utility values of the two or more conditions using the multiplicative formula reported by Ara and Brazier(89).

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

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

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

Using the selected utility values for chronic pain, neurologic and psychiatric conditions and the method described above for assigning utility decrements for multiple conditions based on the proportion of the cohort with these conditions in each health state, the utility values by health state are as shown in Table 39.

Table 39: Utility decrements due to chronic conditions, by health state

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

AHP, acute hepatic porphyria.

9.4.3 Disutility of AEs

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

9.5 Resource use and costs

The following costs are considered in the analysis:

- Cycle cost of the intervention/comparator (drug and administration cost)
- Per-event cost of attacks, all treated in hospital
- Cycle cost of AHP chronic conditions
- Cost for treatment of AEs
- Cost of opioid addiction
- Transportation cost (givosiran administration, treatment adverse events and attack treatment)
- Monetary value of the use of time by patients (givosiran administration, treatment of AEs and attacks treatment)
- Monetary value of the use of time by caregivers (attacks treatment)
- End-of-life care cost

The current analysis was developed with the aim of including costs that would closely represent the actual costs of AHP management in Denmark.

Where needed, costs were updated to 2021 prices using the monthly index of net price excluding Energy for Denmark, PRIS114(96). When the month of estimation of the original cost was not known, January was used as a reference.

Pharmacologic therapy

The cost of the pharmacologic therapy includes both the drug and the administration costs. Drug cost is the pharmacy purchase price (PPP) published by Medicinpriser.dk(97). The dose considered in the model is 2.5 mg per kg of body weight per administration. For the dose calculation, the model considers the average weight of the European patients in ENVISION, corresponding to 65.3 kg, as the weight of European patients in ENVISION is expected to be more representative of the weight of patients in Denmark than the weight of US ENVISION patients. Thus, the total dose per administration is 163 mg. BSC is assumed to have no incremental price associated with its use, as patients in the givosiran arm can also receive established clinical management and thus the cost of BSC should cancel out across treatment arms in the model (Table 40).

Table 40: Drug price

	Mg per vial	Unit	Price (DKK)	Price per mg (DKK)	Price per vial (DKK)
Givosiran	189	1	[redacted]	[redacted]	[redacted]
BSC	NA	NA	0	0	0

BSC, best supportive care; NA, not applicable.

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As givosiran is administered once per month, 6 administrations are considered per cycle of the analysis. No vial sharing is included in the base case, meaning that any opened vial may not be reused and therefore the entire cost of a vial is counted even if the dose administered is less than the entire vial. This was varied in a scenario analysis where vial sharing is allowed and cost per mg is estimated.

A relative dose intensity (RDI) for givosiran of [redacted] was estimated based on [redacted] missed doses out of [redacted] doses in patients remaining on treatment in ENVISION, and is used to adjust the total dose. Table 41 presents a summary of givosiran drug cost per administration and per cycle.

Table 41: Givosiran drug cost per cycle

	Dose per admin (mg/kg)	Admin per cycle	[redacted]	Drug cost per cycle (DKK) no vial sharing (basecase analysis)	Drug cost per cycle (DKK) with vial sharing (scenario analysis)
Givosiran	2.5	6	[redacted]	[redacted]	[redacted]

RDI, relative dose intensity.

Givosiran is administered SC. The cost of SC administration was estimated using the 2021 DRG tariff list in Denmark (DRG 2021, 07MA98: MDC07 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE802C: Porphyria hepatica Procedure: BWAA31 Medicingivning ved subkutan injektion) (Table 42).

Table 42: Givosiran administration cost

	Cost (DKK)	Source
SC administration	2,610	DRG 2021, 07MA98: MDC07 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE802C: Porphyria hepatica Procedure: BWAA31 Medicingivning ved subkutan injektion

SC, subcutaneous.

Based on 6 administrations per cycle and the respective tariff per administration, the resulting administration cost per cycle is DKK 15,660. The cost of administration for BSC was assumed to be DKK 0.

The total cost of givosiran treatment per cycle with no vial sharing, including both drug acquisition and administration costs, is DKK 2,160,655. For patients who interrupt treatment, a DKK 0 pharmacological treatment cost is applied.

Hospitalisation for AHP attacks

The cost of AHP attacks is applied as a per-event cost to the proportion of the cohort having an attack. In Denmark all AHP related attacks are expected to be treated in the hospital with the use of rescue haemin. As requested in the DMC guidelines, to estimate the cost of AHP attacks we considered the Danish DRG tariff associated with porphyria and we added the cost of rescue haemin, which was assumed to not be included within the DRG tariff:

- Hospitalisation cost, based on the Danish DRG tariff published in 2021 (07MA10: Metabolisk leversygdom, Diagnosis: DE802C: Porphyria hepatica);
- Haemin based on the 2021 price for Normosang of DKK 20,077 for 4 vials (Medicinpriser.dk), dosed at 3 mg/kg once daily for 4 days. Based on the average weight of the model cohort, this corresponds to a total of 4 vials per hospitalisation.

The average of 4 days IV haemin rescue treatment is considered conservative as the mean duration of attacks that required haemin or that were treated in a healthcare facility was 7.3 days in the EXPLORE study.

Incorporating these costs (Table 43) yields a total cost per AHP attack of DKK 49,127.

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Table 43: Resource use and unit cost for treatment of AHP attacks in hospital

	Resource utilization	Unit cost (DKK)	Total units	Total cost (DKK)	Source
Hospitalisation	100%	N/A	N/A	29,050	DRG 2021
Haemin	100%	5,019.3	4	20,077	Medicinpriser.dk

DKK, Danish kroner; N/A, not available.

Cost of chronic conditions

In addition to the per-event cost of acute attacks, the model considers the per-cycle cost associated with chronic conditions, which is applied to the proportion of the cohort with each condition in each health state based on prevalence data reported by Neeleman et al. 2018 (Table 20).

The ongoing annual cost of managing each chronic condition in Denmark was obtained from cost studies, independently from the presence of AHP. No studies conducted in Denmark were identified and references used included mostly refers to study conducted in the Nordics and reporting costs in Euros. Euros were converted to DKK using Nationalbankens Statistikbank, DNVALA (98), as requested in the DMC guidelines (74). All costs were inflated to 2021 price level using the PRIS114 inflation index (96), as previously mentioned. Table 44 presents a summary of the annual cost of all AHP chronic conditions considered in the model, with respective sources.

Table 44: Annual costs of AHP chronic conditions (updated to 2021 price level)

Chronic condition	Annual cost (2021 DKK)	Source	Notes
Pain			
Headaches	21,708	Gustavsson et al., 2012(99)	Total annual direct cost of headache of 2,772 Euros reduced of the cost of non-pain medications of 323 Euros. The cost was converted from Euros to DKK at the conversion rate of reference year.
Chest pain	54,894	Mourad et al., 2013(100)	Total annual direct cost of 6,797 Euros. The cost was converted from Euros to DKK at the conversion rate of reference year.
Back pain	38,399	Gustavsson et al., 2012(99)	Total annual direct cost of specific back conditions of 5,001 Euros reduced of the cost of non-pain medications of 669 Euros. The cost was converted from Euros to DKK at the conversion rate of reference year.
Abdomen pain	21,584	Gustavsson et al., 2012(99)	Cost of "other conditions associated with chronic pain" reported in the study used as a proxy. Total annual direct cost of 2,775 Euros reduced of the cost of non-pain medications of 340 Euros. The cost was converted from Euros to DKK at the conversion rate of reference year.
Upper Extremities pain	21,584	Gustavsson et al., 2012(99)	Assumed equal to back pain
Lower Extremities pain	21,584	Gustavsson et al., 2012(99)	Assumed equal to back pain

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Chronic condition	Annual cost (2021 DKK)	Source	Notes
Genitalia pain	21,584	Gustavsson et al., 2012(99)	Assumed equal to back pain
Neurological			
Paraesthesias	21,584	Gustavsson et al., 2012(99)	Assumed equal to upper/lower extremities pain
Motor weakness	23,022	Liedgens et al. 2016 (101)	Total annual cost of neuropathic pain taken as a proxy. The cost was converted from GBP to DKK at the conversion rate of reference year.
Paralysis	63,080	Fineberg et al. 2013 (102)	Total direct medical cost of neuromuscolar disorder. The cost was converted from Euros to DKK at the conversion rate of reference year.
Urinary incontinence	6,614	The Guardian, 2016 (103)	Total annual cost to the NHS in UK of urine incontenence. The cost was converted from GBP to DKK at the conversion rate of reference year.
Advanced Neuropathy	32,531	Gustavsson et al., 2012(99)	Total annual direct cost of neuropathies of 4171 Euros. The cost was converted from Euros to DKK at the conversion rate of reference year.
Psychiatric			
Anxiety	23,618	Sandelin et al., 2013 (104)	Total annual direct cost of anxiety in DKK
Depression	18,379	Ekman et al., 2013 (105)	Total annual cost of depression was reported equal to 17,279 Euros. Only 12% of total cost were direct costs and were therefore considered. The cost was converted from Euros to DKK at the conversion rate of reference year.
Psychosis/Hallucinations	59,183	Gustavsson et al. 2011 (106)	Total annual direct cost for treating psychosis. The cost was converted from Euros to DKK at the conversion rate of reference year.
Insomnia	33,540	Dragioti et al., 2017 (107)	Total annual direct cost of insomina, average between different levels of severity. The cost was converted from Euros to DKK at the conversion rate of reference year.
Suicidality	18,379	Ekman et al., 2013 (105)	Assumed equal to depression

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

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At each cycle of the analysis, the cycle cost of each chronic condition is applied to the prevalent cohort (i.e., multiplied by proportion of cohort affected) in each health state as defined in Table 20. The sum of the weighted cycle costs of all chronic conditions considered represents the total economic impact associated with AHP chronic consequences by disease severity (i.e., by health state) in each cycle of the analysis (Table 45).

Table 45: Summary of overall cost impact of chronic conditions by health state

Health-state	Cycle cost (DKK)
Asymptomatic	[redacted]
Symptomatic	[redacted]
Recurrent	[redacted]
Severe	[redacted]

Cost of treatment-related AEs

As in the case of AHP attacks, the cost of the severe treatment-related AEs included in the analysis is applied per event to the proportion of the cohort having each respective AE in each cycle, as long as the cohort remains on treatment. The cost of each adverse event was obtained from the respective DRG tariff for Denmark (2021 tariffs), as summarized in Table 46.

Table 46: Adverse events cost

Health-state	Cycle cost (DKK)	Reference
Asthenia	3,987	23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Udmattelse
Lipase increased	2,610	07MA98: MDC07 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR748D: Abnorm serumlipase
Iron overload	3,987	23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR790C: Abnorm mængde jern i blodet
Headache	3,987	23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR519: Hovedpine UNS

Cost of opioid addiction

In patients with AHP, frequent use of opiates (especially at the high doses often needed to manage AHP-related pain) can increase the risk of addiction (27,108). In qualitative research on the disease experience of patients with repeated AHP attacks, the majority of respondents taking prescription opioids raised concerns over long-term use, and many reported struggling with opiate addiction (32). Therefore, the cost of opioid addiction was incorporated in the model.

After inflation to 2021, the per-cycle (6-month) cost of opioid addiction for a patient with opioid addiction was estimated at DKK 6,061, based on the annual cost of opioid addiction per patient reported in the study by Shei et al.(109). The cost reported in Euros was transformed in DKK and inflated to 2021 price level. In the absence of data on the prevalence of opioid addiction by health state in a sufficiently large and representative sample of patients with AHP, it was assumed that the prevalence of opioid addiction would be 82% in the Recurrent health state based on Neeleman et al.(22); the same prevalence was assumed for the Severe health state.

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Opioid addiction cost was not applied in symptomatic and asymptomatic health-state since these patients have few or no attacks and therefore the use of opioids is limited.

Transportation cost

Transportation costs are included in the model assuming one return journey to the hospital/health-care setting for:

- each givosiran administration;
- each hospitalisation related to attacks;
- each occurrence of AEs.

Table 47 shows the average km per visit, considering a return journey, and the most updated cost (DK) per km reported by the DMC (110). The transportation cost per visit to the hospital/health-care setting, DKK 98.56, is estimated by multiplying the average km by the cost (DK) per km.

Table 47: Transportation unit cost

	Model input	Reference
Average km per visit (return journey)	28.00	Medicinrådet 'Estimating unit costs'(110)
Cost (DKK) per km	3.52	Medicinrådet 'Estimating unit costs'(110)

Use of time by patients and caregivers

In accordance with the DMC guidelines, the model considers costs associated with use of time for patients and caregivers in connection with treatment. These correspond to use of time for administration of givosiran and rescue haemin, and for healthcare visits for treatment-related AEs. The value of time is calculated at a common rate for all patients and caregivers. It includes leisure time and is not related to employment. The value of increased or decreased leisure time is determined by the average salary in Denmark. The most recent average wage per hour in Denmark was obtained from the DMC(110) and corresponds to DKK 179.

For the patient, the use of time for givosiran administration is assumed to be 1 hour, which incorporates time to receive the injection and transportation. An assumption of 1 hour per AE is based on the duration of each visit required to manage an AE. Finally, it is assumed that each patient spends 7.3 days per administration of rescue haemin based on the average duration of attack reported in EXPLORE. 7.3 days seems appropriate as a proxy given that patients receive haemin treatment for 4 days are the likely to remain hospitalised for few more days for careful monitoring until rescue heam has effectively reduced ALA/PBG levels, ameliorated symptoms and ensure no side effects. Table 48 shows the value of the use of time for patients for each event.

Table 48: Value of use of time for patients

Event	Use of time	Cost (DKK)
Givosiran administration	1 hour	179.00
Treatment-related AEs	1 hour	179.00
Rescue haemin administration	7.3 days	10,440.36*

* daily salary estimated multiplying the average salary per day by 8 hours
AE, adverse event.

For caregivers, only use of time for rescue haemin administration is considered since it is assumed that patients do not require assistance for givosiran administration or any healthcare visits to monitor treatment-related AEs. Based on a consultation with the clinical expert in Denmark (Prof. Frystyk), it is assumed that

caregivers spend 1 hour per day in hospital supporting patients while they receive rescue therapy with haemin (75). The value of the use of time of caregivers (DKK 1,305) is calculated by multiplying the time spent supporting patients during rescue haemin therapy by the average hourly wage (Table 49).

Table 49: Value of use of time for caregivers

Event	Use of time	Cost (DKK)
Rescue haemin administration	7.3 hours*	1,305.04

* 3.10 hours per day duration of attack

Municipality cost

No evidence was identified concerning home care service in AHP. An option explored was to assume home care service following attack treatment and use caregiver time as a proxy. However due to the uncertainty around this input and to avoid double counting, it was preferred to assume no municipality cost in the model. This is to be considered a conservative assumption given that BSC cohort has more attacks than givosiran cohort and would therefore incur higher home service cost than patients treated with givosiran.

End-of-life care cost

An end-of-life care cost is included in the current analysis and is estimated based on resource use reported in the NICE technology appraisal document for ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [TA451](111) (Table 50). The total end-of-life cost of DKK 66,160 is included in the model as a one-off cost and is applied to the proportion of new deaths at each cycle of the model. Since in the base case we apply the same mortality HR vs general population in each health-state, the impact of the end-of-life care cost cancels out between givosiran and BSC (i.e. cost difference is 0).

Table 50: Data to estimate end-of-life care cost

	Model input	Reference
Proportion being treated in hospital	51.5%	NICE TA 451 (111)
EOL hospital days	21.50	NICE TA 451 (111)
Cost of palliative care in hospital (DKK per day)	4,171.00	DRG 2021, 26MP47: Specialiseret Palliativ indsats, Lille, Diagnosis: DZ515S: Kontakt mhp. specialiseret palliativ indsats Procedure: BXBA0 Specialiseret palliativ indsats med lægelig intervention
Proportion being treated in hospice	23.1%	NICE TA 451 (111)
EOL hospice days	17.40	NICE TA 451 (111)
Cost of community palliative care per day (2021 DKK)	4,983.41	Kapacitet på hospicerne og udgifter forbundet med en udvidelse på Hospice Søholm og Gudenå Hospice - 600.000 kr. kommunalt, 1.154.000 kr. Regionalt. The cost was 2017 and inflated to 2021
EOL care cost (2021 DKK)	66,160	

EOL, end of life.

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9.6 Results

9.6.1 Base case overview

A summary of base-case settings for the cost-effectiveness analysis is presented in Table 51.

Table 51: Base-case model settings

Parameter	Setting
Type of model	Markov model
Perspective	Restricted societal perspective
Time horizon	Lifetime
Cycle length	6 months
Discount rate of costs and outcomes	3.5% until 35 years in the model, 2.5% until 70 years in the model and 1.5% thereafter
Age at start, weight (kg) and % female	ENVISION EU
Average AAR by health-state	ENVISION
Efficacy	
Givosiran	Cycle 1 from ENVISION double-blind period Cycles 2 and 3 from ENVISION OLE Recycling (last observation carried forward) until year 5 of the analysis, then freeze
BSC	Cycle 1 from ENVISION double-blind period Cycle 2+: no transitions except to death health-state
Chronic conditions considered	Based on Neeleman et al. 2018(22) (in severe health-state the prevalence is assumed equal to recurrent health-state)
HRQoL	
Patients	Disutility of attack from EXPLORE + health-state utility decrement from literature (utility decrements are applied to utility of general population decreasing by age)
Mortality of chronic conditions	HR vs general population of 1.3 per Baravelli et al. 2020(50) applied to all AHP health states
Included costs	Pharmaceutical costs Drug administration costs Attack hospitalisation cost Chronic conditions costs Opioid addiction costs AE costs Transportation cost Use of time by patients and caregivers End-of-life care costs

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Parameter	Setting
Price per vial of givosiran	[redacted]
Cost of givosiran treatment	No vial sharing, RDI per ENVISION

AAR, annualized attack rate; AE, adverse event; AHP, acute hepatic porphyria; BSC, best supportive care; HR, hazard ratio; OLE, open-label extension; RDI, relative dose intensity.

9.6.2 Base case results

The base-care results for givosiran compared with BSC in terms of life-years gained, QALYs, costs and ICER (per QALY) from the restricted societal perspective in Denmark are presented in Table 52. Givosiran compared with BSC yields a discounted ICER of DKK [redacted]/QALY.

Table 52: Base-case results

Per patient	Givosiran	BSC	Difference
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Per patient	Givosiran	BSC	Difference
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]		

AE, adverse event; BSC, best supportive care; EOL, end of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

9.7 Sensitivity analyses

9.7.1 Scenario analysis

Outcomes of various scenario analyses relative to the base case are summarised in Table 53 and discussed in detail below.

Table 53: Outcomes of scenario analyses relative to the base case

#	Scenario	Incremental Costs (DKK)	Incremental QALYs	ICER	% change
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC, best supportive care; DB, double blind; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

1. **Alternative extrapolation of Givosiran efficacy: recycling up to year 3**

In the base case, the model assumes that the transition probabilities observed in the ENVISION OLE period continue over time beyond the duration of the OLE period. A 5-year time point was selected as a reasonable extrapolation limit for this trend. After that point, the cohort is assumed to remain stable (i.e., no further

transitions between AHP severity health states, though transitions to death occur). To address the uncertainty regarding extrapolation of treatment effects beyond observed data for givosiran, a scenario analysis was performed in which health-state transitions were applied up to cycle 6, matching the 3 years of observed data from the ENVISION double-blind period and OLE, with no further health-state transitions thereafter.

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

In contrast to the base-case analysis, which adopts the highly conservative assumption that health-state transitions in the BSC arm occur only in the first model cycle, a scenario analysis was performed in which BSC efficacy was based on the placebo group in ENVISION for the first cycle, and thereafter a per-cycle probability of disease worsening was applied to define transition to a health state one level worse (i.e., from Asymptomatic to Symptomatic, from Symptomatic to Recurrent, and from Recurrent to Severe). The probability of disease worsening was estimated based on data on time from diagnosis and AAR at 6 months in the placebo arm of the ENVISION double-blind trial. The estimated 13% per-cycle probability of disease worsening was applied in the placebo arm from the second cycle up to cycle 10 (year 5). This probability was also applied post-treatment discontinuation in the givosiran arm.

3. **Mortality Scenario Analysis**

In the base-case analysis, all AHP health states are assigned the same mortality HR of 1.3 compared with the general population, based on the increased risk of premature death for the overall AHP cohort in the real-world study reported by Baravelli et al. (HR 1.3, 95% CI 1.0, 1.8)(50). This approach was adopted because the classified subgroups of AHP in this cohort did not have a significant mortality difference compared with the general population (i.e., their HR 95% CIs encompassed 1.0, likely reflecting lower sample sizes in the subgroups), and it was therefore deemed most rigorous to apply the overall HR to all patients. Applying the same HR in the Asymptomatic health state, which more patients in the givosiran arm achieve, as in the other health states should be considered a conservative approach for the base case, since an increased burden of chronic conditions and thus mortality is expected in patients with greater disease severity.

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

4. **Alternative assumption for prevalence of chronic conditions**

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

5. **Inclusion of vial sharing scenario**

In this scenario, vial sharing is assumed to estimate the pharmacological cost of givosiran per cycle. This implies that a cost per mg was estimated (DKK 1,991) and was multiplied by the average mg per administration, 163.2mg, based on 2.5mg/kg and the average weight in ENVISION EU (65.3). The resulting

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pharmacological cost of givosiran per cycle estimated considering vial sharing (and after applying the RDI) is DKK [redacted].

9.7.2 Deterministic sensitivity analyses

To evaluate the sensitivity of model results to variation in input parameters, a series of one-way sensitivity analyses were performed in which key model parameters were varied one at a time around their base-case values. The 95% confidence limits were used as the high and low values when reported in the data reference. If not reported, the 95% CI was approximated by setting high and low values at the base-case value ± 1.96x standard error (SE). When the SE was not reported, 10% of the base-case value was used as a proxy. The change in base case results following lower and upper variation in the 15 most influential model parameters are presented in Figure 26 and in Table 54.

[redacted]

Table 54: Change in 15 most influential model variables

	Change		Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]					

	Change		Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AAR: annualised attack rate; AHP: acute hepatic porphyria; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; ToT: time on treatment.

9.7.3 Givosiran price sensitivity

The change in ICER (per QALY) following variations in the maximum PPP price of givosiran (DKK 361,169 per vial) is presented in [redacted] and Table 55.

[redacted]

[redacted]

Table 55: Results of price sensitivity analysis

Change on max PPP price	Givosiran price per vial	ICER (DKK/QALY)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

9.7.4 Probabilistic sensitivity analyses

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

The results of the probabilistic sensitivity analysis are described in Table 56, Figure 28 and Figure 29 .

Table 56: Probabilistic sensitivity analysis results

	Costs (DKK)			QALY			ICER
	Givosiran	BSC	Incremental	Givosiran	BSC	Incremental	(DKK/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]

[redacted]

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10. Budget impact analysis

The budget impact model was developed to estimate the expected budget impact of recommending givosiran as standard treatment in Denmark. The budget impact analysis has been embedded within the CEA model and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the population in the cost per patient model.

The costs included in the budget impact model are undiscounted, and patient cost and transportation cost have not been included as per the guidelines by the DMC.

The analysis compares the costs for the Danish regions per year over five years in the scenario where givosiran is recommended as standard treatment and the scenario where givosiran is not recommended as standard treatment. The total budget impact per year is the difference between the two scenarios.

10.1 Number of patients

[redacted] In the scenario where givosiran is not recommended, all patients are assumed to be on BSC (Table 57), while in the scenario where givosiran is recommended, all patients will begin treatment with givosiran (Table 58).

Table 57: Number of patients expected to be treated over the next five-year period - if givosiran is not recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Givosiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 58: Number of patients expected to be treated over the next five-year period - if givosiran is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Givosiran	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10.2 Budget impact result

Based on the base case settings, the estimated budget impact of recommending givosiran as standard treatment in Denmark at PPP was [redacted] in year 1 and [redacted] in year 5 as shown in Table 59.

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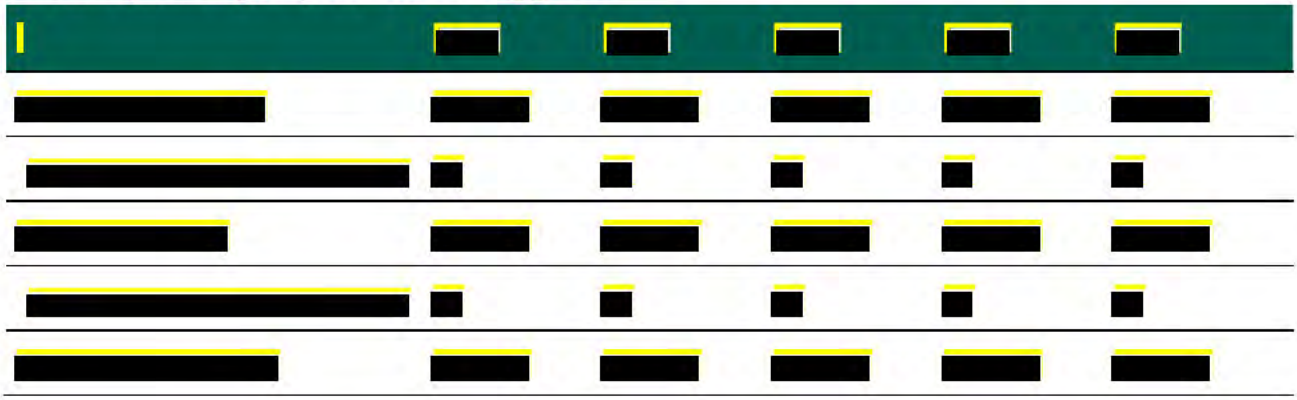
Table 59: Expected budget impact of recommending givosiran



10. Discussion on the submitted documentation

This single technology assessment relates to givosiran as a treatment of AHP in adults and adolescents aged 12 years and older. AHP patients with recurrent attacks experience an extensive burden of disease in connection with attacks, in particular due to the extreme pain experienced during attacks. However, HRQoL may also be significantly affected between attacks, e.g. due to the constant restrictions in order not to trigger acute attacks and the concerns/worries about new attacks. HRQoL may also be reduced due to chronic pain, anxiety and depression, and the reduced ability to perform daily activities. In addition, patients with AHP suffer long-term complications including chronic kidney disease (CKD), hypertension, hepatocellular carcinoma (HCC), and anaemia, and their occurrence increases with higher rates of acute attacks.

There are no comparator treatments for givosiran in Denmark—until givosiran, patients afflicted with AHP have lacked any treatment options to prevent AHP-related acute attacks and have had to rely on supportive therapy to manage the chronic pain that occurs as part of this condition (17). The management of patients with recurrent acute attacks is challenging (64). Options currently available for preventing acute attacks include lifestyle modifications and avoidance of medications that are known to precipitate attacks (3,64).

Givosiran, is the first disease-modifying, preventative treatment for AHP, and is intended for use as a long-term therapy, with rescue therapy as an adjunctive measure for patients who experience a breakthrough acute attack. While attacks are reduced by almost 75% in patients who receive givosiran, there remains a need for a treatment that can ameliorate breakthrough acute attacks when they do occur (18).

The efficacy and safety of givosiran was demonstrated in the ENVISION (Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria) a phase 3 randomised, double-blind, placebo-controlled, multicentre with an open-label extension period (OLE). The design of the phase 3 ENVISION RCT reflects the current management of AHP. Supportive therapy with analgesics and rescue therapy with haemin for the treatment of acute attacks was permitted in both treatment arms.

The clinical benefits observed for givosiran in ENVISION represents a breakthrough in the management for AHP patients. In summary in ENVISION givosiran resulted in significant and clinically meaningful reduction in the composite annualized attack rate, compared to best supportive care, of 74% ($p<0.001$) and 73% ($p<0.001$) in patients with AIP and AHP, respectively. This was accompanied by a significant reduction in the number of days with haemin use compared to best supportive care. Importantly, approx. a 3-fold higher proportion of patients with AIP/AHP were attack free at 6-months when treated with givosiran compared with best supportive care (17).

Givosiran transforms the standard of care for AHP as the only treatment for prophylaxis of acute attacks that is supported by robust RCT evidence (17,65). There are no comparators that occupy the same place in therapy as

givosiran, a disease-modifying, preventative treatment for AHP and consequently a positive recommendation from DMC would meet a major unmet need for Danish patients

A cost-effectiveness analysis was developed following the DMC guidelines to assess the cost-effectiveness of givosiran compared with BSC for the treatment of AHP in Denmark. AHP health-state transitions and associated costs were compared between givosiran and BSC. The model incorporated key clinical data from ENVISION and the literature—notably, the EXPLORE natural history study and the real-world data of Neeleman et al. 2018—and was developed to be representative of Danish healthcare setting by using unit costs and health care resource utilization from Denmark (or adapted from other sources to the Danish context). Key model parameters were validated by a panel of clinical experts and/or a Danish clinical expert, Prof. Jan Frystyk (head of Department and head of Research Department of Endocrinology, Odense University Hospital & Institute of Clinical Research, Faculty of Health Sciences, University of Southern Denmark in Odense).

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

It should be noted that overall, most assumptions in the model are conservative with respect to the ICER for givosiran vs BSC.

Over the CEA time horizon (lifetime), this model projects a substantial gain of [redacted] QALYs (discounted) for patients who received givosiran compared with those who received BSC. This was attributable to patients spending fewer years in more advanced AHP health states, and thus experiencing fewer acute attacks and a lower burden of chronic conditions. As a consequence of these benefits to patients, givosiran also reduced the impact of AHP on caregivers. The benefit of this QALY gain to patients should be viewed in context of the loss of QALYs patients with AHP experience compared with the general population.

In the base-case analysis, the total lifetime cost for a patient treated with givosiran was DKK[redacted] (discounted), which is DKK[redacted] more than the lifetime costs incurred by a patient treated with BSC (DKK[redacted]). The resulting ICER for givosiran compared with BSC was DKK[redacted]/QALY. The model takes a very conservative assumption that BSC cohort does not worsen over time. Notably, the ICER decreased by 28% to DKK[redacted]/QALY once a probability of disease worsening reflective of observed increase in AAR by time from diagnosis is applied for the first 5 years of the analysis.

The PSA confirmed the robustness of the base-case results. The one-way sensitivity analysis showed that the CEA results are most sensitive to changes in parameters defining the ToT curve of givosiran. Across all other changes the ICER remains close to basecase and well below 2.4 million DKK.

Interpretation of the results of this CEA should take into account the value of a superior drug targeting a small and well-defined group of patients with a very serious disease that previously lacked a complete treatment. Therefore, givosiran should be viewed as an important breakthrough to reduce the burden of AHP on patients, caregivers, and society.

11. List of experts

- Jan Frystyk, Head of Department and Head of Research, Department of Endocrinology, Odense University Hospital & Institute of Clinical Research, Faculty of Health Sciences, University of Southern Denmark. Email: jan.frystyk@rsyd.dk, Phone: +45 2330 0330

12. References

1. Medicinrådet. Medicinrådets protokol for vurdering vedrørende givosiran til behandling af akut hepatisk porfyri. :1–14.
2. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. J Am Coll Cardiol. 2018;71(9):1021–34.
3. Balwani M, Wang B, Anderson KE, Bloomer JR, Bissell DM, Bonkovsky HL, et al. Acute hepatic porphyrias: Recommendations for evaluation and long-term management [Internet]. Vol. 66, Hepatology. John Wiley and Sons Inc.; 2017 [cited 2021 Jun 8]. p. 1314–22. Available from: https://pubmed.ncbi.nlm.nih.gov/28605040/
4. Gill L, Burrell S, Chamberlayne J, Lombardelli S, Mora J, Mason N, et al. Patient and caregiver experiences of living with acute hepatic porphyria in the UK: a mixed-methods study. Orphanet J Rare Dis. 2021;16(1):187.
5. Bissell DM, Anderson KE, Bonkovsky HL. Porphyria. Longo DL, editor. N Engl J Med [Internet]. 2017 Aug 31 [cited 2021 Jun 8];377(9):862–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28854095
6. Besur S, Hou W, Schmeltzer P, Bonkovsky HL. Clinically important features of porphyrin and heme metabolism and the porphyrias. Metabolites. 2014 Nov;4(4):977–1006.
7. Gouya L, Ventura P, Balwani M, Bissell DM, Rees DC, Stolzel U, et al. EXPLORE: a prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. Hepatology [Internet]. 2019/09/13. 2020 Nov 1 [cited 2021 Jun 8];71(5):1546–58. Available from: https://pubmed.ncbi.nlm.nih.gov/31512765/
8. Ramanujam VMS, Anderson KE. Porphyria diagnostics-part 1: A brief overview of the porphyrias. Curr Protoc Hum Genet [Internet]. 2015 [cited 2021 Jun 8];2015:17.20.1-17.20.26. Available from: https://pubmed.ncbi.nlm.nih.gov/26132003/
9. Szlendak U, Bykowska K, Lipniacka A. Clinical, Biochemical and Molecular Characteristics of the Main Types of Porphyria. Adv Clin Exp Med. 25(2):361–8.
10. Stein PE, Badminton MN, Rees DC. Update review of the acute porphyrias. Br J Haematol. 2017 Feb;176(4):527–38.
11. Elder G, Harper P, Badminton M, Sandberg S, Deybach J-CC. The incidence of inherited porphyrias in Europe. J Inherit Metab Dis [Internet]. 2013 Sep 1 [cited 2021 Jun 28];36(5):849–57. Available from: https://onlinelibrary.wiley.com/doi/full/10.1007/s10545-012-9544-4
12. European Porphyria Network. Providing better healthcare for patients and their families. 2010.
13. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report for Givlaari. 2020.
14. Danish Medicines Agency. Danish Summary of Product Charactertistics for Normosang (Haemin). 2015.
15. Stein P et al. Best practice guidelines on: Clinical management of acute attacks of porphyria and their complications 2017. 2017.
16. Anderson KE, Bloomer JR, Bonkovsky HL, Kushner JP, Pierach CA, Pimstone NR, et al. Recommendations for the diagnosis and treatment of the acute porphyrias. Ann Intern Med. 2005 Mar;142(6):439–50.
17. Balwani M, Sardh E, Ventura P, Peiró PA, Rees DC, Stölzel U, et al. Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria. N Engl J Med [Internet]. 2020 Jun 11 [cited 2021 Jun 8];382(24):2289–301. Available from: https://www.nejm.org/doi/full/10.1056/nejmoa1913147
18. Alnylam Pharmaceuticals. CLINICAL STUDY REPORT 2 INTERIM ANALYSIS FOR ALN-AS1-003 (GIVOSIRAN) DATED - Data on file. 2020;1(June):1–181.
19. EMA. European Public Assessment Report. Givlaari, INN-givosiran.
20. Bonkovsky HL, Maddukuri VC, Yazici C, Anderson KE, Bissell DM, Bloomer JR, et al. Acute porphyrias in the USA: features of 108 subjects from porphyrias consortium. Am J Med. 2014 Dec;127(12):1233–41.
21. Montgomery Bissell D, Wang B. Acute hepatic porphyria [Internet]. Vol. 3, Journal of Clinical and Translational Hepatology. Xia and He Publishing Inc.; 2015 [cited 2021 Jun 8]. p. 17–26. Available from: https://pubmed.ncbi.nlm.nih.gov/26357631/
22. Neeleman RA, Wagenmakers MAEMEM, Koole-Lesuis RH, Mijnhout GS, Wilson JHPP, Friesema ECHH, et al. Medical and financial burden of acute intermittent porphyria. J Inherit Metab Dis [Internet]. 2018 Sep 1 [cited 2021 Jun 8];41(5):809–17. Available from: https://pubmed.ncbi.nlm.nih.gov/29675607/
23. Schmitt C, Lenglet H, Yu A, Delaby C, Benecke A, Lefebvre T, et al. Recurrent attacks of acute hepatic porphyria: major role of the chronic inflammatory response in the liver. J Intern Med [Internet].

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2018/03/03. 2018;284(1):78–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29498764
24. Pallet N, Karras A, Thervet E, Gouya L, Karim Z, Puy H. Porphyria and kidney diseases. Clin Kidney J [Internet]. 2018;11(2):191–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29644058
25. Laafi J, Homedan C, Jacques C, Gueguen N, Schmitt C, Puy H, et al. Pro-oxidant effect of ALA is implicated in mitochondrial dysfunction of HepG2 cells. Biochimie [Internet]. 2014;106:157–66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25220386
26. Peoc'h K, Manceau H, Karim Z, Wahlin S, Gouya L, Puy H, et al. Hepatocellular carcinoma in acute hepatic porphyrias: A Damocles Sword. Mol Genet Metab. 2019 Nov;128(3):236–41.
27. Pischik E, Kauppinen R. An update of clinical management of acute intermittent porphyria. Appl Clin Genet [Internet]. 2015 Sep 1 [cited 2021 Jun 8];8:201–14. Available from: https://pubmed.ncbi.nlm.nih.gov/26366103/
28. Yasuda M, Gan L, Chen B, Kadirvel S, Yu C, Phillips JD, et al. RNAi-mediated silencing of hepatic Alas1 effectively prevents and treats the induced acute attacks in acute intermittent porphyria mice. Proc Natl Acad Sci U S A. 2014 May;111(21):7777–82.
29. Danish KOL statement on AHP health states - Danish expert clinicians.
30. Simon A, Pompilus F, Querbes W, Wei A, Strzok S, Penz C, et al. Patient Perspective on Acute Intermittent Porphyria with Frequent Attacks: A Disease with Intermittent and Chronic Manifestations. Patient. 2018 Oct;11(5):527–37.
31. Balwani M. What Hematologists Need to Know About Acute Hepatic Porphyria. Clin Adv Hematol Oncol. 2016;
32. Naik H, Stoecker M, Sanderson SC, Balwani M, Desnick RJ. Experiences and concerns of patients with recurrent attacks of acute hepatic porphyria: A qualitative study. Mol Genet Metab [Internet]. 2016 Nov 1 [cited 2021 Jun 8];119(3):278–83. Available from: https://pubmed.ncbi.nlm.nih.gov/27595545/
33. Balwani M, Gouya L, Rees D, Stein P, Stölzel U, Aguilera P, et al. GS-14-ENVISION, a phase 3 study to evaluate efficacy and safety of givosiran, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1, in acute hepatic porphyria patients. J Hepatol. 2019 Apr;70(1):e81–2.
34. Gill L. The evolving diagnosis and care of patients with acute hepatic porphyria (AHP) in the UK: from 2006 to 2018. 2019;
35. Pallet N, Mami I, Schmitt C, Karim Z, François A, Rabant M, et al. High prevalence of and potential mechanisms for chronic kidney disease in patients with acute intermittent porphyria. Kidney Int. 2015 Aug;88(2):386–95.
36. Kauppinen R, Mustajoki P. Prognosis of acute porphyria: occurrence of acute attacks, precipitating factors, and associated diseases. Med [Internet]. 1992;71(1):1–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1549056
37. Stewart MF. Review of hepatocellular cancer, hypertension and renal impairment as late complications of acute porphyria and recommendations for patient follow-up [Internet]. Vol. 65, Journal of Clinical Pathology. 2012 [cited 2021 Jun 29]. p. 976–80. Available from: https://pubmed.ncbi.nlm.nih.gov/22851509/
38. Mydlík M, Derzsiová K. Kidney damage in acute intermittent porphyria. Przegląd Lek. 2011;68(9):610–3.
39. Landray MJ, Emberson JR, Blackwell L, Dasgupta T, Zakeri R, Morgan MD, et al. Prediction of ESRD and death among people with CKD: The chronic renal impairment in Birmingham (CRIB) prospective cohort study. Am J Kidney Dis. 2010 Dec;56(6):1082–94.
40. Denny SD, Kuchibhatla MN, Cohen HJ. Impact of anemia on mortality, cognition, and function in community-dwelling elderly. Am J Med. 2006 Apr;119(4):327–34.
41. Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute Hepatic Porphyrias: Review and Recent Progress. Hepatol Commun [Internet]. 2019 Feb [cited 2021 Jun 8];3(2):193–206. Available from: https://pubmed.ncbi.nlm.nih.gov/30766957/
42. ANDERSSON C, LITHNER F. Hypertension and renal disease in patients with acute intermittent porphyria. J Intern Med. 1994 Aug;236(2):169–75.
43. Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis c in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: A systematic review and economic evaluation. Vol. 15, Health Technology Assessment. 2011. p. 1–208.
44. Lang E, Schäfer M, Schwender H, Neumann NJ, Frank J. Occurrence of malignant tumours in the acute hepatic porphyrias. In: JIMD Reports. Springer; 2015. p. 17–22.
45. Baravelli CM, Sandberg S, Aarsand AK, Nilsen RM, Tollånes MC. Acute hepatic porphyria and cancer

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risk: a nationwide cohort study. J Intern Med. 2017 Sep;282(3):229–40.
46. Innala E, Andersson C. Screening for hepatocellular carcinoma in acute intermittent porphyria: A 15-year follow-up in northern Sweden. J Intern Med. 2011 May;269(5):538–45.
47. Saberi B, Naik H, Overbey JR, Erwin AL, Anderson KE, Bissell DM, et al. Hepatocellular Carcinoma in Acute Hepatic Porphyrias: Results from the Longitudinal Study of the U.S. Porphyrias Consortium. Hepatology. 2020 May;73(5):2021.
48. Lissing M, Vassiliou D, Floderus Y, Harper P, Bottai M, Kotopouli M, et al. Primary liver cancer in acute hepatic porphyria: a national cohort study. Vol. 73, Journal of Hepatology. 2020.
49. Jaramillo-Calle DA, Aguirre Acevedo DC. Acute Hepatic Porphyrias in Colombia: An Analysis of 101 Patients. In: JIMD Reports [Internet]. Springer; [cited 2021 Jun 8]. p. 65–72. Available from: http://link.springer.com/10.1007/8904_2018_125
50. Baravelli CM, Aarsand AK, Sandberg S, Tollånes MC, Tollanes MC. Sick leave, disability, and mortality in acute hepatic porphyria: a nationwide cohort study. Orphanet J Rare Dis [Internet]. 2020 Feb 21 [cited 2021 Jun 8];15(1):56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32085780
51. Jeans JB, Savik K, Gross CR, Weimer MK, Bossenmaier IC, Pierach CA, et al. Mortality in patients with acute intermittent porphyria requiring hospitalization: A United States case series. Am J Med Genet. 1996 Nov;65(4):269–73.
52. Ferro MA, Rhodes AE, Kimber M, Duncan L, Boyle MH, Georgiades K, et al. Suicidal Behaviour Among Adolescents and Young Adults with Self-Reported Chronic Illness. Can J Psychiatry. 2017;62(12):845–53.
53. Gill L, Burrell S, Chamberlayne J, Lombardelli S, Mora J, Mason N, et al. Burden of Illness in Acute Hepatic Porphyria (AHP): Insights from Patient and Caregiver Members of the British Porphyria Association.
54. Gouya L, Balwani M, Bissell DM, Rees D, Stölzel U, Phillips J, et al. Impact of acute hepatic porphyrias on quality of life and work loss: An analysis of EXPLORE natural history study. J Hepatol. 2018 Apr;68:S622.
55. Millward LM, Kelly P, King A, Peters TJ. Anxiety and depression in the acute porphyrias. J Inherit Metab Dis. 2005 Dec;28(6):1099–107.
56. Millward LM, Kelly P, Deacon A, Senior V, Peters TJ. Self-rated psychosocial consequences and quality of life in the acute porphyrias. J Inherit Metab Dis. 2001 Nov;24(7):733–47.
57. American Porphyria Foundation. The Voice of the Patient: Patient-Focused Drug Development Meeting - Acute Porphyrias. 2017.
58. Bonkovsky H, Baptist WF, Center M, Anderson K, Desnick R. The Voice of the Patient Report of an Externally-Led Patient-Focused Drug Development Meeting Acute Porphyrias AUTHORS American Porphyria Foundation.
59. Puy H, Gouya L, Deybach JC. Porphyrias. Lancet [Internet]. 2010 Mar [cited 2021 Jun 8];375(9718):924–37. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20226990
60. Bronisch O, Stauch T, Haverkamp T, Beykirch MK, Petrides PE. Acute porphyrias: a German monocentric study of the biochemical, molecular genetic, and clinical data of 62 families. Ann Hematol. 2019 Dec;98(12):2683–91.
61. Alnylam Pharmaceuticals. Observational study report ALN-AS1-NT-001 (EXPLORE): Part A. 2018.
62. BresMed Health Solutions. Interviews to elicit the burden of illness of acute hepatic porphyria in patients and caregivers: Final report. 2019.
63. Pro.medicin.dk. Porfyri. 2019.
64. Anderson KE. Acute hepatic porphyrias: Current diagnosis & management. Mol Genet Metab [Internet]. 2019;128(3):219–27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31311713
65. Sardh E, Harper P, Balwani M, Stein P, Rees D, Bissell DM, et al. Phase 1 Trial of an RNA Interference Therapy for Acute Intermittent Porphyria. N Engl J Med [Internet]. 2019 Feb 7 [cited 2021 Jun 8];380(6):549–58. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1807838
66. European Medicines Agency (EMA). Summary of Product Characteristics for GIVLAARI (givosiran). 2020.
67. Kuter DJ, Keel S, Parker CJ, Rees DC, Stölzel U, Ventura P, et al. Eighteen-Month Interim Analysis of Efficacy and Safety of Givosiran, an RNAi Therapeutic for Acute Hepatic Porphyria, in the Envision Open Label Extension. Blood. 2020 Nov;136(Supplement 1):13–13.
68. Willandt B, Langendonk JG, Biermann K, Meersseman W, D'Heygere F, George C, et al. Liver Fibrosis Associated with Iron Accumulation Due to Long-Term Heme-Arginate Treatment in Acute Intermittent

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Porphyria: A Case Series. JIMD Rep. 2016;25:77–81.
69. Recordati Rare Diseases UK Ltd. SmPC: Normosang 25 mg/ml, concentrate for solution for infusion. 2019.
70. Clement ND, MacDonald D, Simpson AHRW. The minimal clinically important difference in the Oxford knee score and Short Form 12 score after total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc. 2014 Aug;22(8):1933–9.
71. Parker SL, Mendenhall SK, Shau DN, Adogwa O, Anderson WN, Devin CJ, et al. Minimum clinically important difference in pain, disability, and quality of life after neural decompression and fusion for same-level recurrent lumbar stenosis: understanding clinical versus statistical significance. J Neurosurg Spine. 2012 May;16(5):471–8.
72. Sardh E, Gouya L, Rees DC, Stein P, Stölzel U, Aguilera Peiro P, et al. Overall Health, Daily Functioning, and Quality of Life in Acute Hepatic Porphyria Patients: ENVISION, a Phase 3 Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Dig Liver Dis. 2020 Feb;52:e35.
73. CHMP. European public assesment report for Givlaari (givosiran). 2020.
74. Medicinrådet. Metodevejledning for omkostningsanalyser af nye laegemidler og indikationer i hospitalssektoren.
75. BresMed Health Solutions Ltd, BresMed Health Solutions Ltd. 2661: Givosiran acute hepatic porphyria clinician interview report. 2020.
76. Jensen CE, Sørensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. Appl Health Econ Health Policy [Internet]. 2021 Feb 2 [cited 2021 Apr 12];1–13. Available from: https://doi.org/10.1007/s40258-021-00639-3
77. Finansministeriet. Dokumentationsnotat – den samfundsøkonomiske diskonteringsrente. 2021;1–19.
78. Rahman I, Åkesson A, Wolk A. Relationship between age at natural menopause and risk of heart failure. Menopause [Internet]. 2015 Jan 3 [cited 2021 Jun 8];22(1):12–6. Available from: https://pubmed.ncbi.nlm.nih.gov/24824644/
79. Bylesjö I, Wikberg A, Andersson C, Bylesjo I, Wikberg A, Andersson C. Clinical aspects of acute intermittent porphyria in northern Sweden: a population-based study. Scand J Clin Lab Invest [Internet]. 2009 Sep [cited 2021 Jun 8];69(5):612–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19401933
80. Anderson K, Sassa S, Bishop D, J. D. Disorders of heme biosynthesis: X-linked sideroblastic anemia and the porphyrias. In: The Metabolic and Molecular Bases of Inherited Disease. 8th editio. New York; 2001.
81. National Institute for Health and Care Excellence. Single Technology Appraisal: Fremanezumab for preventing migraine [ID1368] Committee Papers [Internet]. Vol. 2020. 2020 [cited 2021 Jun 8]. Available from: https://www.nice.org.uk/guidance/ta631/documents/committee-papers-2
82. Hift RJ, Meissner PN. An analysis of 112 acute porphyric attacks in Cape Town, South Africa: Evidence that acute intermittent porphyria and variegate porphyrio differ in susceptibility and severity. Medicine (Baltimore) [Internet]. 2005 Jan [cited 2021 Jun 8];84(1):48–60. Available from: https://pubmed.ncbi.nlm.nih.gov/15643299/
83. Andersson C, Innala E, Backstrom T, Bäckström T. Acute intermittent porphyria in women: clinical expression, use and experience of exogenous sex hormones. A population-based study in northern Sweden. J Intern Med [Internet]. 2003 Aug 1 [cited 2021 Jun 8];254(2):176–83. Available from: https://pubmed.ncbi.nlm.nih.gov/12859699/
84. Innala E, Bäckström T, Bixo M, Andersson C, Backstrom T, Bixo M, et al. Evaluation of gonadotropin-releasing hormone agonist treatment for prevention of menstrual-related attacks in acute porphyria. Acta Obs Gynecol Scand [Internet]. 2010 Jan 16 [cited 2021 Jun 8];89(1):95–100. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20021268
85. Danmarks Statistik. HISB8: Dødelighedstavle (2-års tavler) efter køn, alder og dødelighedstavle [Internet]. 2021. Available from: https://www.statbank.dk/statbank5a/SelectVarVal/Define.asp?Maintable=HISB8&PLanguage=0
86. McDermott AM, Toelle TR, Rowbotham DJ, Schaefer CP, Dukes EM. The burden of neuropathic pain: Results from a cross-sectional survey. Eur J Pain [Internet]. 2006 [cited 2021 Jun 8];10(2):127. Available from: https://pubmed.ncbi.nlm.nih.gov/16310716/
87. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Mak [Internet]. 2011 Nov [cited 2021 Jun 8];31(6):800–4. Available from: https://pubmed.ncbi.nlm.nih.gov/21422468/

88. Ara R, Brazier J. Estimating health state utility values for comorbid health conditions using SF-6D data. Value Heal [Internet]. 2011 Jul [cited 2021 Jun 8];14(5):740–5. Available from: https://pubmed.ncbi.nlm.nih.gov/21839413/
89. Ara R, Brazier J. Estimating Health State Utility Values for Comorbidities [Internet]. Vol. 35, PharmacoEconomics. Springer International Publishing; 2017 [cited 2021 Jun 8]. p. 89–94. Available from: https://pubmed.ncbi.nlm.nih.gov/29052158/
90. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value Heal [Internet]. 2011 [cited 2021 Apr 14];14(4):539–45. Available from: https://pubmed.ncbi.nlm.nih.gov/21669378/
91. Papaioannou, D., Brazier, J.E., Paisley S. NICE DSU Technical Support Document 9: The identification, review and synthesis of health state utility values from the literature. 2010.
92. Hoxer CS, Zak M, Benmedjahed K, Lambert J. Utility valuation of health states for haemophilia and related complications in Europe and in the United States. Haemophilia [Internet]. 2019 Jan 1 [cited 2021 Jun 8];25(1):92–100. Available from: https://pubmed.ncbi.nlm.nih.gov/30461134/
93. Stafford MR, Hareendran A, Ng-Mak DS, Insinga RP, Xu R, Stull DE. EQ-5D™-derived utility values for different levels of migraine severity from a UK sample of migraineurs. Health Qual Life Outcomes [Internet]. 2012 Jun 12 [cited 2021 Jun 8];10:65. Available from: /pmc/articles/PMC3407525/
94. Hawton A, Green C. Health Utilities for Multiple Sclerosis. Value Heal [Internet]. 2016 Jun 1 [cited 2021 Jun 8];19(4):460–8. Available from: https://pubmed.ncbi.nlm.nih.gov/27325338/
95. Kolovos S, Bosmans JE, van Dongen JM, van Esveld B, Magai D, van Straten A, et al. Utility scores for different health states related to depression: individual participant data analysis [Internet]. Vol. 26, Quality of Life Research. Springer International Publishing; 2017 [cited 2021 Jun 8]. p. 1649–58. Available from: https://pubmed.ncbi.nlm.nih.gov/28260149/
96. Danmarks Statistik. PRIS114: Nettoprisindeks (2015=100) efter varegruppe og enhed - Statistikbanken - data og tal [Internet]. 2020 [cited 2020 Sep 4]. Available from: https://www.statbank.dk/statbank5a/SelectVarVal/Define.asp?Maintable=PRIS114&PLanguage=0
97. Lægemiddelstyrelsen. www.medicinpriser.dk [Internet]. [cited 2020 Mar 3]. Available from: https://medicinpriser.dk/default.aspx
98. Nationalbankens Statistikbank. DNVALA: Valutakurser efter valuta, kurstype og opgørelsesmetode (Årsobservationer). 2020.
99. Gustavsson A, Bjorkman J, Ljungcrantz C, Rhodin A, Rivano-Fischer M, Sjolund KF, et al. Socio-economic burden of patients with a diagnosis related to chronic pain--register data of 840,000 Swedish patients. Eur J Pain [Internet]. 2012 [cited 2021 Jun 8];16(2):289–99. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22323381
100. Mourad G, Alwin J, Strömberg A, Jaarsma T. Societal costs of non-cardiac chest pain compared with ischemic heart disease - A longitudinal study. BMC Health Serv Res [Internet]. 2013 Oct 9 [cited 2021 Jun 9];13(1):1–11. Available from: http://www.biomedcentral.com/1472-6963/13/403
101. Liedgens H, Obradovic M, De Courcy J, Holbrook T, Jakubanis R. A burden of illness study for neuropathic pain in Europe. Clin Outcomes Res [Internet]. 2016 Apr 27 [cited 2021 Jun 9];8:113–26. Available from: https://pubmed.ncbi.nlm.nih.gov/27217785/
102. Fineberg NA, Haddad PM, Carpenter L, Gannon B, Sharpe R, Young AH, et al. The size, burden and cost of disorders of the brain in the UK. J Psychopharmacol [Internet]. 2013/07/26. 2013 Sep [cited 2021 Jun 8];27(9):761–70. Available from: /pmc/articles/PMC3778981/
103. The Guardian. How much have I cost the NHS? [Internet]. [cited 2021 Jun 8]. Available from: https://www.theguardian.com/society/ng-interactive/2016/feb/08/how-much-have-i-cost-the-nhs
104. Sandelin R, Kowalski J, Ahnemark E, Allgulander C. Treatment patterns and costs in patients with generalised anxiety disorder: One-year retrospective analysis of data from national registers in Sweden. Eur Psychiatry [Internet]. 2013 Feb [cited 2021 Jun 9];28(2):125–33. Available from: https://www.cambridge.org/core/journals/european-psychiatry/article/abs/treatment-patterns-and-costs-in-patients-with-generalised-anxiety-disorder-oneyear-retrospective-analysis-of-data-from-national-registers-in-sweden/9057031C75F44DA534E3D6FEDEAAD3EA
105. Ekman M, Granström O, Omérov S, Jacob J, Landén M. The societal cost of depression: Evidence from 10,000 Swedish patients in psychiatric care. J Affect Disord [Internet]. 2013 Sep 25 [cited 2021 Jun 9];150(3):790–7. Available from: https://pubmed.ncbi.nlm.nih.gov/23611536/
106. Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, et al. Cost of disorders of the brain in Europe 2010. Eur Neuropsychopharmacol [Internet]. 2011 Oct [cited 2021 Jun 9];21(10):718–

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79. Available from: https://pubmed.ncbi.nlm.nih.gov/21924589/
107. Dragioti E, Bernfort L, Larsson B, Gerdle B, Levin L-Å. Association of insomnia severity with well-being, quality of life and health care costs: A cross-sectional study in older adults with chronic pain (PainS65+). Eur J Pain. 2017 Oct 16;22.
108. Bloomer JR, McGuire BM. Intermittent unexplained abdominal pain: is it porphyria? Clin Gastroenterol Hepatol. 2007;5(11):1255–8.
109. A S, M H, NY K, CJ E, HG B, WC D. Estimating the health care burden of prescription opioid abuse in five European countries. Clinicoecon Outcomes Res [Internet]. 2015 Sep 15 [cited 2021 Sep 8];7:477–88. Available from: https://pubmed.ncbi.nlm.nih.gov/26396536/
110. Medicinrådet. Værdisætning af enhedsomkostninger. 2020;(1.3):1–16. Available from: https://medicinraadet.dk/media/12930/vaerdisaetning-af-enhedsomkostninger-vers-13.pdf
111. National Institute for Health and Care Excellence. Single Technology Appraisal - Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia - Committee Papers [TA451] [Internet]. 2017 [cited 2021 Jun 9]. Available from: https://www.nice.org.uk/guidance/ta451/documents/committee-papers
112. Laafi J, Homedan C, Jacques C, Gueguen N, Schmitt C, Puy H, et al. Pro-oxidant effect of ALA is implicated in mitochondrial dysfunction of HepG2 cells. Biochimie. 2014;106:157–66.
113. Cleeland CS. The Brief Pain Inventory - User Guide. 2009.
114. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. J Pain. 2008 Feb;9(2):105–21.
115. Benedetto FA, Tripepi G, Mallamaci F, Zoccali C. Rate of atherosclerotic plaque formation predicts cardiovascular events in ESRD. J Am Soc Nephrol. 2008 Apr;19(4):757–63.
116. Hayes CJ, Bhandari NR, Kathe N, Payakachat N. Reliability and Validity of the Medical Outcomes Study Short Form-12 Version 2 (SF-12v2) in Adults with Non-Cancer Pain. Healthc (Basel, Switzerland). 2017 Apr;5(2).
117. Rampakakis E, Ste-Marie PA, Sampalis JS, Karellis A, Shir Y, Fitzcharles MA. Real-life assessment of the validity of patient global impression of change in fibromyalgia. RMD Open. 2015;1(1):e000146.
118. Altman DG. Practical statistics for medical research. D. Vol. 10, Statistics in Medicine. London: Chapman and Hall/CRC; 1991. 624 p.

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Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

Search strategy

Not applicable; see section 7. Based on the new DMC method guideline, the DMC can accept that systematic literature review is not carried out if one or several studies have already directly compared the new pharmaceutical with the relevant comparator. Alnylam has discussed this with the DMC prior to the submission, and the DMC acknowledged that it would not be necessary to conduct and present a systematic literature review for the present application.

Systematic selection of studies

Not applicable, see above

Quality assessment

Not applicable, see above

Unpublished data

The data-on file used for this submission were full study reports from ENVSION and ENVISION-OLE and were developed to support regulatory submissions to EMA/FDA. The data and analyses therefore adhere to the most stringent quality criteria.

24-month data from ENVISION-OLE are expected to be presented at United European Gastroenterology congress (UEG) 2021 and American College of Gastroenterology (ACG) 2021 in October, but is unavailable as of now. Data presented in this dossier from the AHP-population is not planned to be published, as the primary publication and regulatory submissions relied mainly on data from the 6 month DB phase from the primary efficacy population, which was the AIP population.

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Appendix B: Main characteristics of included studies

Table 60: ENVISION and ENVISION-OLE – Main Study Characteristics

ENVISION and ENVISION-OLE: A Study to Evaluate the Efficacy and Safety of Givosiran (ALN-AS1) in Patients With Acute Hepatic Porphyrias (AHP)	NCT number: NCT03338816
Objective	*The purpose of this study is to evaluate the effect of subcutaneous givosiran (ALN-AS1), compared to placebo, on the rate of porphyria attacks in patients with Acute Hepatic Porphyrias (AHP).*
Publications – title, author, journal, year	*Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria by Balwani et al., The New England Journal of Medicine, 2020.*
Study type and design	*Phase 3 Randomised, Double-blind, Placebo-Controlled Multicenter Study With an Open-label Extension. Patients were randomly assigned 1:1 using quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessor). The main study is completed, but the Open-label extension is ongoing, estimated to be completed in August, 2021.*
Sample size (n)	*94 participants enrolled*
Main inclusion and exclusion criteria	***Inclusion Criteria:*** • *≥ 12 years of age* • *Diagnosed with Acute Hepatic Porphyria (Acute Intermittent Porphyria, Hereditary Corproporhyria, Variegate Porphyria, aminolevulinic acid (ALA) dehydratase deficient porphyria)* • *Elevated urinary or plasma porphobilinogen (PBG) or ALA values within the past year,* • *Have active disease, with at least 2 documented porphyria attacks within the last 6 months* • *Willing to discontinue or not initiate the use of prophylactic haemin throughout the study.* • *Women of child bearing potential must have a negative serum pregnancy test, not be nursing, and use acceptable contraception* ***Exclusion Criteria:*** • *Clinically significant abnormal laboratory results* • *Anticipated liver transplantation* • *History of multiple drug allergies or intolerance to subcutaneous injections* • *Active HIV, hepatitis C virus, or hepatitis B virus infection(s)* • *History of recurrent pancreatitis*
Intervention	*Givosiran 2.5 mg/kg administered subcutaneously (SC), monthly (QM), for 6 months during the 6-Month Double-blind (DB) period. This is followed by givosiran 2.5 mg/kg or 1.25 mg/kg SC, QM for 29 months during the Open-label Extension (OLE) Period.*
Comparator(s)	*Matching placebo (normal saline [0.9% NaCl]) was administered SC, QM, for 6 months during the 6-Month DB period. This is followed by givosiran 2.5 mg/kg or 1.25 mg/kg SC, QM for 29 months during the OLE period.*

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ENVISION and ENVISION-OLE: A Study to Evaluate the Efficacy and Safety of Givosiran (ALN-AS1) in Patients With Acute Hepatic Porphyrias (AHP)	NCT number: NCT03338816

Follow-up time	-
Is the study used in the health economic model?	*Yes*
Primary, secondary and exploratory endpoints	**Primary Endpoint:** Annualized Rate of Porphyria Attacks in Participants With Acute Intermittent Porphyria (AIP) Porphyria attacks were defined as meeting all of the following criteria: an acute episode of neurovisceral pain in the abdomen, back, chest, extremities and/or limbs, no other medically determined cause, and required treatment with intravenous (IV) dextrose or haemin, carbohydrates, or analgesics, or other medications such as antiemetics at a dose or frequency beyond the participant's usual daily porphyria management. The annualized rate of porphyria attacks is a composite endpoint which included porphyria attacks requiring hospitalisation, urgent healthcare visit, or IV haemin administration at home. **Secondary Endpoints:** 1. Annualized Rate of Haemin Administration in Participants With AIP. 2. Annualized Rate of Porphyria Attacks in Participants With AHP. 3. Area Under the Curve (AUC) of the Change From Baseline in Weekly Mean Score of Daily Worst Pain as Measured by the Brief Pain Inventory-Short Form (BPI-SF) Numeric Rating Scale (NRS) in Participants With AIP. 4. Average Change From Baseline in Weekly Mean Score of Daily Worst Pain as Measured by the Brief Pain Inventory-Short Form (BPI-SF) Numeric Rating Scale (NRS) in Participants With AIP. 5. AUC of the Change From Baseline in Weekly Mean Score of Daily Worst Fatigue Score as Measured by the Brief Fatigue Inventory-Short Form (BFI-SF) NRS in Participants With AIP. 6. Average Change From Baseline in Weekly Mean Score of Daily Worst Fatigue Score as Measured by the Brief Fatigue Inventory-Short Form (BFI-SF) NRS in Participants With AIP. 7. AUC of the Change From Baseline in Weekly Mean Score Daily Worst Nausea Score as Measured by NRS in Participants With AIP. 8. Average Change From Baseline in Weekly Mean Score Daily Worst Nausea Score as Measured by NRS in Participants With AIP. 9. Change From Baseline in the Physical Component Summary (PCS) of the 12-Item Short Form Survey (SF-12) in Participants With AIP. **Exploratory Endpoints:** (18) • Evaluate the effects of givosiran, compared to placebo, in patients with AIP and in patients with any AHP over the 6-month DB period on: o Rate of all porphyria attacks (requiring hospitalisation, urgent healthcare visit, IV haemin administration at home, or treated at home without IV haemin) o Analgesic usage (opioid and non-opioid) o Additional HRQoL measures, including missed days of work/school

	○ Patient experience questionnaire and patient's impression of health status change • Assess the treatment effect of givosiran at evaluated doses over the OLE period in patients with AIP and in patients with any AHP who had previously been randomised to placebo treatment • Assess the long-term treatment effect of givosiran in patients with AIP and in patients with any AHP • Characterize the PK of and assess the anti-drug antibodies (ADA) of givosiran in patients with any AHP
Method of analysis	The primary endpoint and most secondary efficacy endpoints were assessed in patients with AIP with an identified mutation to allow for a more homogeneous population for an assessment of efficacy. All analysis were repeated in the full ITT (AHP-population) and showed not differences between the AIP/AHP as expected. The ITT (AHP-population), also served as the basis of the safety analysis. The primary analyses of the annualized attack rate and number of days of haemin use were based on a negative binomial regression model adjusted according to the use of haemin prophylaxis and the historical annualized attack rate. The analyses of longitudinal secondary efficacy end points were based on a mixed model for repeated measures. For the end points capturing daily worst scores for pain, fatigue, and nausea, we calculated the area under the curve of change during the 6-month intervention period on the basis of the change from baseline in weekly mean scores. When the normality assumption was violated, a nonparametric Wilcoxon signed rank test was conducted to reanalyze the data. Secondary end points were analyzed in a prespecified hierarchical order to control for the overall type I error. Further details for statistical analysis of endpoints reported in this dossier and the parameterisation of the endpoints are provided in Appendix D Table 63 and Table 62, respectively.
Subgroup analyses	Pre-specified subgroup analyses of the primary composite endpoint in the ENVISION trial (AAR in AIP) were conducted on the following parameters.: • Age at Screening (< or ≥ median age in the overall population) • Race (White or Non-white) • Gender (Female or Male) • Region group 1: North America (United States and Canada) or Other (outside North America) • Region group 2: Europe or Other (outside Europe) • Baseline body mass index (BMI) (<25 or ≥25) • Prior haemin prophylaxis status (Yes or No) • Historical attack rates prior to randomisation based on the haemin prophylaxis status prior to the study (high or low) screening: • High attack rate was defined as AAR ≥7 for patients on a haemin prophylaxis regimen at the time of screening, and AAR ≥12 for patients not on a haemin prophylaxis regimen at screening • Prior chronic symptoms when not having attacks (Yes or No) • Prior chronic opioid use when not having attacks (Yes or No) The analyses were also repeated for the entire AHP population with no differences between AHP and AIP.
Other relevant information	None

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Appendix C: Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 61: Baseline Characteristics of patients included in ENVISION

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety						
Characteristic	**Patients with Acute Hepatic Porphyria**			**Patients with Acute Intermittent Porphyria**		
	Placebo (N=46)	Givosiran (N=48)	Overall (N=94)	Placebo (N=43)	Givosiran (N=46)	Overall (N=89)
Age — yr	37.4±10.5	40.1±12.1	38.8±11.4	37.3±10.5	40.7±12.0	39.0±11.4
Female sex — no. (%)	41 (89)	43 (90)	84 (89)	39 (91)	41 (89)	80 (90)
Body-mass index†	25.5±6.4	24.3±5.2	24.9±5.8	25.7±6.3	24.3±5.2	24.9±5.8
Race — no. (%)						
White	34 (74)	39 (81)	73 (78)	33 (77)	37 (80)	70 (79)
Black	1 (2)	0	1 (1)	0	0	0
Asian	7 (15)	8 (17)	15 (16)	6 (14)	8 (17)	14 (16)
Other	4 (9)	1 (2)	5 (5)	4 (9)	1 (2)	5 (6)
Acute intermittent porphyria with identified mutation (%)	43 (93)	46 (96)	89 (95)	43 (100)	46 (100)	89 (100)
Nonacute intermittent porphyria§						
All subtypes	3 (7)	2 (4)	5 (5)	N/A	N/A	N/A
Hereditary coproporphyria	0	1 (2)	1 (1)			
Variegate porphyria	1 (2)	1 (2)	2 (2)			
Acute hepatic porphyria without identified mutation	2 (4)	0	2 (2)¶			
No. of years since diagnosis	8.3±8.5	11.1±11.2	9.7±10.0	8.4±8.7	11.5±11.3	10.0±10.2

Previous haemin prophylaxis — no. (%)						
Yes	18 (39)	20 (42)	38 (40)	17 (40)	20 (43)	37 (42)
No	28 (61)	28 (58)	56 (60)	26 (60)	26 (57)	52 (58)
Historical annualized attack rate‖						
High — no. (%)	21 (46)	24 (50)	45 (48)	20 (47)	23 (50)	43 (48)
Low — no. (%)	25 (54)	24 (50)	49 (52)	23 (53)	23 (50)	46 (52)
Median rate (IQR)	7 (4–14)	8 (4–18)	8 (4–16)	8 (4–14)	8 (4–18)	8 (4–16)
Previous chronic symptoms — no. (%)**						
Yes	26 (57)	23 (48)	49 (52)	24 (56)	22 (48)	46 (52)
No	20 (43)	25 (52)	45 (48)	19 (44)	24 (52)	43 (48)
Previous long-term opioid use — no. (%)††						
Yes	13 (28)	14 (29)	27 (29)	12 (28)	14 (30)	26 (29)
No	33 (72)	34 (71)	67 (71)	31 (72)	32 (70)	63 (71)

** Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range, and NA not applicable.*
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was reported by the investigator after discussion with the patient.
§ Porphyria subtypes other than acute intermittent porphyria include hereditary coproporphyria, variegate porphyria, delta-aminolevulinic acid (ALA) dehydratase–deficiency porphyria with an identified mutation, and acute hepatic porphyria without an identified mutation. No patients with ALA dehydratase–deficiency porphyria were enrolled in this trial.
¶ The two patients with acute hepatic porphyria without an identified mutation were considered by the trial investigator to have acute intermittent porphyria on the basis of biochemical analysis.
‖ The historical annualized attack rate was calculated as the number of attacks resulting in a composite of hospitalisation, a visit to a health care facility, or haemin use at home during the 6 months before randomization. For patients who were receiving haemin prophylaxis before the initiation of the trial, the attack rate was considered to be high if the historical annualized attack rate was 7 or more and low if the attack rate was less than 7 (attack rate of ≥12 and <12, respectively, for patients who were not receiving previous haemin prophylaxis). One patient in the placebo group did not meet the inclusion criterion of a history of at least 2 composite porphyria attacks, since the patient had 2 attacks that were treated at home without intravenous haemin, which was identified as a protocol deviation.
*** Symptoms were considered to be chronic if patients had symptoms of porphyria daily or on most days when they were not having an attack, as reported by the investigator. Information was reported on a screening questionnaire administered by trial staff members.*
†† Opioid use was defined as long-term if patients reported taking an opioid for porphyria daily or most days when they were not having an attack, as reported on the screening questionnaire

Comparability of patients across studies

Not applicable as only one study is included.

Comparability of the study populations with Danish patients eligible for treatment

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

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

Thus, the ENVISION study captured the heterogeneity of the AHP patient population encountered in clinical practice who would be eligible for givosiran, namely adults and young people aged 12 years or older with recurrent severe AHP attacks. Given the Danish population consists of a single digit number of patients eligible for givosiran treatment, the study population is generalisable for the effect of givosiran in the Danish population. Moreover, the Porphyria center in Odense, Denmark, was one of the 36 clinical trial sites in ENVISION.

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Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

In Table 62, all outcomes presented in this dossier is presented in terms of outcome measure, definition, validity and clinical relevance.

Table 62: Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Annualized rate of Porphyria Attacks	Porphyria attacks were defined as meeting all of the following criteria: an acute episode of neurovisceral pain in the abdomen, back, chest, extremities and/or limbs No other medically determined cause Required treatment with intravenous (IV) dextrose or haemin, carbohydrates, or analgesics, or other medications such as antiemetics at a dose or frequency beyond the participant's usual daily porphyria management. The annualized rate of porphyria attacks is a composite endpoint which included 1) porphyria attacks requiring hospitalisation, 2) urgent healthcare visit, or 3) IV haemin administration at home. For the purposes of this study, the following definitions were used to identify each non-overlapping component of porphyria attack events: Porphyria attacks requiring hospitalisation: porphyria attacks that prompted a hospitalisation, defined as an admission to an inpatient unit or a visit to an emergency department that results in an at least 24-hour stay. Porphyria attacks requiring urgent healthcare visit: porphyria attacks that prompted urgent healthcare visits, defined as an urgent, unscheduled office/practice, infusion center, or an emergency department visit that did not meet the criteria for a hospitalisation. Porphyria attacks requiring IV haemin at home: porphyria attacks at home requiring IV haemin. "Home" was defined as any location that did not meet the criteria for a hospitalisation or urgent healthcare visit.	The definition of the composite endpoint employed in ENVISION was chosen based on an analysis of the observational natural history study EXPLORE (7) in which the 3-component primary endpoint captured the vast majority of severe attacks in a patient population similar to ENVISON.	Acute porphyria attacks are clinically meaningful and potentially life-threatening events that are the major contributors to disease burden in patients with AHP. The porphyria attack composite endpoint comprises clinical events requiring major specific medical intervention and can be objectively measured. The decision to use this 3-component measure as the primary endpoint was also based on results from EXPLORE (7), an observational natural history study in a patient population similar to ENVISON, which demonstrated that the majority of all attacks met the composite endpoint definition. There is no well-defined MCID for acute porphyria these attacks, but as the attacks are debilitating any statistically significant reduction would be considered beneficial and clinical relevant.

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Outcome measure	Definition	Validity	Clinical relevance
Change from baseline/AUC in Urinary PBG / Urinary ALA	The baseline creatinine normalized urinary ALA/PBG values were defined as the median of measurements taken on or prior to Day 1. Any samples taken during an attack or within 3 days after receiving haemin on or prior to Day 1 were excluded from the baseline calculation. If all available samples on or prior to Day 1 met the exclusion criteria, the last non-missing value on or prior to Day 1 was used as the baseline value for the patient	Objectively laboratory measurement assessed by standardised assay.	The accumulation of ALA and possibly PBG causes injury to the nervous system and other organs, resulting in potentially life-threatening acute attacks and chronic disease manifestations (5,112) Direct association of lowering and reduction in annualized attack rate demonstrated in ENVISION (17).
Annualized Rate of Haemin Administration	Annualized rate of haemin doses was evaluated as annualized days of haemin use.	Objectively measured clinical event registered by prescriber	Considered beneficial, since haemin is potentially associated with both acute side effects (e.g., headache, fever, and phlebitis) and chronic side effects (e.g., iron overload, venous obliteration, and complications with indwelling central venous catheters) (68,69)
Area Under the Curve (AUC) of the Change From Baseline in Weekly Mean Score of Daily Worst Pain as Measured by the Brief Pain Inventory-Short Form (BPI-SF) Numeric Rating Scale (NRS)	Participants rated worst daily pain score in an eDiary using the 11-point BPI-SF NRS, in which 0=no pain and 10=worst pain. Daily eDiary entries were averaged into a weekly (i.e. 7 day) score. The change from baseline in weekly mean scores is defined as the post baseline weekly mean score minus the baseline score. Lower scores indicate an improvement. The 6-month AUC was calculated based on change from baseline in weekly mean scores.	Extensively validated instrument across numerous indications. Cronbach alpha reliability ranges from 0.77 to 0.91 (113)	The Brief Pain Inventory (BPI) rapidly assesses the severity of pain and its impact on functioning and it is widely used in both research and clinical settings. There is no MCID defined for the AUC for the BPI-SF. Pain is one of the most common symptoms affecting patients during and between attacks as demonstrated from the EXPLORE natural history study (7), reducing this symptom could lead to improved disease control and potentially reduce the need for chronic opioids in between attacks.
Average Change From Baseline in Weekly Mean Score of Daily Worst Pain as Measured by the Brief Pain Inventory-Short Form (BPI-SF) Numeric Rating Scale (NRS)	Participants rated worst daily pain score in an eDiary using the 11-point BPI-SF NRS, in which 0=no pain and 10=worst pain. Daily eDiary entries were averaged into a weekly (i.e. 7 day) score. The change from baseline in weekly mean scores is defined as the postbaseline weekly mean score minus the baseline score. Lower scores indicate an improvement.	Extensively validated instrument across numerous indications. Cronbach alpha reliability ranges from 0.77 to 0.91 (113)	The Brief Pain Inventory (BPI) rapidly assesses the severity of pain and its impact on functioning and it is widely used in both research and clinical settings. The MCID has been defined as 2-points in a range of studies (114). Pain is one of the most common symptoms affecting patients during and between attacks as demonstrated from the EXPLORE natural history study (7), reducing this symptom could lead to

Outcome measure	Definition	Validity	Clinical relevance
			improved disease control and potentially reduce the need for chronic opioids in between attacks
AUC of the Change From Baseline in Weekly Mean Score of Daily Worst Fatigue Score as Measured by the Brief Fatigue Inventory-Short Form (BFI-SF) NRS	Participants rated daily worst fatigue score in an eDiary using the 11-point BFI-SF NRS, in which 0=no fatigue and 10=worst fatigue. Daily eDiary entries were averaged into a weekly (i.e. 7 day) score. The change from baseline in weekly mean scores is defined as the post baseline weekly mean score minus the baseline score. Lower scores indicate an improvement. The 6-month AUC was calculated based on change from baseline in weekly mean scores.	Extensively validated instrument across numerous indications. Cronbach alpha reliability ranges from 0.82 to 0.97	The Brief Fatigue Inventory (BFI) is used to rapidly assess the severity and impact of fatigue. The six interference items correlate with standard quality-of-life measures. There is no MCID defined for the AUC for the BFI-SF. Fatigue is one of the most common symptoms affecting patients during and between attacks as demonstrated from the EXPLORE natural history study (7), reducing this symptom could lead to improved disease control.
Average Change From Baseline in Weekly Mean Score of Daily Worst Fatigue Score as Measured by the Brief Fatigue Inventory-Short Form (BFI-SF) NRS	Participants rated daily worst fatigue score in an eDiary using the 11-point BFI-SF NRS, in which 0=no fatigue and 10=worst fatigue. Daily eDiary entries were averaged into a weekly (i.e. 7 day) score. The change from baseline in weekly mean scores is defined as the postbaseline weekly mean score minus the baseline score. Lower scores indicate an improvement.	Extensively validated instrument across numerous indications. Cronbach alpha reliability ranges from 0.82 to 0.97	The Brief Fatigue Inventory (BFI) is used to rapidly assess the severity and impact of fatigue. The six interference items correlate with standard quality-of-life measures. There is no MCID defined for the for the BFI-SF. Fatigue is one of the most common symptoms affecting patients during and between attacks as demonstrated from the EXPLORE natural history study (7), reducing this symptom could lead to improved disease control.
AUC of the Change From Baseline in Weekly Mean Score Daily Worst Nausea Score as Measured by NRS	Participants rated worst daily nausea score in an eDiary using an 11-point NRS, in which 0=no nausea and 10=worst nausea. Daily eDiary entries were averaged into a weekly (i.e. 7 day) score. The change from baseline in weekly mean scores is defined as the postbaseline weekly mean score minus the baseline score. Lower scores indicate an improvement. The 6-month AUC was calculated based on change from baseline in weekly mean scores.	Strong correlation of the visual analog scale (VAS) and numeric rating scale (NRS) for nausea severity measurement has been demonstrated to detect changes in described symptom change and rated satisfaction (115).	The Daily Worst Nausea Score as Measured by NRS is used to rapidly assess the severity and impact of nausea. Nausea is one of the most common symptoms affecting patients during and between attacks as demonstrated from the EXPLORE natural history study (7), reducing this symptom could lead to improved disease control. No well-defined MCID,

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Outcome measure	Definition	Validity	Clinical relevance
Average Change From Baseline in Weekly Mean Score Daily Worst Nausea Score as Measured by NRS	Participants rated worst daily nausea score in an eDiary using an 11-point NRS, in which 0=no nausea and 10=worst nausea. Daily eDiary entries were averaged into a weekly (i.e. 7 day) score. The change from baseline in weekly mean scores is defined as the postbaseline weekly mean score minus the baseline score. Lower scores indicate an improvement.	Strong correlation of the visual analog scale (VAS) and numeric rating scale (NRS) for nausea severity measurement has been demonstrated to detect changes in described symptom change and rated satisfaction (115).	The Daily Worst Nausea Score as Measured by NRS is used to rapidly assess the severity and impact of nausea. Nausea is one of the most common symptoms affecting patients during and between attacks as demonstrated from the EXPLORE natural history study (7), reducing this symptom could lead to improved disease control. No well-defined MCID, but a change of 1-2 points on NRS was associated with a described symptom change and rated satisfaction (115).
Change From Baseline in the Physical Component Summary (PCS) of the 12-Item Short Form Survey (SF-12)	The SF-12 is a survey designed for use in patients with multiple chronic conditions. This 12-item scale can be used to assess the physical and mental health of respondents. 10 of the 12 questions are answered on a 5 point likert scale and 2 are answered on a 3 point likert scale. The questions are then scored and weighted into 2 subscales, physical health and mental health. Respondents can have a score that ranges from 0-100 with 100 being the best score and indicating high physical or mental health. A 3 point change in SF-12 score reflects a meaningful difference. A higher score indicates improvement.	Extensively studied and used as a valid measure of health-related quality of life in a variety of population groups (116)	The SF-12 is a widely used 12-item health survey that generates an 8-scale profile of functional health and well-being (8 domains) as well as a physical and mental health summary measurement (Physical Component Summary [PCS] and Mental Component Summary [MCS], respectively). The MCID is 2 to 5 points representing a clinically meaningful difference for the PCS, according to published data for other chronic diseases whereas the MCID for MCS has previously been reported as 5-10 point (70,71).
Patient Global Impression of Change (PGIC)	PGIC at Month 6, assesses a patient's perceived overall health status change since the beginning of the study using a single-item scale. The PGIC is 1 question answered according to a 7-point global rating of change scale (ranging from very much improved to very much worse) for the assessment of a patient's perceived overall health status change since the beginning of the study	PGIC asks the patient to rate change in their overall status, which relates to multiple domains of health. Higher PGIC scores (improvements) have been found to be associated with improvements in symptoms such as e.g. pain and HrQOL (117)	Assess a patient's perceived overall health status change since the beginning of the study using a single-item scale. PGIC is therefore a patient-reported measure of overall health status. Included in the PPEQ questionnaire are five items that assess change in the patient's ability to perform usual daily activities, two items that assess change in their perceptions about AHP treatment, and one item that assesses the extent to which the study drug helped patients to return back to a more normal life.

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Outcome measure	Definition	Validity	Clinical relevance
Porphyria Patient Experience Questionnaire (PPEQ)	PPEQ at Month 6, is a set of questions to assess treatment experience and impacts to the patient's life that are not collected by the other HRQoL assessments. The PPEQ comprises 8 questions to assess treatment experience, activities of daily living, and functional status on a 5-point global rating of change scale. Included in the PPEQ questionnaire are five items that assess change in the patient's ability to perform usual daily activities, two items that assess change in their perceptions about AHP treatment, and one item that assesses the extent to which the study drug helped patients to return back to a more normal life. In total it contains 8 items. Seven of the eight items have a five-point change rating scale (much better, minimally better, no change, minimally worse, and much worse). The eighth item inquires about how often subjects felt the study drug was helping them to return back to a more normal life (always, most of the time, sometimes, rarely, and never).	The validity of PPEQ has not been established.	The PPEQ is a *de novo* PRO developed for Alnylam Assess treatment experience and impacts to the patient's life that are not collected by the other HRQoL assessments. The outcomes measure consist of eight measures of which five assess change in the patient's ability to perform usual daily activities, two items that assess change in their perceptions about AHP treatment, and one item that assesses the extent to which the study drug helped patients to return back to a more normal life

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Results per study

Table 63: ENVISION Study Results for the AHP-population

Exploratory endpoints where no statistical testing is applied, are not given in table 62, but provided in section 8.1.2.1.

Abbreviations: NA = not available, NR = not relevant. AAR = annualized attack rate

Results for AHP patients – 6 month data-cut - ENVISION NCT03338816											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Mean AAR	Givosiran	48	3.35 (2.37, 4.74)	8.91	NA	NA	0.27	0.17-0.43	<0.001	Mixed model repeated measures (MMRM) - negative binomial regression model adjusted according to the use of haemin prophylaxis and the historical annualized attack rate. The relative risk is expressed as a risk-ratio. e.g. 0.27 translates to a 73 % reduction in AAR.	Primary publication Balwani et al. 2020 (17)
	Placebo	46	12.26 (9.22, 16.29)								
[redacted]										[redacted]	Data-on file, clinical study report for ENVISON, data-cut 10 January 2020 (18)
[redacted]										[redacted]	Data-on file, clinical study report for ENVISON, data-cut 10 January 2020 (18)

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Results for AHP patients – 6 month data-cut - ENVISION NCT03338816

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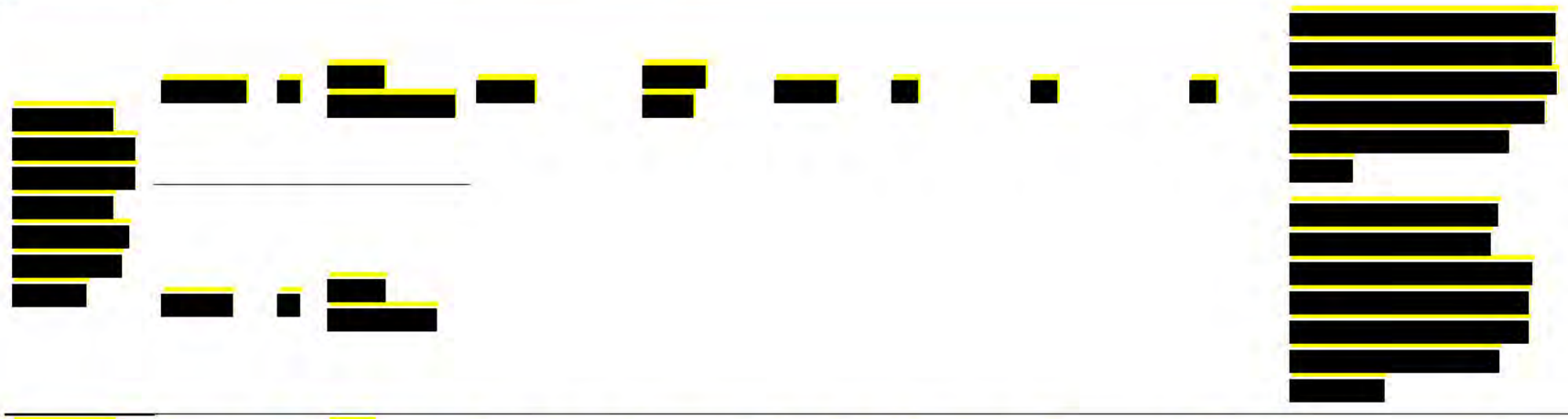
Data-on file, clinical study report for ENVISON, data-cut 10 January 2020 (18)

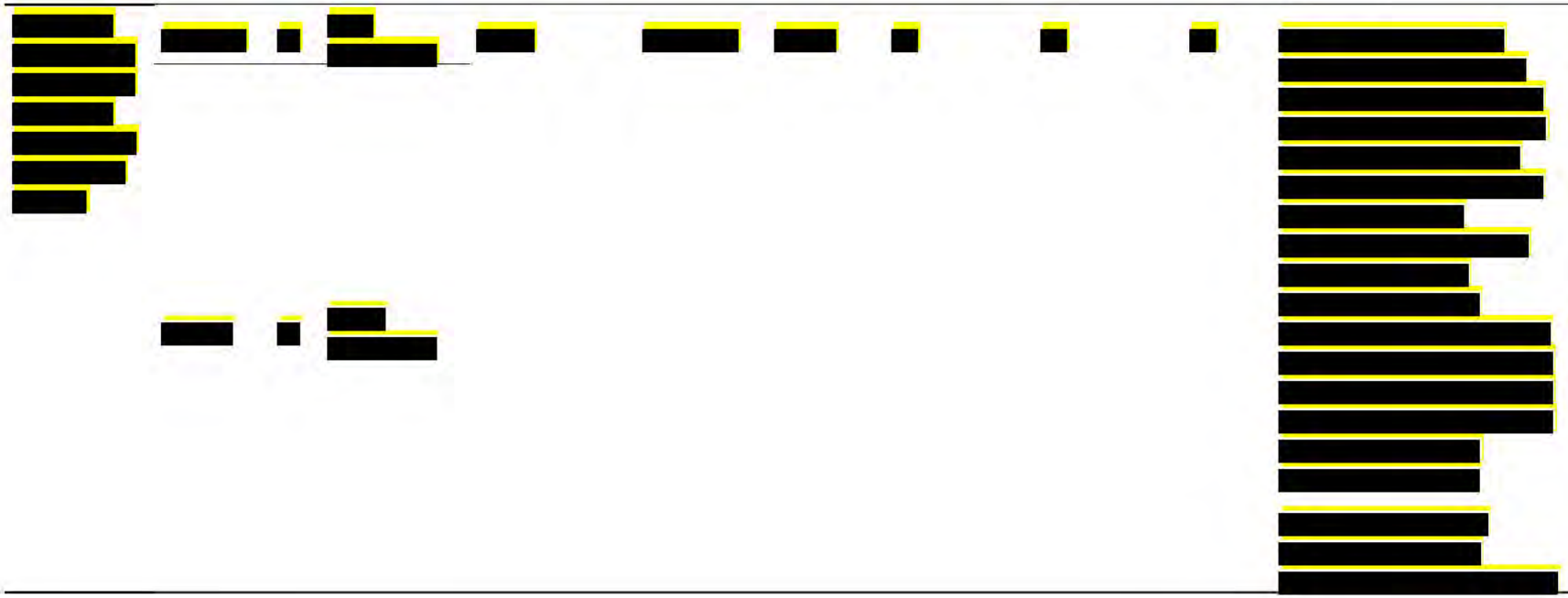
Data-on file, clinical study report for ENVISON, data-cut 10 January 2020 (18)

Data-on file, clinical study report for ENVISON, data-cut 10 January 2020 (18)

Results for AHP patients – 6 month data-cut - ENVISION NCT03338816



Data-on file, clinical study report for ENVISON, data-cut 10 January 2020 (18)



Data-on file, clinical study report for ENVISON, data-cut 10 January 2020 (18)

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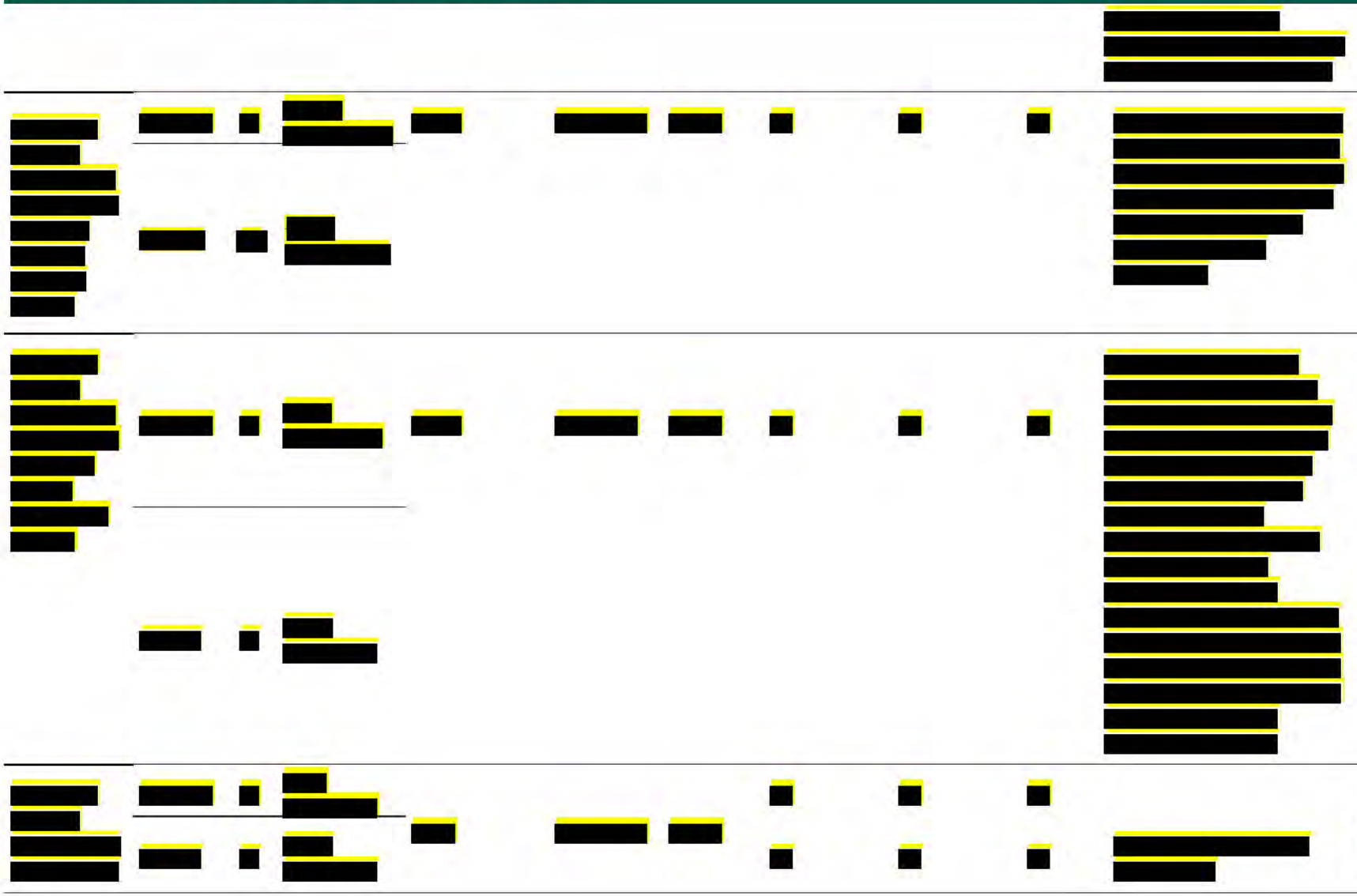
Results for AHP patients – 6 month data-cut - ENVISION NCT03338816



Data-on file, clinical study report for ENVISON, data-cut 10 January 2020 (18)

Data-on file, clinical study report for ENVISON, data-cut 10 January 2020 (18)

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Results for AHP patients – 6 month data-cut - ENVISION NCT03338816

Data-on file, clinical study report for ENVISON, data-cut 10 January 2020 (18)

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Results for AHP patients – 6 month data-cut - ENVISION NCT03338816

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Table 64: ENVISION Study Results for the AIP population

Exploratory endpoints where no statistical testing is applied are not given in table 63, but provided in section 8.1.2.1.

Abbreviations: NA = not available, NR = not relevant. AAR = annualized attack rate.

Results for AIP patients – 6 month DB data-cut - ENVISION NCT03338816											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Mean AAR at 6 months follow up	Givosiran	46	3.35 (2.37, 4.74)	8.91	NA	NA	0.27	0.17-0.43	<0.001	Mixed model repeated measures (MMRM) - negative binomial regression model adjusted according to the use of haemin prophylaxis and the historical annualized attack rate. The relative difference is expressed as a rate ratio (95% CI) for the comparison between givosiran and placebo, e.g. 0.27 translates to a 73 % reduction in AAR.	Primary publication Balwani et al. 2020 (17)
	Placebo	43	12.26 (9.22, 16.29)								
ALA Least-squares mean (95%CI) at 6 months	Givosiran	46	3.92 (-0.6, 8.4)	-18.3	(-24.9, -11.8)	**<0.001**	NR	NR	NR	Same method as for Daily worst score for fatigue Least-squares mean	Primary publication Balwani et al. 2020 (17)
	Placebo	43	22.3 (17.5, 27.0)								
ALA Median change from	Givosiran	46	1.3 (0.9 to 4.6)	-12.8	(-16.1, -7.8)	<0.001	NR	NR	NR	Same method as for Daily worst score for pain. ANCOVA	

Results for AIP patients – 6 month DB data-cut - ENVISION NCT03338816										
baseline (IQR) at 6 mo	Placebo	43	16.2 (8.0, 23.0)						with Wilcoxon signed-rank test.	Primary publication Balwani et al. 2020 (17)
PBG Least-squares mean (95%CI) at 6 months	Givosiran	46	12.9 (3.7, 22.1)	–36.2	(-49.7, -22.7)	<0.001	NR	NR	NR	Same method as for Daily worst score for fatigue Least-squares mean	Primary publication Balwani et al. 2020 (17)
	Placebo	43	49.1 (39.3, 59.0)								
PBG Median change from baseline (IQR) at 6 mo	Givosiran	46	4.4 (1.6, 15.3)	-27.5	(-34.0, -21.0)	<0.001	NR	NR	NR	Same method as for Daily worst score for pain. ANCOVA with Wilcoxon signed-rank test.	Primary publication Balwani et al. 2020 (17)
	Placebo	43	35.1 (25.6, 50.0								
Mean annualized no. of days of haemin use	Givosiran	46	6.77 (4.20, 10.92)	22.94	NA	NA	0.23	0.11-0.45	<0.001	Same as above for AAR.	Primary publication Balwani et al. 2020 (17)
	Placebo	43	29.71 (18.41, 47.94)								
Median annualized no. of days of haemin use	Givosiran	46	0.00	27.61	NR	NR	NR	NR	NR	No statistical testing	Primary publication Balwani et al. 2020 (17)
	Placebo	43	27.61								
Daily worst score for pain median of change in AUC from baseline (IQR)	Givosiran	46	-11,5 (-29.2, 3.0)	-10.1	–22.8, 0.9 (IQR)	0.046	NR	NR	NR	Calculated the area under the curve of change during the 6-month intervention period on the basis of the change from baseline in weekly mean scores. Because of a significant deviation from normal distribution, ANCOVA were not valid. A nonparametric	Data-on file, clinical study report for ENVISON, data-cut 10 January 2020 (18)
	Placebo	43	-5.3 (-23.0, 11.1)								

Results for AIP patients – 6 month DB data-cut - ENVISION NCT03338816										
									stratified Wilcoxon signed-rank test was therefore conducted	
Daily worst score for pain median average change from baseline (IQR)	Givosiran	46	–0.570 (-0.97, -0.18)	–0.4	–1.0, 0.1	0.049	NR	NR	NR	The LS Means, treatment difference in LS Mean, their corresponding SEMs and 95% CIs and p-value for comparing Givosiran 2.5 mg/kg versus Placebo are derived using the ANCOVA model with treatment and stratification factors (prior haemin prophylaxis status and historical attack rates) as fixed effects, and the corresponding weekly mean score at baseline as a covariate. A difference < 0 represents a favorable outcome for Givosiran Because of a significant deviation from normal distribution, ANCOVA were not valid. A nonparametric stratified Wilcoxon signed-rank test was therefore conducted	Data-on file, clinical study report for ENVISON, data-cut 10 January 2020 (18)
	Placebo	43	-0.010 (-0.42, 0.40)							
Daily worst score for fatigue Least-squares mean (95% CI of change in	Givosiran	46	-11.148 (-20.10, -2.20)	-6.940	-19.84, 5.96	0.2876	NR	NR	NR	Calculated the area under the curve of change during the 6-month intervention period on the basis of the change from baseline in weekly mean scores. ANCOVA for significance.	Primary publication Balwani et al. 2020 (17)
	Placebo	43	-4.208 (-13.53. 5.12)							

Results for AIP patients – 6 month DB data-cut - ENVISION NCT03338816										
AUC from baseline										
Daily worst score for fatigue Least-squares mean (95% CI) of average change from baseline	Givosiran	46	-0.502 (-0.90, -0.10)	-0.321	-0.90, 0.25	0.2698	NR	NR	NR	The LS Means, treatment difference in LS Mean, their corresponding SEMs and 95% CI and p-value for comparing Givosiran 2.5 mg/kg versus Placebo are derived using ANCOVA model with treatment and stratification factors (prior haemin prophylaxis status and historical attack rates) as fixed effects, and the corresponding weekly mean score at baseline as a covariate. A difference < 0 represents a favorable outcome for Givosiran	Primary publication Balwani et al. 2020 (17)
	Placebo	43	-0.182 (-0.60, 0.23)							
Daily worst score for nausea Least-squares mean (95% CI) of change in AUC from baseline	Givosiran	46	1.481 (-5.10, 8.06)	5.492	-4.00, 14.98	0.3266	NR	NR	NR	Same method as for daily worst fatigue	Primary publication Balwani et al. 2020 (17)
	Placebo	43	-4.011 (-10.88, 2.86)							
Daily worst score for nausea Least-squares mean of average	Givosiran	46	0.067 (-0.23, 0.36)	0.248	-0.17, 0.67	0.2459	NR	NR	NR	Same method as for daily worst fatigue	Primary publication Balwani et al. 2020 (17)
	Placebo	43	-0.181 (-0.49, 0.12)							

Results for AIP patients – 6 month DB data-cut - ENVISION NCT03338816											
change from baseline											
SF-12 Physical component Least-squares mean change from baseline	Givosiran	46	5.369 (3.05, 7.69)	3.939	0.59, 7.29	0.0216	NR	NR	NR	The LS Means, treatment difference in LS Mean, their corresponding SEMs and 95% CIs and p-value for comparing Givosiran 2.5 mg/kg versus Placebo are derived using the MMRM model with the corresponding value at baseline as a continuous fixed covariate, stratification factors (prior haemin prophylaxis status and historical attack rates), visit, treatment, and treatment-by-visit interaction as fixed effects, and patient as a random effect	Primary publication Balwani et al. 2020 (17)
	Placebo	43	1.431 (-1.00, 3.86)								
SF-12 Mental Component mean change from baseline	Givosiran	46	3.655 (0.74, 6.57)	2.370	NR	NR	NR	NR	NR	Add	Data-on file, clinical study report for ENVISON, data-cut 10 January 2020 (18)
	Placebo	43	1.299 (-1.25, 3.85)								

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Appendix E: Safety data for intervention and comparator

Table 65: Key Safety Outcomes in ENVSION in the AHP-population (ITT)

Outcome	Study arm	N	Result, n/N, %	Abs. Difference	95% CI	*P* value	Relative Difference	95% CI	*P* value	Description of methods used for estimation	References
Proportion of patients who experience adverse events	Givosiran	48	43/48 - 89.6%	9.15%	-5.2%;23.5%	NT	1.11	0.94-1.32	0.221	The absolute difference is calculated using the Chi-squared test. The relative risk, its standard error and the 95% confidence interval are calculated according to standard methods (118).	Primary publication Balwani et al. 2020 (17)
	Placebo	46	37/46 - 80.4%								
Proportion of patients who experience serious adverse events	Givosiran	48	10/48 – 20.8%	12.1 %	-1.9-26.2	NT	2.40	0.81 – 7.10	0.115	Same as above	Primary publication Balwani et al. 2020 (17)
	Placebo	46	4/46 – 8.7%								
Proportion of patients who discontinue treatment due to adverse events	Givosiran	48	1/48 - 2.1 %	2.1%	-2.0%;6.1%	NT	2.88	0.12 – 68.89	0.525	Same as above For calculations of relative risk and statistical testing 0.5 were added to each cell in the 2x2, as 0 events occurred in the comparator arm	Primary publication Balwani et al. 2020 (17)
	Placebo	46	0/46 – 0 %								
Proportion of patients who	Givosiran	48	22/48 - 45.8 %	19.75	0.78;38.71%	NT	1.76	0.99 – 3.12	0.545	Same as above	Primary publication

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experience adverse reactions	Placebo	46	12/46 – 26.1 %	Balwani et al. 2020 (17)

NT, not tested.

Appendix F Comparative analysis of efficacy and safety

Not relevant for the application, as there is only one direct head-to-head study (ENVISION), and results are presented in Appendix E.

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Appendix G – Extrapolation

Please find description in the main text.

Appendix H – Literature search for HRQoL data

The description of HRQoL target literature search methods and results has been reported directly in Section 9.4.2 of this document.

Appendix I Mapping of HRQoL data

Not applicable

Appendix J Probabilistic sensitivity analyses

	Expected value	Standard error	Reason / Rationale / Source	Probability distribution	Refers to cell (in the Excel model)
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Expected value	Standard error	Reason / Rationale / Source	Probability distribution	Refers to cell (in the Excel model)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	Expected value	Standard error	Reason / Rationale / Source	Probability distribution	Refers to cell (in the Excel model)
[redacted]					

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Appendices K, L ... etc. Company-specific appendices

None

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Response document for DMC - second round of questions

Concerning request for additional supporting information for the assessment of of Givlaari™ (givosiran) for patients with acute hepatic porphyria

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1. DMC Request

Alnylam Pharma on the 30th of August received a request from the DMC for additional information to support the assessment of Givlaari™ (givosiran) for patients with acute hepatic porphyria. The DMC in an additional email sent on the 30th of August confirmed, that Alnylam should provide median values for both the AHP and AIP population whenever possible.

Alnylam acknowledges the requests made by the DMC, and has provided detailed answers for all points raised by the DMC in the section below.

2. Requests and Responses

Can a clinical effect be expected after pausing or ending treatment with givosiran? And if so, how long can the effect be expected to last? If available, please provide data on this matter.

Response: There is no published data to date that supports the continued treatment effect of givosiran after pausing or ending treatment. In Alnylam's application for givosiran and included cost-effectiveness model we assume patients who discontinue givosiran, as predicted by our time-on-treatment function, transition between health-states based on the best supportive care arm transition probabilities. This assumption is consistent with the fact that there are no data available to inform clinical effect on what happens after patients discontinue givosiran. Given current evidence, we believe this is the most evidence-based approach to the modelling and the most conservative, since we apply the BSC probabilities (worsening over time) at every cycle, whereas in the BSC arm they are applied only in cycle 1 and then the cohort is assumed to remain stable.

[redacted]

Please provide data on the percentual change in AAR from baseline

Response: There are two main ways of presenting the percentual changes in AAR, which are both already given in the application. One is the between-group percentual difference in attack-rate between the givosiran and placebo group, and the other is within group changes over time from baseline.

The between-group percentual difference is provided in the dossier by the rate-ratio in AAR between the givosiran and placebo group, which is directly transferable to a relative percentual difference in AAR between the groups. The difference in AAR between the treatment groups is given as a rate ratio, where a rate ratio of 1 would refer to the same attack rate being observed in the treatment arms. A rate ratio of 0.27 in AAR as noted for the AHP-group translates to the AHP group treated with givosiran experience 0.27 times as many attacks as the comparator group meaning a 73 % lower AAR. The AAR is provided in Table 9.

For the AHP group the rate ratio of the AAR between the givosiran and placebo group is: RR: 0.27 (0.17, 0.43), translating to a 73 % reduction (95 % CI: 57%-83%).

For the AIP group the rate ratio of the AAR between the givosiran and placebo group is: RR: 0.26 (0.16, 0.41), translating to a 73 % reduction (95 % CI: 59%-84%).

The within group changes over time from baseline analyzed as a relative % -change in AAR are also already given in the application. This information can be found on p. 40, table 11, the %-change in AAR from baseline to 6 months and

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18 months OLE-phase data-cuts are given for both the givo/givo group as well as for the placebo/givo group (within group changes from baseline). The table is also provided below.

Table 1: Comparison of AAR at DB- and OLE-phase in the ENVISION trial compared to baseline AAR – AHP population

Parameter	Placebo/Givosiran, n = 46	Givosiran/Givosiran (n = 48
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

AHP=acute hepatic porphyria; DB=double-blind; OLE: open-label extension

For the outcomes daily worst score for fatigue, daily worst score for nausea, change from baseline in physical component score and change from baseline in mental component score, mean values are currently provided. Please also provide the median values.

Response:

Median values for the outcomes daily worst score for fatigue, daily worst score for nausea, change from baseline in physical component score and change from baseline in mental component score are provided below (Table 2). Where available, Alnylam has reported the median values for the outcomes requested both for the AHP and AIP population. As for the other outcomes presented in the main dossier, there are no differences between the AIP and AHP group.

For full transparency, although median values are presented here, hypothesis testing was not conducted to evaluate whether these values were statistically different between groups – which is why p-values were not presented. Hypothesis testing was conducted for all primary and secondary efficacy analyses from ENVISION using pre-specified parametric analysis, which calculated mean values. As described in the *New England Journal of Medicine* publication of our Phase 3 trial (Balwani et al.), analyses of longitudinal secondary efficacy end points were based on a mixed model for repeated measures. The end points capturing daily worst scores for pain, fatigue, and nausea, were calculated using the area under the curve of change during the 6-month intervention period on the basis of the change from baseline in weekly mean scores. Only when the normality assumption was violated, a nonparametric Wilcoxon signed-rank test was conducted to reanalyze the data. Since this assumption was not violated for the outcome measures reported here, these analyses were not conducted. Secondary end points were analyzed in a prespecified hierarchical order to control for the overall type I error.

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Table 2: Key secondary 6-month double-blinded phase – ENVISION trial – DMC requested outcomes reported as medians

6-month follow-up	AHP			AIP		
	Placebo (n=46)	Givosiran (n=48)	Difference*, p-value*	Placebo (n=43)	Givosiran (n=46)	Difference*, p-value*
Secondary endpoints						
Daily worst score for nausea*						
Baseline values	1.500	1.000	[redacted]	1.571	1.000	[redacted]
Median of change in AUC from baseline	2.055	4.145	[redacted]	1.500	4.145	[redacted]
Median of average change from baseline	0.088	0.184	[redacted]	0.065	0.184	[redacted]
Daily worst score for fatigue*						
Baseline values	4.500	4.143	[redacted]	4.571	4.071	[redacted]
Median of change in AUC from baseline	1.573	-6.157	[redacted]	0.948	-6.157	[redacted]
Median of average change from baseline	0.090	-0.282	[redacted]	0.078	-0.282	[redacted]
SF-12*						
PCS Median at baseline	36.360	40.300	[redacted]	35.985	40.300	[redacted]
PCS median at 6 months	40.530	45.720	[redacted]	40.670	46.380	[redacted]
PCS median change at 6 months	1.430	4.200	[redacted]	1.455	4.200	[redacted]
MCS Median at baseline	40.780	39.020	[redacted]	NA	NA	[redacted]
MCS median at 6 months	41.950	43.220	[redacted]	NA	NA	[redacted]
Median change from baseline at 6 months	1.140	2.610	[redacted]	NA	NA	[redacted]

Abbreviations: AUC: area under curve; MCS: SF-12 Mental Component Summary Score; NA: not available; NT: not tested; PCS: SF-12 Physical Component Summary score; PGIC: Patient Global Impression of Change Questionnaire; PPEQ: Porphyria Patient Experience Questionnaire.
Note: Scores for pain, fatigue, and nausea were measured on a numerical rating scale ranging from 0 to 10, with higher scores indicating more severe symptoms. Scores on the Physical Component Summary of the 12-Item Short-Form Health Survey, version 2 (SF-12), range from 0 (worst functioning) to 100 (best functioning), with published literature in other chronic diseases suggesting that a change of 2 to 5 points represents a clinically meaningful difference.
Sources: data on file from Alnylam Pharmaceuticals. CLINICAL STUDY REPORT 2 INTERIM ANALYSIS FOR ALN-AS1-003 (GIVOSIRAN) DATED - Data on file. 2020;1(June):1–181.

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Response document for DMC

Concerning request for additional supporting information for the assessment of of Givlaari™ (givosiran) for patients with acute hepatic porphyria

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1. DMC Request

Alnylam Pharmaceuticals on the 7th of September received a request from the DMC for additional information for the health economic section to support the application of Givlaari™ (givosiran) for patients with acute hepatic porphyria (AHP).

Alnylam acknowledges the requests made by the DMC, and has provided detailed answers in the section below for all points raised by the DMC.

2. Requests and Responses

Issues regarding the health economic model**:**

Please clarify:

- **You assume that patients will be hospitalized for an average of 7.3 days when experiencing an attack. It seems like a long time to be hospitalized. Please describe a typical hospitalization and explain how much of the time the patient will be treated with hemin.**

Response*:* The costing of a hospitalization when a patient experience an attack has been based on the DRG tariff, "07MA10: Metabolisk leversygdom, Diagnosis: DE802C: Porphyria hepatica". Using this DRG tariff, we assume that patients are maximally hospitalized for 6 days, as the upper limit of days admitted for this DRG code is 6 days. Furthermore, during the KOL consultation, the physician confirmed that the average hospitalization would be 5-6 days. We therefore believe this DRG tariff to be representative of the cost of hospitalization.

As hemin is administered to the patients during the hospitalization, we apply the cost associated with 4 days of hemin treatment to the hospitalization cost, as treatment duration described in the Danish product resume of Normosang (1). We take this to be a conservative assumption, since the maximum amount of hemin used during an attack should, in principle, be as long as the duration of the attack episode (i.e., as much as 6 days) – but the maximum amount of hemin used in the model is limited, per the Danish product resume (i.e., no more than 4 days).

The mean of 7.3 days from the EXPLORE study was therefore not used to define the duration of hospitalization within the health economic model, thus neither used for the cost estimation of the hospitalization of an AHP attack. However, as the disutility of an attack was defined using the EXPLORE study, we did apply the mean duration of an attack of 7.3 days to which an utility decrement is calculated and applied to patients, who experience an attack.

During the KOL consultation, the physician noted that an average attack duration of 7.3 days (in line with EXPLORE), would not be unusual based on his experience. We also note that there may be a minor discrepancy in the duration of the attack disutility (7.3 days) and the duration of the hospitalization stay (5 – 6 days) because there may be minor differences in how long it takes the patient to resolve from the symptoms of the attack; this may not necessarily fully happen during the duration of the hospital stay.

During the same KOL consultation, the physician described a typical hospitalization as following: "*All patients that come to the hospital for an attack need to go through ER first (at least in Odense). Acute attacks are confirmed in ER, then a treatment plan is made (including COVID testing). Heme treatment will only be administered when patients are hospitalized (not in ER) and carefully monitored.*

ER department high turnover, short stay department. No longer stays so therefore no option to administer heme. Patients do not have the option to come back the next day for another heme infusion since the travel distance to the hospital is often quite far (+3 hours)".

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- **You use an HR of 1.3 against the general population to estimate the mortality of AHP patients. This is based on data collected between 1992 and 2017. In general, liver cancer is one of the leading causes of death among these patients but in recent years there has been much more control of patients, so patients have a better survival prognosis. Based on this, we believe that data from as far back as from 1992 may overestimate the mortality of these patients. Please explain why you find this study relevant to use or find a more up-to-date estimate of mortality for AHP patients.**

Response: Baravelli et al., 2020 (2) provides the most recent estimate of mortality for AHP patients, and most relevant source for Denmark, as the study has been conducted in Norway.

We note that liver cancer is one of the leading courses of death among AHP patients. However, during the period of data collection in Baravelli et al., 2020, no other AHP-specific therapies were introduced until the arrival of givosiran, therefore we still believe that the data in Baravelli et al., 2020 should still be considered relevant for these patients.

However, we did acknowledge the uncertainty surrounding the mortality estimate during the development of this application, as we conducted an scenario analysis, where the impact of applying the lower bound CI of the HR (HR = 1) reported in Baravelli et al., 2020, was tested in the health economic model. This scenario analysis indicated that applying a HR of 1 for the mortality of AHP patient would [redacted] the ICER by ≈ [redacted]%. The full results of this scenario analysis are presented in section 9.7.1, Table 53.

- **Do you expect givosiran treatment to affect the number of patients receiving a liver transplant?**

Response*:* A reduction in long-term consequences of AHP like HCC (and hence the need for liver transplant) could be expected with givosiran due to control of ALA and PBG levels (3–5)— the toxic heme intermediates driving the acute and chronic aspects of AHP — there are currently no long-term data to inform this question or model the possibility.

- **A study from the US is used to estimate the cost of opioid dependence. The study includes costs for lost earnings, which is not in line with the Danish Medicines Council's method. Please explain why you find the study relevant to use and why you believe that the costs of treating opioid addiction from the US can be used directly as a measure of the costs in Denmark.**

Response*:* The model uses cost from Shei et al. 2015 as reference (6), which reports the incremental health care costs associated with prescription opioid in the EU5. This reference does not include cost for lost earnings. We believe our reference manger swapped the original reference(6) with another publication by Amin Shei in 2015 (7), focused on the US, where costs are estimated. The reference has been amended in the application. Apologies for the confusion.

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3. References

1. Danish Medicines Agency. Danish Summary of Product Charactertistics for Normosang (Haemin). 2015.
2. Baravelli CM, Aarsand AK, Sandberg S, Tollånes MC, Tollanes MC. Sick leave, disability, and mortality in acute hepatic porphyria: a nationwide cohort study. Orphanet J Rare Dis [Internet]. 2020 Feb 21 [cited 2021 Jun 8];15(1):56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32085780
3. Peoc'h K, Manceau H, Karim Z, Wahlin S, Gouya L, Puy H, et al. Hepatocellular carcinoma in acute hepatic porphyrias: A Damocles Sword. Mol Genet Metab. 2019 Nov;128(3):236–41.
4. Anderson KE, Bloomer JR, Bonkovsky HL, Kushner JP, Pierach CA, Pimstone NR, et al. Recommendations for the diagnosis and treatment of the acute porphyrias. Ann Intern Med [Internet]. 2005;142(6):439–50. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15767622
5. Pischik E, Kauppinen R. An update of clinical management of acute intermittent porphyria. Appl Clin Genet [Internet]. 2015 Sep 1 [cited 2021 Jun 8];8:201–14. Available from: https://pubmed.ncbi.nlm.nih.gov/26366103/
6. Shei A, Hirst M, Kirson NY, Enloe CJ, Birnbaum HG, Dunlop WCN. Estimating the health care burden of prescription opioid abuse in five European countries. Clin Outcomes Res [Internet]. 2015 Sep 15 [cited 2021 Sep 8];7:477–88. Available from: https://pubmed.ncbi.nlm.nih.gov/26396536/
7. Shei A, Rice JB, Kirson NY, Bodnar K, Enloe CJ, Birnbaum HG, et al. Characteristics of high-cost patients diagnosed with opioid abuse. J Manag Care Pharm [Internet]. 2015 Oct 19 [cited 2021 Jun 8];21(10):902–12. Available from: www.amcp.org

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Response document for DMC

Concerning request for additional supporting information for the assessment of of Givlaari™ (givosiran) for patients with acute hepatic porphyria

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1. DMC Request

Alnylam Pharmaceuticals on the 1st of October received a request from the DMC for additional information to support the application of Givlaari™ (givosiran) for patients with acute hepatic porphyria (AHP).

Alnylam acknowledges the requests made by the DMC, and has provided detailed answers in the section below for all points raised by the DMC.

2. Requests and Responses

During the assessment process regarding givosiran, we have identified a number of issues that we kindly ask you to address:

- In table 9 in the application, the median AAR (Q1, Q3) for givosiran in the AHP population is presented as 1.04 (2.37, 4.74). It seems strange that the median is not within the range. Please verify this.

Response: Apologies for the mistake, the confidence interval seems to have been duplicated from the mean AAR estimate provided above. The correct median AAR estimate for the AHP population is 1.04 (0.00, 6.35).

- In table 10, the following note is provided for several of the endpoints: "*Secondary endpoints were analysed using a prespecified hierarchical order in the AIP population at 6-month intervention period unless otherwise stated. p-values of other outcomes are reported as nominal, as the endpoint did not meet the conditions of the prespecified hierarchical order". Can you please provide a more thorough explanation of the statistical method? Also please explain whether the note applies for all the analyses of the specific endpoints (e.g. all four types of analyses provided for SF-12). The expert committee wishes to be presented to the CI and preferably also p-values for all endpoints. Please provide these estimates or clearly state why such estimates cannot be presented.

Response:
For the final analyses of the primary 6-month DB period presented in this report, a 2-sided significance level of 0.049 was used to test the efficacy endpoints, reflecting a penalty of 0.001 for the unblinded interim analysis. A fixed-sequence testing strategy for the primary and secondary endpoints was implemented to control the overall type I error rate. The primary endpoint was compared between treatment arms at the 2-sided significance level of 0.049. If the test for the primary endpoint was statistically significant, then the secondary endpoints were each to be tested at the same 2-sided significance level of 0.049 in the following hierarchical order:

- Urinary ALA levels in patients with AIP at 3 months
- Urinary ALA levels in patients with AIP at 6 months
- Urinary PBG levels in patients with AIP at 6 months
- Annualized rate of administered hemin doses (evaluated by annualized days of hemin use) in patients with AIP over the 6-month DB period
- Annualized rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home in patients with any AHP over the 6-month DB period
- Daily worst pain score as measured by BPI-SF NRS in patients with AIP over the 6- month DB period
- Daily worst fatigue score as measured by BFI-SF NRS in patients with AIP over the 6-month DB period
- Daily worst nausea score as measured by NRS in patients with AIP over the 6-month DB period
- Change from baseline in the PCS of the SF-12 in patients with AIP at 6 months

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If the test of an endpoint was not statistically significant at the 2-sided 0.049 significance level, the subsequent endpoints were not tested but nominal p values were described.
According to the test hierarchy above, the p-value for endpoints of daily worst score for fatigue and beyond are considered nominal in interpretation.

It should be recognized, that Alnylam has provided results for all efficacy outcomes for both the AHP and AIP subgroup whenever possible, and that there are only few outcomes were data is not available. In the few cases were statistical testing is not carried out (no p-values or CI) this is mainly for the AHP group, because the primary efficacy analysis was carried out on the AIP group. Given that 95% of patients in ENVISION had AIP, the key results in AHP and AIP cohorts were virtually identical, as would be expected. Therefore, there would be no value in performing new analyses on every endpoint solely for the purposes of creating a comprehensive set of matching results for both of these cohorts. As also seen for all primary and secondary outcomes, where results is available for both populations, the comparative efficacy estimates are virtually identical, and consequently there is no reason to believe this would be the case for the few outcomes where data is not available for the AHP group.
As for the exploratory endpoints it is common practice to not carry out any statistical testing for such outcomes, especially since strong inferences should not be made for results after the conditions for the testing hierarchy have not been met.

- In table 10, the following note is provided: "‡Because of a significant deviation from normal distribution, the planned methods of a mixed model for repeated measures or analysis of covariance were not valid. A nonparametric stratified Wilcoxon signed-rank test was therefore conducted. The median of the between-group difference was estimated with the use of the Hodges–Lehmann method". Kindly provide a more thorough explanation of the applied analyses, e.g. what was stratified for. Please also provide relevant plots as a means to visualize the deviation from normal distribution.

Response:
For ALA, a non-parametric Wilcoxon rank sum test was conducted because of a significant deviation from a normal distribution of data ($p<0.0001$, Figure 14.4.2.3.1).
For PBG, a non-parametric Wilcoxon rank sum test was conducted because of the significant deviation from a normal distribution of data ($p<0.0001$).
For daily worst pain, a non-parametric stratified Wilcoxon test (with stratification factors prior hemin prophylaxis status and historical attack rate) was conducted because of the significant deviation from a normal distribution of data ($p<0.0001$).

Note that for ALA and PBG, a non-parametric Wilcoxon was prespecified as the primary method when normal assumption is violated. However, for pain scores, it was not anticipated that the data would violate normal assumptions therefore the method was not prespecified in the SAP.

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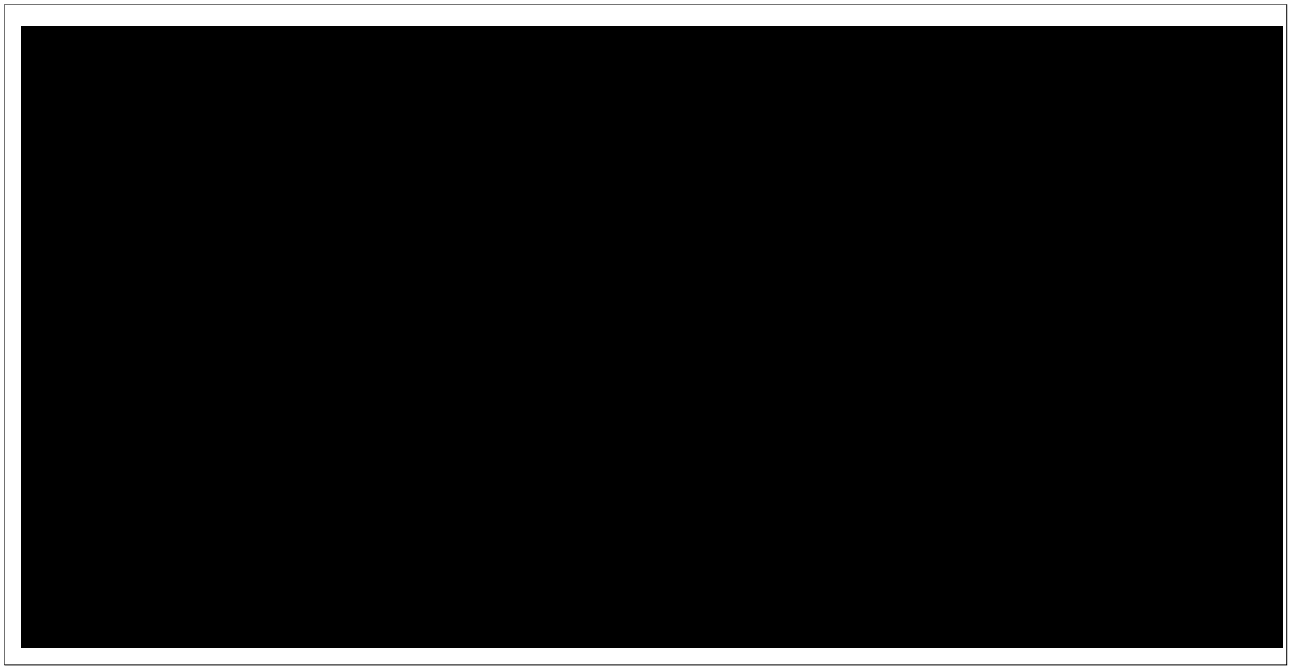
Figure 1 Quantile-quantile (Q-Q) Plot for Checking Normality Assumption of Change from Baseline in Weekly Mean Score of Daily Worst Pain Score during the 6-Month Double-Blind Period (AIP-population)



- In figure 10, only data from 9 patients in each treatment arm is provided at 24 months of follow-up. Was there a large dropout of patients at this time, or could patients change to compassionate treatment? Or is data not yet available for all patients? Please provide data for all patients with as long a follow-up period as possible.

Response: Only 9 patients are shown at 24-month follow-up since, at the time of data-cut, these were the only patients who had reached the follow-up time of 24 months and thus were included in the analysis and represented in the figure. As clearly shown in Figure 2 for the 36-month ENVISION OLE-data, there was very low discontinuation/lost to follow-up rates throughout the DB and OLE period.

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

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

As presented in our initial submission, the ENVISION primary composite endpoint of annualised attack rate (AAR) continued to decline out to final 36-month follow-up (Figure 2 and Table 2) (**data-on file)**. These results thus confirm the sustained and continuing improvement in acute attack status in patients receiving givosiran across 3 years of follow-up. It is apparent from these data that AAR is trending towards complete cessation of attacks in patients on givosiran. In other words, there is no evidence of waning efficacy – instead, all available evidence suggests that efficacy is increasing over the period of observation.

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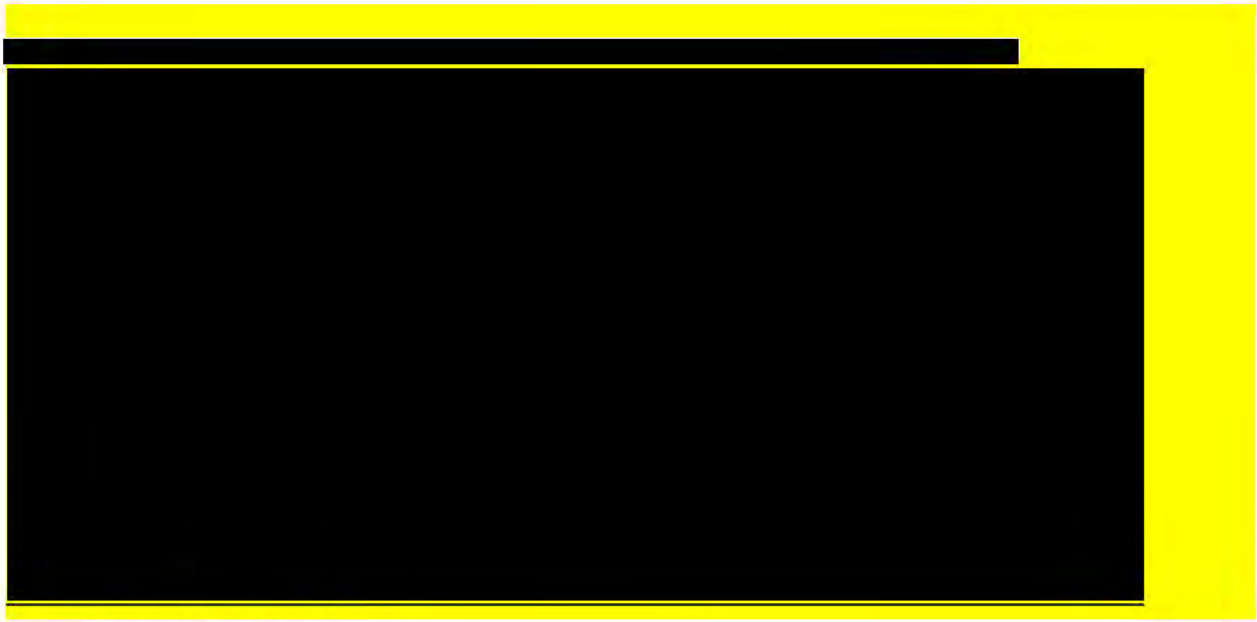

Source: Alnylam, ENVISION data on file

DB: double-blind; Givo: givosiran; Pbo: placebo; OLE: open-label extension

Table 2: Summary of attack rate in the ENVISION trial and OLE at baseline and Months 6, 18, and 36

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

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Mean (SEM)§	[redacted]	[redacted]	[redacted]

Sources: Alnylam, ENVISION Clinical Study Report 2(1); Alnylam, ENVISION data on file
AAR: annualised attack rate; CI: confidence interval; DB: double-blind; OLE: open-label extension; Q1, Q3: interquartile range; SD: standard deviation; SEM: standard error of mean
Note: Placebo/givosiran includes patients receiving placebo in the DB period and givosiran in the OLE period. In the placebo/givosiran group, AAR in the DB period is calculated from study baseline to Month 6, and AARs in the OLE period are calculated using data only post-givosiran treatment from Month 6 (i.e., Day 1 of receiving givosiran in the OLE) to Month 18 or Month 36. Givosiran/givosiran includes patients receiving givosiran in the DB and OLE periods. In the givosiran/givosiran group, AARs in the DB and OLE periods are calculated from study baseline (i.e., Day 1 of receiving givosiran in the DB period) to Months 6, 18, or 36.
*Calculated from the individual patient's AAR.
†Derived using the negative binomial regression model with treatment group and stratification factors (prior hemin prophylaxis status and historical attack rates) as fixed effects, and the logarithm of the follow-up time as an offset variable.
‡One patient whose follow-up duration after taking givosiran was <85 days was excluded from the analysis.
§Duration-weighted mean AAR is presented. Standard error of the mean is calculated using Cochran's formula (1977).

- On page 39 in the application, it is stated that "EMA in their assessment report also considered gender as a specific subgroup, and demonstrated that this factor did not have any influence on givosiran efficacy or safety". The expert committee is, however, interested in potential gender effects and wishes to be presented to gender specific analyses of AAR.

Response:

Alnylam has conducted a subgroup analysis of AAR stratified by sex for demonstrating the AAR for givosiran vs. placebo for male is [redacted] and for female [redacted], respectively (data-on file) (Figure 3).
This is consistent with the observations of the EMA, showing that the confidence intervals are clearly overlapping. Consistent with the pathology of the condition, the majority of patients enrolled in ENVISION were female. Therefore, we do not believe any inferences should be made on any numerical sex-related differences in AAR or any measure of efficacy since these may be driven by the relatively small N of men.

Figure 3: Forest Plot of Porphyria Attacks Requiring Hospitalization, Urgent Healthcare Visit, or IV Hemin Administration at Home during the 6-Month Double-Blind Period, Subgroup Analysis, Negative Binomial Regression. Study Population: AIP Patients in Full Analysis Set (*graphic is confidential*)

AIP=Acute intermittent porphyria; CI=Confidence interval; IV=Intravenous

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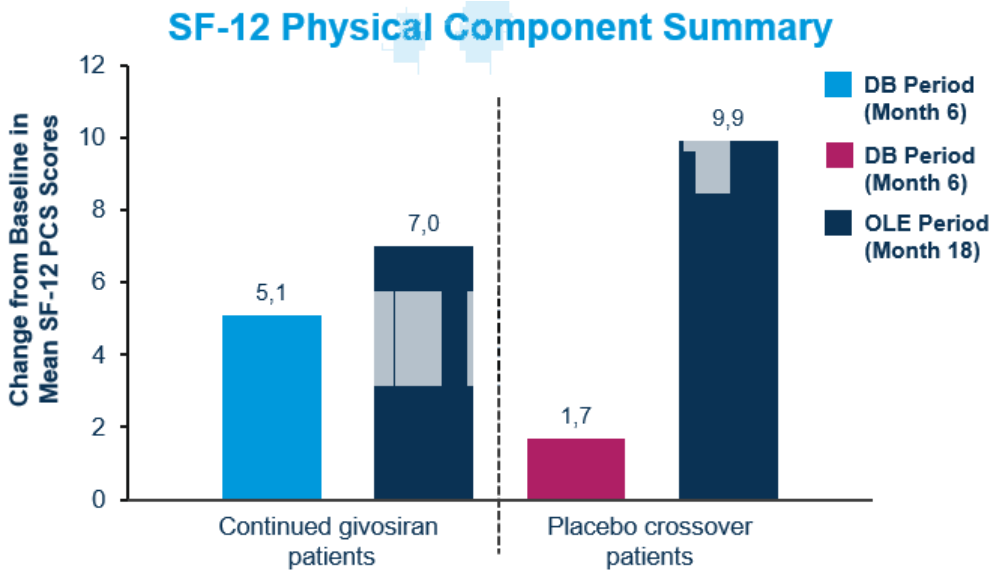
Rate ratio and corresponding CIs are derived using negative binomial regression model with treatment group, stratification factors (prior hemin prophylaxis
status and historical attack rates), the logarithm of the follow-up time as an offset variable.
A rate ratio < 1 represents a favorable outcome for Givosiran 2.5 mg/kg.

- The expert committee wishes to see data regarding quality of life at a longer follow-up than 6 months, and preferably also data from the transition period, when patients change from treatment with placebo to givosiran. Please provide such data, if available.

Response:
PCS SF-12 data is provided below until 18 months of follow-up for the AHP-population. At present no further longitudinal follow-up data is available from the OLE period as the this data is still ongoing data processing for the 36-month data-cut as mentioned above. For patients in the givosiran/givosiran group, continued treatment with givosiran led to sustained improvement in the mean SF-12 PCS score through 18 months of treatment. During the DB period, treatment with givosiran resulted in an improvement in the PCS with a mean change from baseline (Day 1) of 5.1 after 6 months of treatment (Figure 4). Continued treatment in the OLE period led to additional improvement with mean changes from baseline of 7.0 at 18 months of treatment.
As shown in Figure 4 the placebo/givosiran group during the 6-month DB period showed less improvements in the PCS score with a mean change from baseline of 1.7. After the placebo group started givosiran treatment in the OLE period, the PCS SF-12 score continued to improve over time through Month 18 after crossing over to givosiran (mean change from baseline 9.9. The mean changes from baseline differ slightly from LS mean changes presented in the dossier for the AHP-population, due to differences in statistical methods used in the calculation.
In conclusion; improvements in QOL scores were observed at Month 6 and Month 18 in patients continuing givosiran treatment, while placebo crossover patients had similar improvements at Month 18 to those seen in givosiran patients in the DB period.

Figure 4: SF-12 Physical Component Summary – 6 month DB and 18 month OLE



Note: Estimates for the clinically meaningful difference are ≥2 points for SF-12 PCS

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- In regards to daily worst pain, please provide data on the proportion of patients achieving the MCID of 2 points. Please also state whether a genotypic – phenotypic link has been observed for this end point.

Response:
Alnylam has conducted responder analysis on the AHP-population for patients achieving an improvement (reduction) of ≥ 2 points on the weekly daily worst pain score throughout the entire DB and OLE period (continuous sustained improvements throughout the periods). Givosiran treated patients had higher response rates than placebo treated patients during the DB period, [redacted] versus [redacted], respectively. For patients with continued givosiran treatment from the DB period, the response rate showed further improvement during the OLE period, from [redacted] to [redacted]. For patients switched from placebo to givosiran during the OLE period, the response rate showed improvement, from [redacted] to [redacted].
Analysis based on genotypic – phenotypic type is not available and is not meaningful as the vast majority of patients are AIP and the analysis will thus not be robust to examine any differences across small subgroups. As examined thoroughly in the dossier, there is no data indicating any differences in response to givosiran across any subgroups. Further there are no clinical or hypothetic rationale, that could explain why efficacy would differ because givosiran acts upstream of the genetic defects in the heam-synthesis pathway that differentiate the AHP subtypes, thus no difference in effect can be expected in AAR reduction and consequently neither in patients reduction in pain.

- If available, please provide data on homocysteine levels in regard to treatment with givosiran.

Response: Unfortunately, no such analysis is available on homocysteine levels during treatment.

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- One of the most frequent adverse reactions with givosiran is nausea (32.4% of patients experience this). Please provide information on the degree of nausea, i.e. is it generally manageable or can it be disabling?

Response: At the end of the 6 month DB phase of ENVISION, 27% of patients in the givosiran group experienced nausea and 11% in the placebo group. The 32.4% noted by the DMC, is from the safety population in the SmPC from data across all trials (safety pool).

A detailed breakdown from ENVISION is available for nausea for the patients receiving placebo and switching to givosiran after 6 month (placebo/givosiran) and for the patients receiving givosiran throughout the study (givosiran/givosiran) in the table below. As seen for the givosiran/givosiran group, [redacted] of patients experienced mild nausea, [redacted] moderate nausea and [redacted] experienced severe nausea. There were no serious events. Events therefore generally manageable, transient and clearly never disabling as no serious events or events leading to discontinuation was noted in the DB-phase of ENVISION.

[redacted]

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- Section 9.4, that describes the HRQOL used in the model, has several shortcomings which need to be addressed in the application. We need full information on the available EQ-5D data from both EXPLORE and ENVISION. This includes information on the number of completed EQ-5D questionnaires, the timing of collected data (including model stage and whether data was collected 'during attack'), description of missing data and if needed, analysis of missing data, as well as the information on the analysis of mean estimates. Despite potential problems in using EQ-5D data from EXPLORE and ENVISION to estimate health state utilities, we still need the estimates from both studies divided by the model's health states. For ENVISION, estimates should be presented both as divided by treatment arms for the relevant period of time and aggregated.

Response: We did not use the EQ-5D data collected in ENVISION to estimate the utility values by health state because, as can be observed in Figure 5, the scatterplot of AAR vs. EQ-5D–derived utility data collected in the double-blind period of ENVISION shows that some patients with very high number of attacks have EQ-5D utility values close to 1 whereas many patients with very few attacks have very low utility values (Pearson correlation coefficient r = [redacted], p= [redacted]). It is possible that the ENVISION study is not of a sufficiently large sample size or long enough duration to reach a "steady state" estimation of the true underlying utility of these patients. In addition, patients in ENVISION had a relatively short average duration of disease, and thus may not yet have accrued the level of health-related quality of life (HRQoL) impairment due to AHP chronic symptoms, comorbidities, and late complications that would be observed in patients with longer disease duration.

Figure 5. AAR vs. EQ-5D collected in the double-blind period of ENVISION (*graphic is confidential)*

Source: Alnylam, ENVISION data on file
AAR: annualized attack rate; EQ-5D: EuroQol 5-dimensions; HRQoL: health-related quality of life

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In addition to the fundamental problem that EQ-5D scores did not correlate with AAR during ENVISION, there are numerous logistical obstacles to using data from this trial to set health-state utilities, including the following critical issues:

1. The EQ-5D assesses instantaneous health status on the day of questionnaire administration(2, 3)—i.e., it has no recall period of the past week, month, etc.—whereas health state based on AAR has to be calculated over some longer time period, which creates a mismatch whenever health state is not stable.
2. Health states in ENVISION are not stable for most patients, and indeed this fact underlies the transition probabilities in the CEM. Therefore, EQ-5D measurements averaged from different time points do not correspond cleanly to a given health state and are confounded by treatment.
3. Results in the double-blind period are confounded by treatment, considering that at 6 months 100% of Severe patients were in the placebo arm whereas 80% of Asymptomatic patients were in the givosiran arm.
4. Per the ENVISION eligibility criteria, no patients were in the Asymptomatic state at baseline, so it is impossible to use baseline EQ-5D measurements to populate all four model health states.
5. Considering attacks during the ENVISION OLE, no patients were in the Severe health state by Month 12 or Month 18 (i.e., when AAR was calculated between Month 6 and Month 12 or between Month 12 and Month 18), so it is impossible to use EQ-5D measurements from the OLE to populate all four CEM health states.
6. The relatively low prevalence of chronic conditions among patients in ENVISION, as noted in question A4 above, likely reflects the short disease duration relative to the timeframe over which these conditions accumulate, as seen in the long-term study by Neeleman et al. (2018).(4) Thus, ENVISION does not allow us to appropriately simulate the HRQoL burden of chronic conditions over the model time horizon.

As shown in Table 3, if we categorize all EQ-5D measurements by AAR at either baseline or 6 months, the resulting utilities lack face validity, since at Month 6 the overall mean EQ-5D index value for patients in the Severe health state is higher than for Recurrent, Symptomatic, and even Asymptomatic patients. These results cannot be used to perform a scenario analysis because they imply that a patient with more than 24 acute porphyria attacks per year has better HRQoL than one with >4 to ≤24 attacks, >0 to ≤4 attacks, or even no attacks, which is not only illogical given the high burden of an acute attack but also runs directly contrary to the opinion of clinician experts, who confirmed that their AHP patients with higher AAR have lower HRQoL.(5)

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Table 3. Mean EQ-5D index values at Month 6 by health state at baseline and Month 6 in the double-blind period of ENVISION

	EQ-5D utility								
	Givosiran			Placebo			All patients		
Health state	n	Mean	SE	n*	Mean	SE	n	Mean	SE
Baseline†									
Asymptomatic	[redacted]								
Symptomatic	[redacted]								
Recurrent	[redacted]								
Severe	[redacted]								
6 Months‡									
Asymptomatic	[redacted]								
Symptomatic	[redacted]								
Recurrent	[redacted]								
Severe	[redacted]								

Source: Alnylam, ENVISION data on file

EQ-5D: EuroQol 5-dimensions; n: number of patients who completed the questionnaire; SE: standard error

*In line with other analyses performed for the model, two placebo patients were excluded for protocol deviation

†Danish EQ-5D tariff; for each patient, the EQ-5D measurement at baseline is considered; patients are classified by health state based on AAR at baseline, and the average utility across observations for patients in each health state is then calculated.

‡ Danish EQ-5D tariff; for each patient, the EQ-5D measurement at Month 6 is considered; patients are classified by health state based on AAR at Month 6, and the average utility across observations for patients in each health state is then calculated.

The same concerns described above regarding the 6-month ENVISION double-blind period being too short a timescale to capture the HRQoL impact of AHP apply equally to the EXPLORE study, which focused on the natural history and current clinical management of AHP over a relatively short time period (6 months with an optional 12-month visit).(6) The median time since first attack in EXPLORE was only 8 years.(6) Consequently, neither ENVISION nor EXPLORE capture long-term data on chronic conditions, and neither provided as comprehensive an assessment of chronic symptom burden in patients with AHP as did Neeleman et al. (2018).(4)

In addition, the eligibility criteria in ENVISION and EXPLORE specifically excluded patients with any condition that could interfere with their participation in these studies. Thus, these studies inherently underestimate the true burden of comorbidities and complications in AHP patients encountered in clinical practice. The relatively small sample sizes in ENVISION and EXPLORE would also yield few (and sometimes no) patients for each possible combination of chronic conditions, precluding rigorous calculation of HRQoL decrements for any given combination.

For the model, therefore, it was more clinically realistic to use the real-world cohort described by Neeleman et al. as the source of prevalence data on chronic conditions when estimating HRQoL. We therefore consider this method in the model to be the most appropriate. Specifically, we obtained the long-term HRQoL decrements associated with each chronic condition associated with AHP separately from the literature and then applied these disutilities to the proportion of the cohort with each condition in every health state based on prevalence data reported in the long-term, real-world study by Neeleman et al. (2018).(4) Patients in the Neeleman et al. cohort had suffered from AHP for a much longer time than patients in ENVISION, and therefore offer a more accurate representation of the full extent of comorbidities and long-term complications that typically occur in this disease. The 88 patients described by Neeleman et al. had a median age at AHP onset of 30 years, and the reported median age at the end of study follow-up was 54 years.(4) This indicates that the average duration of disease in the Neeleman et al. cohort was approximately 24 years at the end of follow-up. In contrast, the mean duration of AHP in the overall ENVISION trial population was only 9.7 years.(7) Thus, ENVISION data cannot be used to characterize the accumulation of these conditions over the relevant timescale of the CEM, namely a lifetime horizon. Modelling health-state utilities based on

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the prevalence of AHP chronic symptoms, comorbidities, and late complications reported by Neeleman et al. is appropriate because this long-term study, which reports data on the occurrence of chronic symptoms/comorbidities and long-term complications of AHP over a 50-year period from 1960 to 2016, is more representative of the relevant timescale of HRQoL impact in this incurable, chronic disease than the 6-month ENVISION study.

3. References

1. Alnylam Pharmaceuticals. Clinical Study Report 2 ALN-AS1-003 (ENVISION): Interim Analysis (dated 20 June 2020). 2020. p. 1-241.
2. Devlin N, Parkin D, Janssen B. Chapter 1, An Introduction to EQ-5D Instruments and Their Applications. Methods for Analysing and Reporting EQ-5D Data [Internet]. Cham (CH)2020.
3. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.
4. Neeleman RA, Wagenmakers M, Koole-Lesuis RH, Mijnhout GS, Wilson JHP, Friesema ECH, et al. Medical and financial burden of acute intermittent porphyria. Journal of inherited metabolic disease. 2018;41(5):809-17.
5. BresMed Health Solutions Ltd. 2661: Givosiran acute hepatic porphyria clinician interview report. 2020 14 January.
6. Gouya L, Ventura P, Balwani M, Bissell DM, Rees DC, Stolzel U, et al. EXPLORE: a prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. Hepatology. 2020;71(5):1546-58.
7. Balwani M, Sardh E, Ventura P, Peiro PA, Rees DC, Stolzel U, et al. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. The New England journal of medicine. 2020;382(24):2289-301.

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Response document for DMC

Concerning request for additional supporting information for the assessment of of Givlaari™ (givosiran) for patients with acute hepatic porphyria

NOTE: This document is confidential information not to be published.

1. DMC Request

Alnylam Pharmaceuticals on the 1st of November received a request from the DMC for additional information to support the application of Givlaari™ (givosiran) for patients with acute hepatic porphyria (AHP).

Alnylam acknowledges the requests made by the DMC, and has provided a detailed answer in the section below for the point raised by the DMC.

2. Requests and Responses

As a means to aid the clinical assessment of givosiran, the expert committee wishes to be presented to EQ-5D quality of life data from ENVISION. We therefore kindly ask you to provide EQ-5D data for the two treatment arms (givosiran and placebo) both at baseline, at 6 months of follow-up and at the longest possible follow-up.

Response:

Table 1. Mean EQ-5D index values at baseline, month 6 and month 18 (latest point available) by treatment arm in the double-blind period and OLE of ENVISION

	EQ-5D utility								
	Givosiran-Givosiran			Placebo			All patients		
Time point	n	Mean	SE	n*	Mean	SE	n	Mean	SE
Baseline†	47	[redacted]	[redacted]	44	[redacted]	[redacted]	91	[redacted]	[redacted]
Month 6†	48	[redacted]	[redacted]	44	[redacted]	[redacted]	92	[redacted]	[redacted]
Month 18†	45	[redacted]	[redacted]	N/A‡			45	[redacted]	[redacted]

Source: Alnylam, ENVISION data on file

EQ-5D: EuroQol 5-dimensions; n: number of patients who completed the questionnaire; SE: standard error

*In line with other analyses performed for the model, two placebo patients were excluded for protocol deviation

†Danish EQ-5D tariff; for each patient, the EQ-5D measurement at a given time-point is considered and the average utility across observations at that time point is then calculated.

‡ No observations are available for placebo during the open label extension since all patients switched to givosiran.

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1. DMC Request

Alnylam Pharmaceuticals on the 5th of November received a request from the DMC for additional information to support the application of Givlaari™ (givosiran) for patients with acute hepatic porphyria (AHP).

Alnylam acknowledges the requests made by the DMC and has provided detailed answers in the section below for all points raised by the DMC.

2. Requests and Responses

In the meantime, we [DMC] have identified a few smaller issues which we would like you to address:

- Is there a maximum dose of givosiran?

Response: Dosing of givosiran is described in the SmPC as follows: "The recommended dose of Givlaari is 2.5 mg/kg once monthly, administered via subcutaneous injection. Dosing is based on actual body weight."(1). Alnylam does not have a stated maximum <u>total</u> dose (i.e., total mg per dosing) for Givlaari that can be shared.

- In the response letter dated October 15, the following is stated: "For patients with continued givosiran treatment from the DB period, the response rate showed further improvement during the OLE period, from [redacted]. For patients switched from placebo to givosiran during the OLE period, the response rate showed improvement, from [redacted]." Please specify the follow-up time for these estimates.

Response: We apologize for not specifying this clearly in our original response.

Data for daily worse pain scores were captured for the first year only in ENVISION and the OLE. Therefore, the DB period refers to weeks 1-24 (6 month DB period) and the OLE period refers to weeks 25-48 (month 6-12 in the OLE).

- On page 42-43 and figure 13 in the application, PGIC data is presented for AHP patients. In table 10, PGIC data is, however, presented for patients with AIP. Please clarify this.

Response: Thank you for noticing this typo - we apologize for this error. The results in table 10 are PGIC data for AHP, and not AIP. This has been amended in the update submission dossier to reflect that the data is for patients with AHP. (Changes have been made in Table 10 on page 37)

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3. References

1. European Medicines Agency (EMA). Summary of Product Characteristics for GIVLAARI (givosiran). 2020.

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Response document for DMC

Concerning request for additional supporting information for the assessment of of Givlaari™ (givosiran) for patients with acute hepatic porphyria

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1. DMC Request

Alnylam Pharmaceuticals on the 24th of November received a request from the DMC for additional information to support the application of Givlaari™ (givosiran) for patients with acute hepatic porphyria (AHP).

Alnylam acknowledges the requests made by the DMC and has provided detailed answers in the section below for all points raised by the DMC.

2. Requests and Responses

In the ENVISION-study, patients with elevated ALT levels can resume at a lower dose (1.25 mg per kilogram) after resolution. Can you inform us of the number of patients receiving the lower dose in the ENVISION-OLE?

Response:

In summary:

- Only a single patient's GIVLAARI dose was lowered to 1.25 mg/kg once monthly due to elevated ALT levels in the ENVISION study and OLE
- While [redacted] additional patients received 1.25 mg/kg once monthly at OLE crossover this was not due to them having elevated ALT levels but instead, was due to a protocol Amendment to collect data on the 1.25 mg/kg dose
- [redacted] patients were on the 1.25 mg/kg dose at the conclusion of the OLE, [redacted] patients were receiving 2.5 mg/kg once monthly due to a further protocol Amendment
- Data generated during OLE period showed a trend toward increased benefit with the 2.5 mg/kg dose compared to the 1.25 mg/kg dose. Furthermore, the approved recommended dose of GIVLAARI in the United States and European Economic Area is 2.5 mg/kg once monthly

During the ENVISION study and OLE, a single patient had their dose of givosiran lowered to 1.25 mg/kg once monthly due to ALT elevation (1). This patient's dose was lowered during the 6-month double-blind (DB) period.

In addition to the one patient noted above, [redacted] patients were assigned at OLE crossover (the conclusion of the DB period where patients on placebo were switched to active treatment) to receive the lower 1.25 mg/kg dose. These [redacted] patients consisted of [redacted] GIVLAARI crossover patients and [redacted] placebo crossover patients. This was a result of protocol Amendment 3 (Section 1.4 of the study protocol [Appendix 16.1.1]) to generate additional data at this dose level and was not due to elevated ALT levels in these [redacted] patients. Patients within this group without adequate disease control were allowed to have their dose increased to 2.5 mg/kg.

Because AHP is a disease in which each attack is serious, highly morbid, and carries potential for irreversible neurologic damage, during the OLE period, protocol Amendment 5 (Section 6.2.3.4 of the protocol [Appendix 16.1.1]) allowed for the dose for all patients receiving the 1.25 mg/kg to be increased to 2.5 mg/kg. The exact patient-to-patient timings for this varied depending on what month the patient was on at the time of the Amendment 5 – Feb 12, 2020. However, all patients had to have completed at least 12 months of the study to allow for 1.25 mg/kg dosing to be assessed for 6 months.

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Thus, at the conclusion of the OLE period [redacted] receiving 1.25 mg/kg GIVLAARI administered once monthly, [redacted] were receiving 2.5 mg/kg GIVLAARI administered once monthly.

It should be noted that, based on the first 6 months of givosiran treatment during the OLE period in patients who received placebo in the DB period (placebo crossover patients), a trend toward increased benefit with the 2.5 mg/kg once monthly dose of givosiran compared to the 1.25 mg/kg once monthly dose was observed, as indicated by greater reductions in composite attacks, hemin use, and ALA and PBG levels. Furthermore prior to the implementation of amendment 5, Investigators requested to increase the dose to 2.5 mg/kg givosiran SC once monthly for [redacted] of the [redacted] patients ([redacted]) receiving 1.25 mg/kg givosiran SC once monthly in the OLE because of inadequate clinical response, as noted above.

Alnylam would like to reinforce that the recommended dose of GIVLAARI is 2.5mg/kg in the United States (2) and European Economic Area (3).

---

3. References

1. Balwani M, Sardh E, Ventura P, Peiró PA, Rees DC, Stölzel U, et al. Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria. N Engl J Med [Internet]. 2020 Jun 11 [cited 2021 Jun 8];382(24):2289–301. Available from: https://www.nejm.org/doi/full/10.1056/nejmoa1913147
2. FDA. GIVLAARI - Prescribing information [Internet]. 2019 [cited 2021 Nov 26]. Available from: www.fda.gov/medwatch.
3. European Medicines Agency (EMA). Summary of Product Characteristics for GIVLAARI (givosiran). 2020.

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Response document for DMC

Concerning request for additional supporting information for the assessment of of Givlaari™ (givosiran) for patients with acute hepatic porphyria

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1. DMC Request

Alnylam Pharmaceuticals on the 3rd of December and on the 7th of December received a request from the DMC for additional information to support the application of Givlaari™ (givosiran) for patients with acute hepatic porphyria (AHP).

Alnylam acknowledges the requests made by the DMC, and has provided detailed answers in the section below for all points raised by the DMC.

2. Requests and Responses

Clarify at which time points during ENVISION and ENVISION-OLE the SF-12 survey was conducted? Are the results based on a single survey being conducted at baseline, at 6 months and at 18 months for each patient? Or are the results based on more surveys for each patients?

Response: SF-12 surveys were collected at screening, month 3, 6, 9, 12, 18, 24, 30 and 36 in ENVISON and the open label extension. The full schedule of assessments can be seen on page 10-16 in the public study protocol on ClinicalTrials.gov[1].

To follow-up on you response letter dated 01-12-2021:
On page 2, it is stated: "Patients within this group without adequate disease control were allowed to have their dose increased to 2.5 mg/kg."
Can you please clarify how adequate disease control was defined?

Response:
Amendment 3 of the clinical trial protocol states that dose escalation from 1.25 mg/kg to 2.5 mg/kg would be allowed if the following criteria are met:

- Tolerability to givosiran at 1.25 mg/kg once monthly has been demonstrated based on no dose interruptions due to LFT elevations at the 1.25 mg/kg once monthly dose level (see Section 6.2.3.1) and no significant safety concerns due to other AEs that would preclude a patient from receiving a higher dose of givosiran as judged by the Investigator and Sponsor.
- Urine ALA levels (mmol/mol Cr) are not stably maintained ≤ULN or are inducible
- Patient has inadequate clinical response (e.g., breakthrough attacks or ongoing chronic symptoms), according to Investigator judgement.

Following implementation of amendment 5 of the clinical trial protocol, all patients receiving 1.25 mg/kg givosiran once monthly, who did not have ongoing clinically relevant transaminase elevations had their dose increased to 2.5 mg/kg givosiran once monthly based on tolerability alone, without any criteria for ALA reduction or clinical activity. As noted previously, at the conclusion of the OLE period [redacted] receiving 1.25 mg/kg GIVLAARI administered once monthly, [redacted] were receiving 2.5 mg/kg GIVLAARI administered once monthly.

[1] https://www.clinicaltrials.gov/ProvidedDocs/16/NCT03338816/Prot_000.pdf

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Response document for DMC

Concerning request for additional supporting information for the assessment of Givlaari™ (givosiran) for patients with acute hepatic porphyria

NOTE: This document is confidential information not to be published.

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DMC Request

Alnylam Pharmaceuticals on the 18th of January received a request from the DMC to provide an updated application containing the most recent data from the ENVISON OLE to support the application of Givlaari™ (givosiran) for patients with acute hepatic porphyria (AHP). After a subsequent meeting on 31st January Alnylam and the DMC agreed that Alnylam would provide:

1. An updated cost-effectiveness model (CEM) incorporating Month-36 data from the ENVISION open-label extension (OLE)
2. An abbreviated document providing a summary of Month-36 data from the ENVISION OLE, a summary of changes to the model made to incorporate these data, and updated CEM results
    - Alnylam was to provide a 'skeleton structure' of this document so there is an opportunity for further discussion / refinement with the DMC ahead of preparation
    - Specifically, the DMC highlighted that it would be useful if Month-36 data were provided for all endpoints previously discussed (i.e. either mentioned in the original application or discussed in a response letter). Where Month-36 data were not available, Alnylam would provide data for the last follow-up period for that specific endpoint and state when it was
3. Provisional agreement to provide the full Month-36 CSR (dependent on availability and ability to share)

These details were confirmed via email communication on 7-8th February. Alnylam on 18th February provided an outline (i.e. the 'skeleton structure' noted above) intended to detail the planned contents of the abbreviated document mentioned in point 2 above. The DMC provided feedback on this outline on 28th February. The numbering of Parts B, C, and D in the abbreviated document will refer back to Alnylam's original submission to allow the DMC to easily track changes made to the submission. Part A provides additional efficacy and safety data to section 8.1.2.1 (efficacy) and 8.1.2.2 (safety) of the original submission.

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PART A: Summary of Updated Data from ENVISION OLE (Month 36)

Data is only be provided for the full AHP population.
An update of all key primary, secondary, and exploratory endpoints including:

- annualized attack rate (AAR)
- proportion of patients with zero attacks
- urinary aminolevulinic acid (ALA)
- porphobilinogen (PBG)
- annualized days of hemin use
- 12-Item Short Form Survey (SF-12)
    - PCS
    - MCS
    - Domains
- EQ-5D VAS and index scores
- Porphyria Patient Experience Questionnaire (PPEQ) (Please note data were only collected through Month 24).
- Need for caregiver
- Safety outcomes

When possible, we will provide 6-month, 18-month and 36-month data together in a table or graph for ease of interpretation.

For the following endpoints it was not possible to present data:

- Patient Global Impression of Change (PGIC)
    - PGIC was not collected beyond month 12 as per ENVISION protocol and has therefore not been included in this summary.
- Mean proportion of days with opioid use
    - This data was not accurately captured after month 12, as it was captured via electronic diaries that measured daily worst pain. Therefore, we do not present any data beyond 12 months.

1.1 Efficacy: Annualized attack rate (AAR)

The median AAR for the porphyria attack composite endpoint (ie, porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home) in the All Givosiran group through Month 36 was [redacted] (Table 1). For reference, the median historical composite AAR for the All Givosiran group was 8.0. The difference between the median historical composite AAR and median AAR for the porphyria attack composite endpoint during givosiran treatment represents an overall reduction of [redacted]%.

Continued treatment with givosiran in the OLE period led to sustained and further reduction in the porphyria attack composite endpoint and the average number of composite attacks per patient in 3-month intervals over time (Table 1 and Figure 1, respectively). The median AAR for the porphyria attack composite endpoint in the givosiran/givosiran group was 0.36 throughout givosiran treatment in the DB and OLE period compared to the median AAR of 1.04 after givosiran treatment during the 6-month DB period (Table 1).

The placebo/givosiran group had similar reductions in AAR for the porphyria attack composite endpoint during givosiran treatment as the givosiran/givosiran group. The median AAR for the porphyria attack composite endpoint during givosiran treatment in the placebo/givosiran group was 0.87 compared to the median AAR for the porphyria attack composite endpoint of 10.65 during the DB period after 6 months of treatment with placebo (Table 1). Patients in the placebo/givosiran group also experienced rapid and sustained reductions in the average number of composite attacks per patient in 3-month intervals following a similar time course as observed for patients in the givosiran/givosiran group during the DB period (Figure 1).

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[redacted]

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

AAR	Placebo/Givosiran (N=46)	Givosiran/Givosiran (N=48)	All Givosiran (N=94)
Baseline			
Median (Q1, Q3)	7.0 (4.0, 14.0)	8.0 (4.0, 18.0)	8.0 (4.0, 16.0)
Mean (SD)	10.7 (9.2)	12.1 (9.0)	11.4 (9.1)
Month 6 (DB period)			
n	46	48	48
Median (Q1, Q3)	10.65 (2.24, 25.93)	1.04 (0, 6.35)	1.04 (0, 6.35)
Mean (95% CI)	12.26 (9.22, 16.29)	3.35 (2.37, 4.74)	3.35 (2.37, 4.74)
Month 18 (OLE)			
n	45[b]	48	93[b]
Median (Q1, Q3)[a]	1.62 (0, 2.94)	0.58 (0, 3.24)	0.72 (0, 3.13)
Mean (SEM)[c]	2.44 (0.49)	2.54 (0.62)	2.50 (0.42)
Month 36 (OLE)			
n	[redacted]	[redacted]	[redacted]
Mean total number of attacks (SEM)	[redacted]	[redacted]	[redacted]
Total follow-up time (person-years)	[redacted]	[redacted]	[redacted]
Median (Q1, Q3)[a]	[redacted]	[redacted]	[redacted]

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AAR	Placebo/Givosiran (N=46)	Givosiran/Givosiran (N=48)	All Givosiran (N=94)
Mean (SEM)[c]	[redacted]	[redacted]	[redacted]

Abbreviations: AAR=annualized attack rate; CI=confidence interval; CSR=clinical study report; DB=double-blind; NA=not applicable; OLE=open-label extension; (Q1,Q3)=interquartile range; SD=standard deviation; SEM=standard error of mean
Notes: Placebo/givosiran includes patients who received placebo in the DB period and givosiran in the OLE period, including data only post givosiran treatment. Givosiran/givosiran includes patients who received givosiran in the DB and OLE periods. All Givosiran 2.5 mg/kg includes patients who received givosiran 2.5 mg/kg once monthly in either the DB or OLE periods (as the first dose).
a Calculated from the individual patient's AAR.
b One patient [redacted] whose follow-up duration after taking givosiran <85 days was excluded from the analysis.
c Duration-weighted mean AAR is presented. Standard error of the mean is calculated using Cochran's formula (1977).

1.2 Efficacy: Proportion of patients with zero attacks

An intrapatient analysis for patients in the givosiran/givosiran group comparing the AAR for the porphyria attack composite endpoint between the OLE and DB periods showed a mean reduction of 51%, indicating additional improvement in the reduction of composite porphyria attacks with continued givosiran treatment through Month 36 (Table 2). When analyzed by 3-month intervals, the proportion of patients in the givosiran/givosiran group who were attack-free continued to increase over time with [redacted] of patients with zero attacks at Month >33-36 ([redacted]).

An intrapatient analysis for patients in the placebo/givosiran group comparing AAR for the porphyria attack composite endpoint during the OLE period (while receiving givosiran) and the DB period (while receiving placebo) showed a mean reduction of [redacted] (Table 2). Similar to the givosiran/givosiran group, when analyzed by 3-month intervals, the proportion of patients in the placebo/givosiran group who were attack-free continued to increase over time with [redacted] of patients with zero attacks at Month >33-36 [redacted]).

[redacted]

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Table 2. Intrapatient Comparison of Porphyria Attack Composite Endpoint During Placebo and Givosiran Treatment (Placebo/Givosiran Patients in the All Givosiran Treated Set)

	All Placebo/Givosiran (n=46)		All Givosiran/Givosiran (n=47)	
	DB Period	OLE Period [a]	DB Period	OLE Period
Total Number of Attacks, Mean	297	[redacted]	90	[redacted]
Total Follow-up Time (years)	21.2	[redacted]	21.9	[redacted]
Number of Patients with 0 Attacks, n (%)	8 (17.4)	[redacted]	23 (48.9)	[redacted]
Mean AAR	14.01	[redacted]	4.13	[redacted]
Median AAR (Q1, Q3)	10.65 (2.24, 25.93)	[redacted]	2.08 (0.00, 6.48)	[redacted]
AAR Rate Ratio [b] (OLE vs DB), 95% CI	[redacted]		[redacted]	

Abbreviations: AAR=annualized attack rate; BL=baseline; CI=confidence interval; DB=double-blind; M=month; OLE=open-label extension; (Q1, Q3)=interquartile range
Notes: The DB period spanned from BL to the M6 visit. The OLE period spanned from the M6 visit through the M36 visit.
a One patient ([redacted]) whose follow-up duration after taking givosiran <85 days was excluded from the descriptive summaries. This patient was included in the negative binomial regression analysis.
b The rate ratio and the corresponding 95% CI for comparing AAR during DB period and AAR during OLE period using the negative binomial regression model with period as a fixed effect and patient as a random effect with exchangeable working correlation matrix, and the logarithm of the follow-up time as an offset variable. A rate ratio <1 represents a favorable outcome for OLE period.

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1.3 Efficacy: Urinary aminolevulinic acid (ALA)

Sustained reduction of urinary ALA levels was observed in the givosiran/givosiran group throughout givosiran treatment (Figure 5) with a median reduction from baseline of [redacted] at Month 36.

Patients in the placebo/givosiran group had rapid and sustained reductions in ALA levels with a time course similar to that observed in givosiran patients in the DB period (Figure 5). Near maximal reduction in ALA was achieved within 2 weeks of crossing over to givosiran treatment, with a median reduction from baseline of [redacted]%. Continued treatment further reduced ALA levels, with a median reduction from baseline of [redacted]% after 30 months of treatment (OLE period).
Intrapatient comparisons conducted in the placebo/givosiran group demonstrated reductions in urinary ALA levels during givosiran treatment compared to placebo treatment, with a median reduction of [redacted] mmol/mol Cr.

[redacted]

1.4 Efficacy: Porphobilinogen (PBG)

Sustained reduction of urinary PBG levels was observed in patients in the givosiran/givosiran group throughout givosiran treatment with a median reduction from baseline of [redacted]% at Month 36.

Patients in the placebo/givosiran group had rapid and sustained reductions in PBG levels with a time course similar to that observed in givosiran patients in the DB period. Near maximal reduction in PBG was achieved within 2 weeks of crossing over to givosiran treatment, with a median reduction from baseline of [redacted]%. Continued treatment further reduced PBG levels, with a median reduction from baseline of [redacted]% after 30 months of treatment (OLE period).

Intrapatient comparisons conducted in the placebo/givosiran group demonstrated reductions in urinary PBG levels during givosiran treatment compared to placebo treatment, with a median reduction of [redacted] mmol/mol Cr.

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1.5 Efficacy: Annualized days of hemin use

The median annualized days of hemin use in the All Givosiran group was [redacted] (Table 3). For reference, the median annualized days of hemin use for givosiran and placebo patients during the DB period were 0 and 14.98, respectively (Table 3).

Continued treatment with givosiran in the OLE period led to sustained reduction in annualized days of hemin use by patients in the givosiran/givosiran group. There were [redacted] median annualized days of hemin use by patients in the givosiran/givosiran group during givosiran treatment through Month 36 (Table 3).

The placebo/givosiran group had similar reductions in annualized days of hemin use during givosiran treatment as the givosiran/givosiran group. The median annualized days of hemin use in the placebo/givosiran group was [redacted] during the OLE period through Month 36 compared to 14.98 median annualized days of hemin use during the DB period after 6 months of treatment with placebo (Table 3).

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Table 3. Summary of Days of Hemin Use During Givosiran Treatment (All Givosiran Treated Set)

Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
During DB Period			
Median annualized days of hemin use (Q1, Q3)	[redacted]	[redacted]	[redacted]
Mean annualized days of hemin use (95% CI)	[redacted]	[redacted]	[redacted]
During Givosiran Treatment			
n	[redacted]	[redacted]	[redacted]
Mean total number of days of hemin use mean (SEM)	[redacted]	[redacted]	[redacted]
Total follow-up time (years)	[redacted]	[redacted]	[redacted]
Median annualized days of hemin use (Q1, Q3)	[redacted]	[redacted]	[redacted]
Mean duration-weighted annualized days of hemin use (SEM)	[redacted]	[redacted]	[redacted]

Abbreviations: CI=confidence interval; CSR=clinical study report; DB=double-blind; NA=not applicable; OLE=open-label extension; (Q1, Q3)=interquartile range; SEM=standard error of mean

Notes: Placebo/givosiran includes patients who received placebo in the DB period and givosiran in the OLE period, including data only post-givosiran treatment. Givosiran/givosiran includes patients who received givosiran in the DB and OLE periods.

[a] One patient [redacted] whose follow-up duration after taking givosiran <85 days was excluded from the analysis.

[b] Duration-weighted mean annualized days of hemin use is presented. Standard error of the mean is calculated using Cochran's formula (1977).

An intrapatient analysis for patients in the placebo/givosiran group comparing annualized days of hemin use during the OLE period (while receiving givosiran) and the DB period (while receiving placebo) showed a mean reduction of [redacted] (Table 4). Similar to the givosiran/givosiran group, when analyzed by 3-month intervals, the proportion of patients in the placebo/givosiran group who did not use hemin continued to increase over time with [redacted] of patients with zero hemin use at Month >33-36 ([redacted]).

An intrapatient analysis for patients in the givosiran/givosiran group comparing the annualized days of hemin use between the OLE and DB periods showed a mean reduction of [redacted], indicating additional improvement in annualized days of hemin use during long-term givosiran treatment (Table 4). When analyzed by 3-month intervals, the proportion of patients in the givosiran/givosiran group who did not use hemin continued to increase over time with [redacted] of patients with zero hemin use at Month >33-36 [redacted]).

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Table 4. Intrapatient Comparison of Annualized Days of Hemin During Placebo and Givosiran Treatment (All Givosiran Treated Set)

	All Placebo/ Givosiran (N=46)		All Givosiran/ Givosiran (N=47)	
	DB Period	OLE Period [a]	DB Period	OLE Period
Total Number of Days of Hemin Use	591	[redacted]	227	[redacted]
Total Follow-up Time (years)	21.2	[redacted]	21.9	[redacted]
Number of Patients with 0 Days Hemin Use, n (%)	12 (26.1)	[redacted]	25 (53.2)	[redacted]
Median Annualized Days of Hemin Use (Q1, Q3)	16.24 (0.00, 45.39)	[redacted]	0.00 (0.00, 12.74)	[redacted]
Mean Annualized Days of Hemin Use	27.90	[redacted]	10.42	[redacted]
Intrapatient Rate Ratio (OLE vs DB) 95% CI [b]	[redacted]		[redacted]	

Abbreviations: DB=double-blind; CI=confidence interval; OLE=open label extension; (Q1, Q3)=interquartile range
Notes: The DB period spanned from baseline to the M6 visit. The OLE period spanned from the M6 visit through the M36 visit.
a One patient ([redacted]) whose follow-up duration after taking givosiran <85 days was excluded from the descriptive summaries. This patient was included in the negative binomial regression analysis.
b The rate ratio and the corresponding 95% CI for comparing annualized days of hemin use during the DB period and that during the OLE period using the negative binomial regression model with period as a fixed effect and patient as a random effect with exchangeable working correlation matrix, and the logarithm of the follow-up time as an offset variable. A rate ratio <1 represents a favorable outcome for the OLE period.

[redacted]

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1.6 Efficacy: SF-12

1.6.1 Physical Component Summary (PCS)

Overall, treatment with givosiran led to an improvement (increase) in the PCS score of the SF-12 for patients in the All Givosiran group. At baseline, the median PCS score for the All Givosiran group was 40.400. Following 6, 12, and 30 months of givosiran treatment, there was an improvement in PCS score with a median increase from baseline of 4.380, 6.230, and [redacted] points, respectively (Table 5).

During the DB period, treatment with givosiran resulted in an improvement in the PCS score with a median change from baseline of 4.200 after 6 months of treatment (Table 5). Continued treatment of patients in the givosiran/givosiran group during the OLE led to additional improvement in PCS score, with a median increase from baseline of 8.905 points through Month 36 (Table 5).

The placebo/givosiran group showed similar improvement in PCS scores after 6 months of givosiran treatment in the OLE period as the givosiran/givosiran group had after 6 months of givosiran treatment in the DB period (median changes from baseline were 4.755 and 4.200 points, respectively). Continued givosiran treatment in the OLE showed additional improvement in PCS score, with a median increase from baseline of [redacted] points after 30 months (Table 5).

The mean change in SF-12 PCS score by treatment group during the DB and OLE periods of the study is shown in Figure 8. For patients in the givosiran/givosiran group, treatment with givosiran led to improvement in the mean PCS score that was sustained through Month 36. The placebo/givosiran group showed improvements in the mean PCS score within 3 months of starting on givosiran treatment in the OLE that further improved over time and was sustained through 30 months of givosiran treatment (Figure 6).

Figure 6. Mean Change from Baseline in Physical Component Summary (PCS) of SF-12 by Visit During the DB and OLE Periods (Full Analysis Set)

[redacted]

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Table 5. Change from Baseline in Physical Component Summary Score (PCS) of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Median (Q1, Q3) Baseline for Givosiran Treatment	40.530 (29.790, 47.700)	40.300 (33.070, 46.565)	40.400 (30.430, 46.590)
Median (Q1, Q3) Change from Baseline			
3 months of treatment	[redacted]	[redacted]	[redacted]
6 months of treatment	4.755 (-0.770, 12.080)	4.200 (-1.470, 12.640)	4.380 (-1.040, 12.080)
12 months of treatment	[redacted]	[redacted]	[redacted]
18 months of treatment	[redacted]	[redacted]	[redacted]
24 months of treatment	[redacted]	[redacted]	[redacted]
30 months of treatment	[redacted]	[redacted]	[redacted]
36 months of treatment	[redacted]	[redacted]	[redacted]

1.6.2 Mental Component Summary (MCS)

Treatment with givosiran led to an improvement (increase) in the MCS score of the SF-12 for the All Givosiran group. At baseline, the median (interquartile range [IQR]) MCS score for All Givosiran-treated patients was 41.145 (33.070, 48.100). Following 6, 12, and 30 months of givosiran treatment, the median (IQR) MCS score had increased to 43.780 (39.200, 50.980), 45.270 (35.830, 51.960) and [redacted] respectively (mean [IQR] change from baseline was 2.100 [-4.560, 10.780]).

For the givosiran/givosiran group, continued treatment led to improvement in the MCS score through Month 36. The median (IQR) MCS score increased from 39.020 (33.285, 47.430) at baseline to [redacted] at Month 36 (median [IQR] change from baseline was [redacted]

For the placebo/givosiran group, givosiran treatment led to improvement in the MCS score through 30 months of treatment. The median (IQR) MCS score increased from 41.950 (32.730, 51.340) at baseline (beginning of OLE period) to [redacted] after 30 months of treatment (median [IQR] change from baseline was [redacted].

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Table 6. Change from Baseline in Mental Component Summary Score (MCS) of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Median (Q1, Q3) Baseline for Givosiran Treatment	41.950 (32.730, 51.340)	39.020 (33.285, 47.430)	41.145 (33.070, 48.100)
Median (Q1, Q3) Change from Baseline			
3 months of treatment	[redacted]	[redacted]	[redacted]
6 months of treatment	2.640 (-4.310, 11.620)	6.530 (-2.030, 9.730)	6.530 (-2.030, 9.730)
12 months of treatment	[redacted]	[redacted]	[redacted]
18 months of treatment	[redacted]	[redacted]	[redacted]
24 months of treatment	[redacted]	[redacted]	[redacted]
30 months of treatment	[redacted]	[redacted]	[redacted]
36 months of treatment	[redacted]	[redacted]	[redacted]

Note: *, only includes Givo/givo data.

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1.6.3 SF-12 domains – change from baseline

The change from baseline for each of the eight domains is reported in Table 7 to Table 14.

Table 7. Change from Baseline in Bodily Pain of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Median (Q1, Q3) Baseline for Givosiran Treatment	39.690 (30.670, 39.690)	39.690 (30.670, 48.710)	39.690 (30.670, 39.690
Median (Q1, Q3) Change from Baseline			
3 months of treatment	[redacted]	[redacted]	[redacted]
6 months of treatment	9.020 (0.000, 18.040)	9.020 (0.000, 18.035)	9.020 (0.000, 18.040)
9 months of treatment	[redacted]	[redacted]	[redacted]
12 months of treatment	[redacted]	[redacted]	[redacted]
18 months of treatment	[redacted]	[redacted]	[redacted]
24 months of treatment	[redacted]	[redacted]	[redacted]
30 months of treatment	[redacted]	[redacted]	[redacted]
36 months of treatment	[redacted]	[redacted]	[redacted]

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Table 8. Change from Baseline in General Health of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Median (Q1, Q3) Baseline for Givosiran Treatment	40.795 (33.840, 47.750)	33.840 (33.840, 47.750)	33.840 (33.840, 47.750)
Median (Q1, Q3) Change from Baseline			
3 months of treatment	[redacted]	[redacted]	[redacted]
6 months of treatment	0.000 (0.000, 13.910)	5.970 (0.000, 13.910)	0.000 (0.000, 13.910)
9 months of treatment	[redacted]	[redacted]	[redacted]
12 months of treatment	[redacted]	[redacted]	[redacted]
18 months of treatment	[redacted]	[redacted]	[redacted]
24 months of treatment	[redacted]	[redacted]	[redacted]
30 months of treatment	[redacted]	[redacted]	[redacted]
36 months of treatment	[redacted]	[redacted]	[redacted]

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Table 9. Change from Baseline in Mental Health of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Median (Q1, Q3) Baseline for Givosiran Treatment	41.260 (35.530, 52.740)	41.260 (35.530, 47.000)	41.260 (35.530, 47.000)
Median (Q1, Q3) Change from Baseline			
3 months of treatment	[redacted]	[redacted]	[redacted]
6 months of treatment	5.735 (0.000, 11.470)	5.730 (0.000, 11.480)	5.730 (0.000, 11.480)
9 months of treatment	NA	5.730 (0.000, 11.470)	5.730 (0.000, 11.470)
12 months of treatment	[redacted]	[redacted]	[redacted]
18 months of treatment	[redacted]	[redacted]	[redacted]
24 months of treatment	[redacted]	[redacted]	[redacted]
30 months of treatment	[redacted]	[redacted]	[redacted]
36 months of treatment	[redacted]	[redacted]	[redacted]

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Table 10. Change from Baseline in Physical Functioning of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Median (Q1, Q3) Baseline for Givosiran Treatment	41.320 (33.450, 49.190)	41.320 (33.450, 57.060)	41.320 (33.450, 57.060)
Median (Q1, Q3) Change from Baseline			
3 months of treatment	[redacted]	[redacted]	[redacted]
6 months of treatment	0.000 (0.000, 7.870)	0.000 (0.000, 7.870)	0.000 (0.000, 7.870)
9 months of treatment	[redacted]	[redacted]	[redacted]
12 months of treatment	[redacted]	[redacted]	[redacted]
18 months of treatment	[redacted]	[redacted]	[redacted]
24 months of treatment	[redacted]	[redacted]	[redacted]
30 months of treatment	[redacted]	[redacted]	[redacted]
36 months of treatment	[redacted]	[redacted]	[redacted]

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Table 11. Change from Baseline in Role Emotional of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Median (Q1, Q3) Baseline for Givosiran Treatment	35.490 (35.490, 51.080)	35.490 (30.290, 45.890)	35.490 (35.490, 45.890)
Median (Q1, Q3) Change from Baseline			
3 months of treatment	[redacted]	[redacted]	[redacted]
6 months of treatment	0.000 (0.000, 10.400)	0.000 (-5.190, 12.995)	0.000 (-5.190, 10.400)
9 months of treatment	[redacted]	[redacted]	[redacted]
12 months of treatment	[redacted]	[redacted]	[redacted]
18 months of treatment	[redacted]	[redacted]	[redacted]
24 months of treatment	[redacted]	[redacted]	[redacted]
30 months of treatment	[redacted]	[redacted]	[redacted]
36 months of treatment	[redacted]	[redacted]	[redacted]

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Table 12. Change from Baseline in Role Physical of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Median (Q1, Q3) Baseline for Givosiran Treatment	40.540 (32.070, 44.770)	36.300 (32.070, 40.540)	38.420 (32.070, 40.540)
Median (Q1, Q3) Change from Baseline			
3 months of treatment	[redacted]	[redacted]	[redacted]
6 months of treatment	4.230 (0.000, 8.460)	4.230 (0.000, 12.700)	4.230 (0.000, 8.470)
9 months of treatment	[redacted]	[redacted]	[redacted]
12 months of treatment	[redacted]	[redacted]	[redacted]
18 months of treatment	[redacted]	[redacted]	[redacted]
24 months of treatment	[redacted]	[redacted]	[redacted]
30 months of treatment	[redacted]	[redacted]	[redacted]
36 months of treatment	[redacted]	[redacted]	[redacted]

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Table 13. Change from Baseline in Social Functioning of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Median (Q1, Q3) Baseline for Givosiran Treatment	39.110 (30.220, 48.010)	39.110 (30.220, 43.560)	39.110 (30.220, 48.010)
Median (Q1, Q3) Change from Baseline			
3 months of treatment	[redacted]	[redacted]	[redacted]
6 months of treatment	0.000 (-8.890, 8.900)	8.890 (0.000, 17.790)	0.000 (0.000, 8.900)
9 months of treatment	[redacted]	[redacted]	[redacted]
12 months of treatment	[redacted]	[redacted]	[redacted]
18 months of treatment	[redacted]	[redacted]	[redacted]
24 months of treatment	[redacted]	[redacted]	[redacted]
30 months of treatment	[redacted]	[redacted]	[redacted]
36 months of treatment	[redacted]	[redacted]	[redacted]

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Table 14. Change from Baseline in Vitality of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Median (Q1, Q3) Baseline for Givosiran Treatment	39.230 (39.230, 49.070)	39.230 (29.390, 49.070)	39.230 (29.390, 49.070)
Median (Q1, Q3) Change from Baseline			
3 months of treatment	[redacted]	[redacted]	[redacted]
6 months of treatment	0.000 (0.000, 9.840)	0.000 (0.000, 9.840)	0.000 (0.000, 9.840)
9 months of treatment	[redacted]	[redacted]	[redacted]
12 months of treatment	[redacted]	[redacted]	[redacted]
18 months of treatment	[redacted]	[redacted]	[redacted]
24 months of treatment	[redacted]	[redacted]	[redacted]
30 months of treatment	[redacted]	[redacted]	[redacted]
36 months of treatment	[redacted]	[redacted]	[redacted]

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1.7 Efficacy: Euro Quality of Life-5 Dimension-5 Level Questionnaire (EQ-5D-5L)

Treatment with givosiran led to an improvement (increase) in the EQ VAS score for the All Givosiran group. At baseline, the median (IQR) EQ VAS score for the All Givosiran group was 70.0 (50.0, 80.0). Following 30 months of givosiran treatment, the EQ VAS score median (IQR) increase from baseline was [redacted] points, respectively.

The median (IQR) EQ VAS score for the givosiran/givosiran group increased from 60.0 (47.5, 80.0) at baseline to [redacted] at Month 36 (median [IQR] change from baseline was [redacted]

The median (IQR) EQ VAS score for the placebo/givosiran group increased from 70.0 (55.0, 80.0) at baseline at the start of the OLE period (Month 6, start of givosiran treatment) to [redacted] after 30 months of givosiran treatment (median [IQR] change from baseline was [redacted]

The mean change in EQ VAS score by treatment group during the DB and OLE periods of the study is shown in Figure 9. For the givosiran/givosiran group, continued treatment with givosiran in the OLE led to additional improvement in the mean EQ VAS score through Month 36 (Figure 7). The placebo/givosiran group showed improvement in the EQ VAS scores within 3 months of starting on givosiran treatment and continued to improve through 30 months of givosiran treatment, as indicated in Figure 7.

Figure 7. Mean Change from Baseline in Euro Quality of Life Visual Analog Scale Score by Visit During the DB and OLE Periods (Full Analysis Set)

[redacted]

Consistent with the improvement observed in VAS scores across 36 months, patients in the givosiran/givosiran group showed improvements in EQ-5D index scores relative to baseline that were sustained to Month 36 (Table 15).

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Table 15. Mean EQ-5D index values at baseline and Months 6, 12, 18, 24, 30 and 36 (latest point available) by treatment arm in the double-blind period and OLE of ENVISION

Time point	EQ-5D utility								
	Givosiran-Givosiran			Placebo			All patients		
	n	Mean	SE	n*	Mean	SE	n	Mean	SE
Baseline†	[redacted]								
Month 6†	[redacted]								
Month 12†	[redacted]				N/A‡				
Month 18†	[redacted]				N/A‡				
Month 24†	[redacted]				N/A‡				
Month 30†	[redacted]				N/A‡				
Month 36†	[redacted]				N/A‡				

Source: Alnylam, ENVISION data on file
EQ-5D: EuroQol 5-dimensions; n: number of patients who completed the questionnaire; OLE: open-label extension; SE: standard error
*In line with other analyses performed for the model, two placebo patients were excluded for protocol deviation
†Danish EQ-5D tariff; for each patient, the EQ-5D measurement at a given time-point is considered and the average utility across observations at that time point is then calculated.
‡ No observations are available for placebo during the open-label extension since all patients switched to givosiran.

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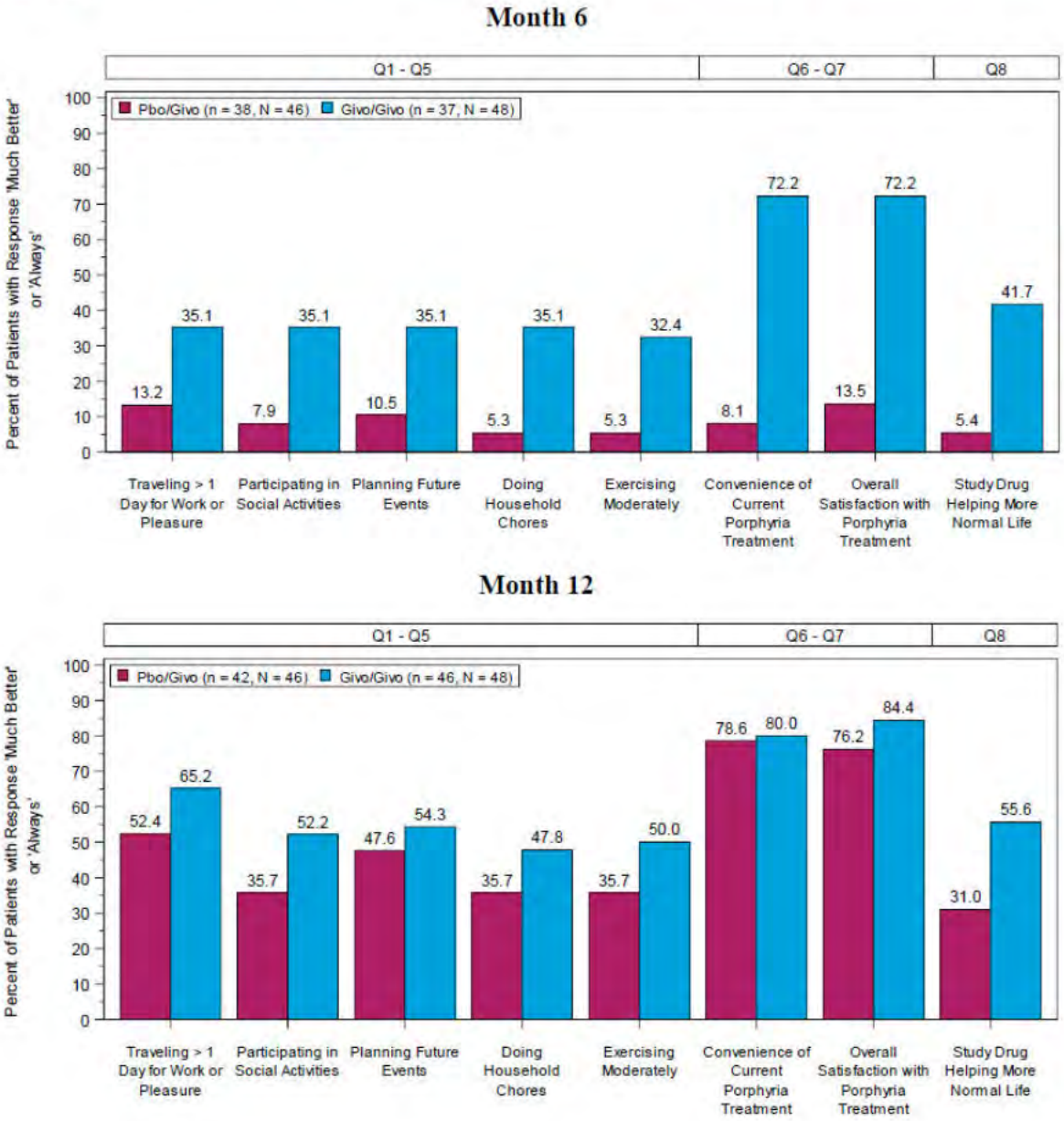
1.8 Efficacy: Porphyria Patient Experience Questionnaire (PPEQ)

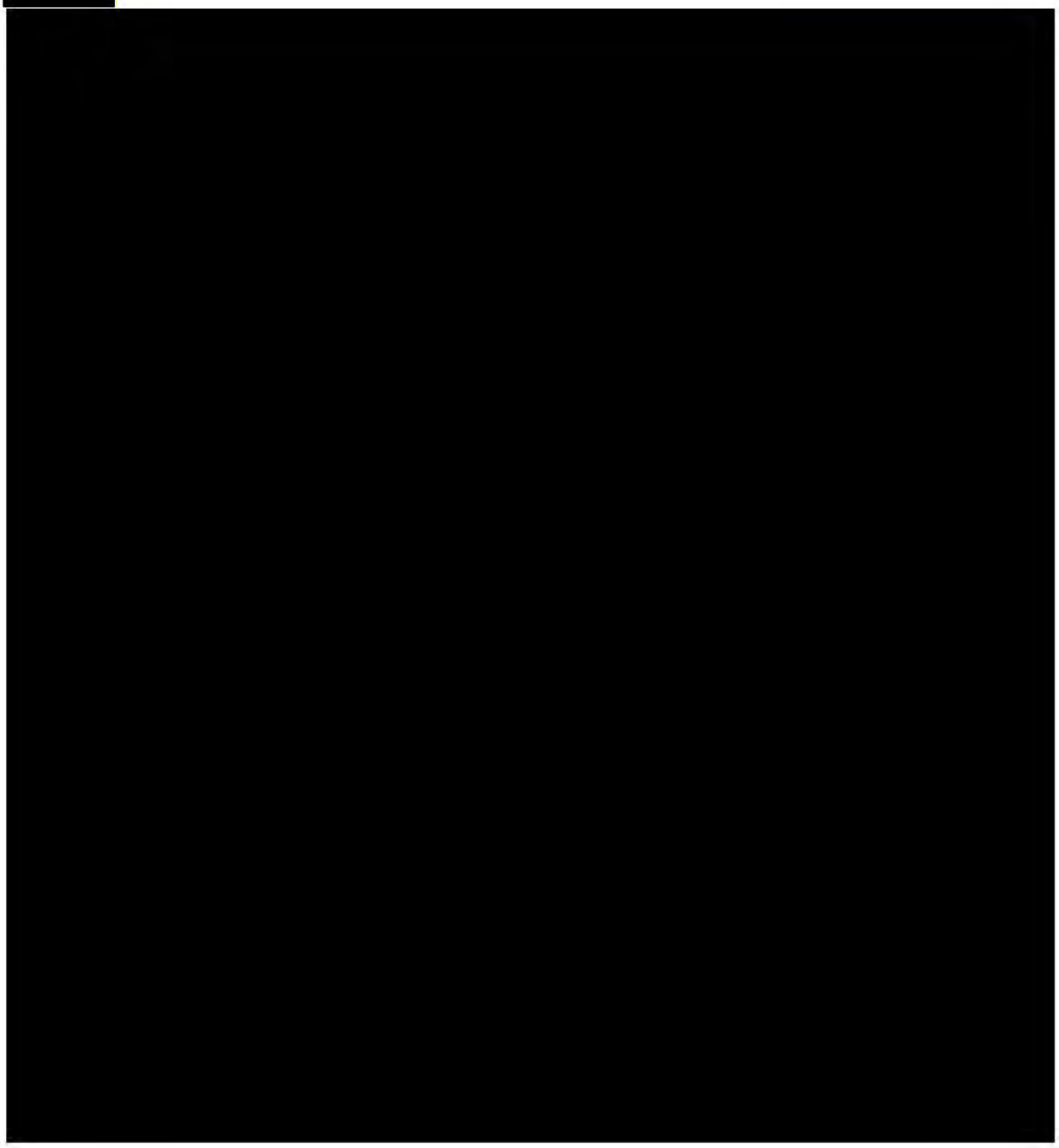
The PPEQ was a custom questionnaire to assess activities of daily living, functional status, and treatment satisfaction of patients with AHP that was assessed through Month 24.

Continued treatment with givosiran led to additional improvement in every PPEQ category over time. As seen in Figure 8 & [redacted], patients in the givosiran/givosiran group reported additional improvements in every PPEQ category from Month 6 to Month 24. Patients in the placebo/givosiran group reported similar improvements at Month 12 (after 6 months of givosiran treatment in the OLE period) as patients in the givosiran/givosiran group had at Month 6 (after 6 months of givosiran treatment; Figure 8 & [redacted]). With continued givosiran treatment through Month 24, patients in the placebo/givosiran group reported additional improvement in every PPEQ category.

Figure 8. Percentage of Patients with Much Better Ability in PPEQ During the DB and OLE Periods at Month 6 and 12 (Full Analysis Set)



[redacted]



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1.9 Efficacy: Need for caregiver

The need for caregivers appeared to be constant for both the placebo/givosiran arm and the givosiran/givosiran arm during the 36-month follow-up, with the median number of hours being 0.0 hours throughout the entire follow-up period for both arms (Table 16).

Table 16. Median number of hours assited by any caregivers in past week by visit during DB and OLE periods

Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)
Median (Q1, Q3) Baseline	[redacted]	[redacted]
[redacted]		
Month 3	[redacted]	[redacted]
Month 6	[redacted]	[redacted]
Month 9	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
Month 24	[redacted]	[redacted]
Month 30	[redacted]	[redacted]
Month 36	[redacted]	[redacted]

1.10 Safety: ENVISION and ENVISION-OLE (Month 36):

Overall, AEs were reported in [redacted] Table 17) at 36 months compared to the 89.6% in the givosiran arm at 6 months. The majority of AEs were mild or moderate in severity.

Serious AEs were reported in [redacted] and [redacted] had an SAE related to study drug treatment (Table 19). A total of [redacted] discontinued treatment due to AEs considered related to givosiran.

Three of these patients ([redacted] also withdrew from the study due to these AEs. [redacted] discontinued treatment due to an SAE of LFT abnormal (ALT >8×ULN) per prespecified protocol stopping rules and withdrew from the study after completion of the DB period.

[redacted] discontinued treatment and withdrew from the study due to SAEs of blood homocysteine increased, and concomitant SAEs of either ISR or pancreatitis during the OLE period.

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[redacted] discontinued treatment due to an AE of drug hypersensitivity during the OLE period and later stopped participation and withdrew from the study.

[redacted]

Table 17. Primary outcomes for adverse events in Safety Population (AHP) at 6 months (DB period)

Adverse events	Placebo (n=46), (%)	Givosiran (n=48), (%)	Risk Ratio (95 %CI), p-value
AE	37 (80.4)	43 (89.6)	1.11 (0.94, 1.32), p = 0.221
Study drug–related AE	12 (26.1)	22 (45.8)	1.76 (0.99 - 3.12), p = 0.055
SAE	4 (8.7)	10 (20.8)	2.40 (0.81, 7.10), p = 0.115
Study drug–related SAE	5 (10.9)	8 (16.7)	1.53 (0.54 - 4.35), p = 0.429
Severe AE	1 (2.2)	3 (6.3)	2.88 (0.31 - 26.65), p = 0.358
Study drug–related severe AE	0.5 (1.1)	3.5 (7.1)	6.71 (0.36 - 126.51), p = 0.205
Any AE leading to discontinuation of the trial regimen	0 (0.0)	1 (2.1)	2.88 (0.12, 68.89), p = 0.525
Study drug–related AE leading to discontinuation	0 (0.0)	1 (2.1)	2.88 (0.12 - 68.89), p = 0.525
Death	0	0	-

Table 18. Overall summary of AEs in the ENVISION trial and OLE from baseline to Month 36

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

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1.10.1 Common adverse events

The most common AEs (reported in ≥20% of patients) included nausea (ISR (fatigue nasopharyngitis (headache), urinary tract infection (UTI;), and upper respiratory tract infection

In general, an analysis of AEs over time by 3-month intervals showed that AEs were stable or decreased over the course of the study (Table 14.4.3.2). Hepatic AEs due to elevations of liver transaminases (ALT and AST) were primarily observed in the 3- to 5-month period after givosiran treatment was initiated. These hepatic AEs were transient in duration. There were no reports of hepatocellular carcinoma in the ENVISION and ENVISION-OLE study (36-month).

Table 19. AEs reported in ≥5% of patients in the ENVISION trial and OLE from baseline to Month 36

Adverse events N (%) patients with ≥1:	Patients, n (%)		
	Placebo/Givosiran	Givosiran/Givosiran	All Givosiran
At least 1 AE			

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Adverse events N (%) patients with ≥1:	Patients, n (%)		
	Placebo/Givosiran [redacted]	Givosiran/Givosiran [redacted]	All Givosiran [redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

1.10.2 Adverse events related to study drug

Adverse events considered related to givosiran treatment by the Investigator were reported [redacted]). As shown in Table 20, related AEs that occurred in ≥10% of patients during givosiran treatment were ISR ([redacted] nausea [redacted] and fatigue [redacted] Nearly all related events of ISR, nausea, and fatigue were nonserious and did not lead to treatment discontinuation or study withdrawal.
A total of [redacted] patients ([redacted] discontinued treatment due to AEs considered related to givosiran (SAE of LFT abnormal, SAEs of ISR and blood homocysteine increased, SAEs of pancreatitis and blood homocysteine increased, and AE of drug hypersensitivity) and [redacted] of these patients [redacted] also withdrew from the study due to AEs considered related to givosiran.

Table 20. Adverse Events Related to Study Drug in ≥5% Patients by Preferred Term During Givosiran Treatment (All Givosiran Treated Set)

Preferred Term	Number (%) of Patients		
	Placebo/Givosiran [redacted]	Givosiran/Givosiran [redacted]	All Givosiran [redacted]
At least 1 AE	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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1.10.3 Severe adverse events

Severe AEs were reported in [redacted] patients ([redacted]%). Severe AEs reported in more than 2 patients were nausea ([redacted] patients [redacted]%]), and vomiting, asthenia, device-related infection, and pulmonary embolism ([redacted] patients [redacted]%] each; Table 21). Severe AEs related to study drug were reported in [redacted] patients [redacted]%). Severe AEs considered related to study drug that were reported in 2 or more patients were asthenia and nausea ([redacted] patients [redacted]%] each), and vomiting and blood homocysteine increased [redacted] patients [redacted]%] each)

Table 21. Severe AEs reported in ≥2 patients in the ENVISION trial and OLE from baseline to Month 36

Severe adverse events N (%) patients with ≥1:	Patients, n (%)		
	Placebo/Givosiran [redacted]	Givosiran/Givosiran [redacted]	All Givosiran [redacted]
At least 1 severe AE	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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1.10.4 Serious adverse events

Serious adverse events were reported in [redacted] patients ([redacted]%), and SAEs reported in more than 1 patient were pulmonary embolism ([redacted] patients), and blood homocysteine increased, COVID-19 pneumonia, CKD, device breakage, and UTI ([redacted] patients each), see Table 22. In addition, [redacted] patients had SAEs related to elevated LFTs (reported as LFT abnormal and transaminases increased). [redacted] patients had SAEs that led to treatment discontinuation and study withdrawal (LFT abnormal; ISR and blood homocysteine increased; pancreatitis and blood homocysteine increased). Serious adverse events considered related to givosiran treatment were reported in [redacted] patients [redacted]%). Related SAEs reported in 2 or more patients were blood homocysteine increased ([redacted] patients) and SAEs related to elevated LFTs (PT terms: transaminases increased and LFT abnormal in [redacted] patient each).

Table 22. Serious Adverse Events in ≥2 Patients by Preferred Term During Givosiran Treatment (All Givosiran Treated Set)

Preferred Term	Number (%) of Patients		
	Placebo/Givosiran [redacted]	Givosiran/Givosiran [redacted]	All Givosiran [redacted]
At least 1 SAE	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE=adverse events; DB=double-blind; COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; OLE=open-label extension; PY=patient-years; SAE=serious adverse event; SOC=system organ class

Notes: Placebo/givosiran includes patients who received placebo in DB period and givosiran in OLE, including data only post-givosiran treatment. Givosiran/givosiran includes patients who received givosiran in DB and OLE periods.

If a patient experienced more than 1 events in a given category, that patient was counted only once in that category. Includes AEs occurring or worsening on or after the first dose of givosiran and through 28 days after the last dose of givosiran or any study drug-related AEs. Preferred terms are sorted by decreasing frequency in the All Givosiran column.

Based on MedDRA Version 23 0.

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1.10.5 Adverse events leading to discontinuation of Study Treatment

Overall, [redacted] patients [redacted]%) discontinued treatment due to AEs, of whom 4 patients ([redacted]%) discontinued due to treatment related AEs. The events are described by patient:

[redacted]

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1.11 Safety: Adverse events of special interest

1.11.1 Hepatic adverse events

Hepatic AEs, as characterized by elevations in serum alanine aminotransferase (ALT) levels, were more frequent in the givosiran group than in the placebo group. While there was considerable variability in ALT levels, most ALT elevations were mild to moderate in severity.

At baseline, [redacted]% of patients had medical history terms within the Hepatobiliary Disorders SOC and [redacted]% of patients reported a medical history of iron overload. A medical history of transaminases increased were reported in [redacted]% of subjects enrolled in the study. Overall, AEs mapping to the Drug-Related Hepatic Disorders SMQ were reported in 18 patients ([redacted] with [redacted] patients [redacted] having AEs within the Investigations SOC, see Table 23.

Table 23. Drug-Related Hepatic Disorders SMQ During Givosiran Treatment (All Givosiran Treated Set)

System Organ Class Preferred Term	Number (%) of Patients Placebo/Givosiran [redacted]	Givosiran/Givosiran [redacted]	All Givosiran [redacted]
At least 1 drug related hepatic disorder SMQ AE	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]
Hepatic steatosis	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]
Gamma-glutamyl transferase increased	[redacted]	[redacted]	[redacted]
Hepatic enzyme increased	[redacted]	[redacted]	[redacted]
International normalised ratio increased	[redacted]	[redacted]	[redacted]
Liver function test abnormal	[redacted]	[redacted]	[redacted]
Transaminases increased	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]
Hypoalbuminaemia	[redacted]	[redacted]	[redacted]

Abbreviations: AE=adverse event; DB=double-blind; MedDRA=Medical Dictionary for Regulatory Activities; OLE=open-label extension; PY=patient-years; SMQ=standardized MedDRA query; SOC=system organ class

Notes: Placebo/givosiran includes patients who received placebo in DB period and givosiran in OLE, including data only post-givosiran treatment. Givosiran/givosiran includes patients who received givosiran in DB and OLE periods.

If a patient experienced more than 1 event in a given category, that patient was counted only once in that category. Includes AEs that occurred or worsened on or after the first dose of givosiran and through 28 days after the last dose of givosiran or any study drug related AEs. SOCs and preferred terms within an SOC are sorted alphabetically. Based on MedDRA Version 23.0.

At Screening and baseline (Day 1), 10 patients in the givosiran/givosiran group (20.8%) and 2 patients in the placebo/givosiran group (4.3%) had ALT elevations >ULN and ≤3×ULN. During the 36-month follow-up, ALT elevations

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>3×ULN were reported in [redacted] patients [redacted]%), with [redacted] patients [redacted]%) having ALT elevations between >5 to ≤10×ULN, as illustrated in Table 24.
AST elevations >3×ULN were reported in [redacted] patients ([redacted]%) during the 36-month follow-up, with [redacted] patients ([redacted]%) having AST elevations >5 to ≤10×ULN. [redacted] of the [redacted] patients with an AST elevation >3×ULN, had a single transient AST elevation to 3.1×ULN at Month 1 without other associated LFT abnormalities at Month 1 or through study completion as illustrated in Table 24.

Table 24. Alanine aminotransferase and aspartate aminotransferase abnormalities in worst post-baseline liver function tests results during givosiran treatment and extended safety follow-up (All givosiran treated set)

Parameter Abnormality Criteria	Number (%) of Patients Placebo/Givosiran [redacted]	 Givosiran/Givosiran [redacted]	 All Givosiran [redacted]
ALT			
≤ULN	[redacted]	[redacted]	[redacted]
>ULN & ≤3×ULN	[redacted]	[redacted]	[redacted]
>3×ULN & ≤5×ULN	[redacted]	[redacted]	[redacted]
>5×ULN & ≤10×ULN	[redacted]	[redacted]	[redacted]
>10×ULN & ≤20×ULN	[redacted]	[redacted]	[redacted]
AST			
≤ULN	[redacted]	[redacted]	[redacted]
>ULN & ≤3×ULN	[redacted]	[redacted]	[redacted]
>3×ULN & ≤5×ULN	[redacted]	[redacted]	[redacted]
>5×ULN & ≤10×ULN	[redacted]	[redacted]	[redacted]
>10×ULN & ≤20×ULN	[redacted]	[redacted]	[redacted]
>20×ULN	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

A boxplot of ALT values compared to the ULN for the givosiran/givosiran group and the placebo/givosiran group by study visit is shown in [redacted]. For the givosiran/givosiran group, elevations of ALT during givosiran treatment tended to occur primarily during the DB period between 3 and 5 months after starting givosiran treatment. For the placebo/givosiran group, elevations of ALT during givosiran treatment tended to occur during the OLE period between 3 and 5 months after starting givosiran treatment at Month 6 (between visits at Month 9 and Month 11).

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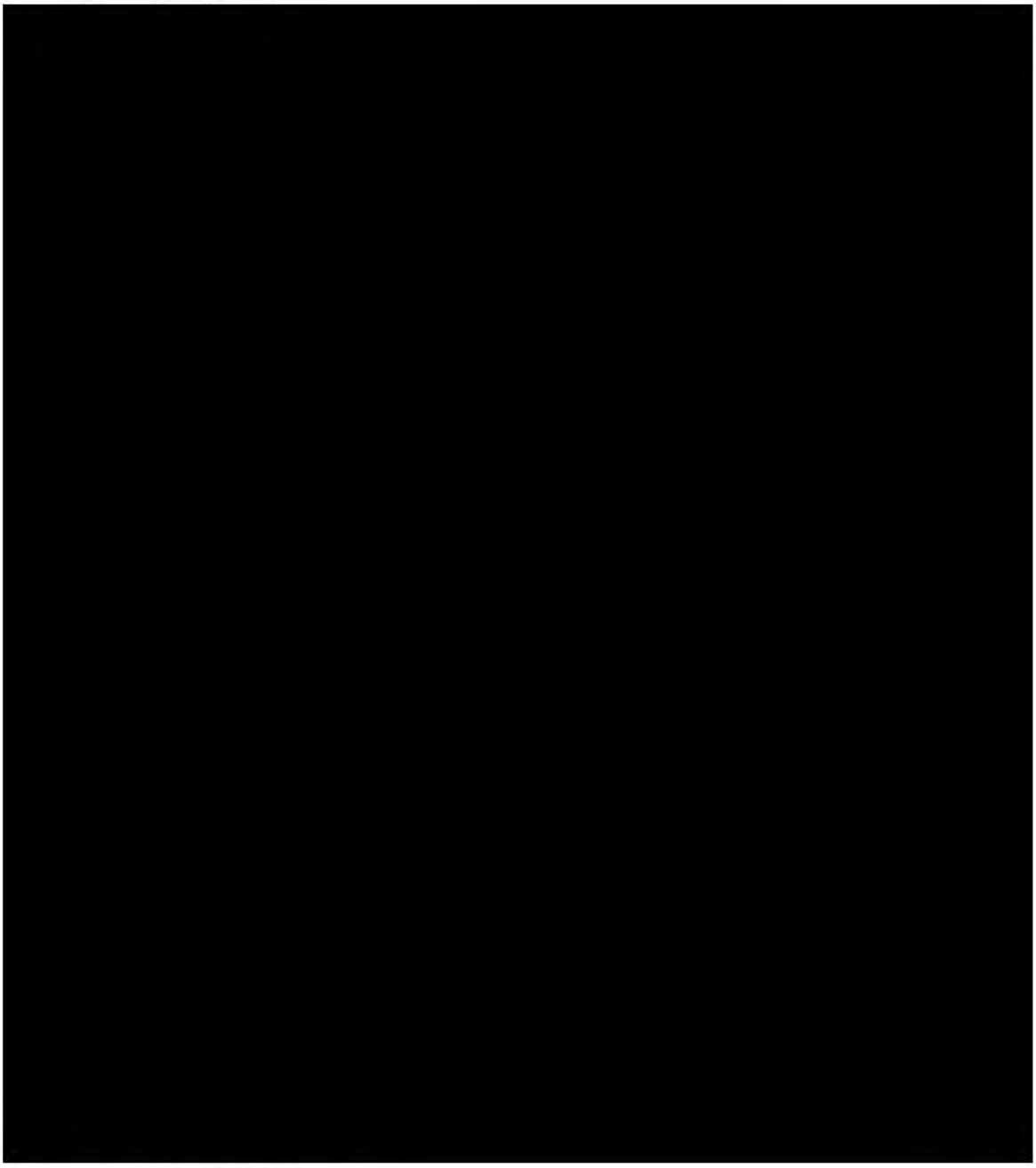
[redacted]. Box Plot of ALT Relative to Upper Limit of Normal Range by Visit During the DB and OLE Periods plus Extended Safety Follow-up (Safety Analysis Set)



Givo: givosiran; ULN: upper limit of normal.

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1.11.2 Renal adverse events

AEs mapping to the chronic kidney disease (CKD) standardized MedDRA query (SMQ) occurred in [redacted] patients ([redacted] with [redacted] patients [redacted]%) having AEs within the Investigations system organ class. The most frequent AEs occurring in ≥5% of patients were blood creatinine increased, GFR decreased, and CKD ([redacted]% each). Nearly all events were reported after increases in creatinine and/or decreases in eGFR that were detected on laboratory monitoring; most events were transient.

SAEs mapping to the CKD SMQ were reported in a total of [redacted] patients; two of which were reported during the DB period. During the DB period, 2 patients with medical histories of CKD and hypertension had SAEs of worsening CKD due to hospitalizations for further evaluation. Both patients had renal biopsies that were interpreted as consistent with the effects of co-morbidities such as hypertension, secondary Fanconi syndrome, and porphyria-associated kidney disease without evidence of adverse drug effect. Both SAEs resolved without treatment or interruption of the study drug. In addition, [redacted] with a medical history of CKD and low eGFR had an SAE of nephropathy during the OLE period that was considered not related to givosiran. At screening and baseline, the patient's eGFR was [redacted] and [redacted] mL/min/1.73 m^2, respectively. Of note, [redacted] also had a non-serious AE of nephropathy during the DB period while on placebo. The [redacted] eGFR varied during the OLE period and the [redacted] was started on hemodialysis

When assessing renal function parameters over time, there was a trend towards a decrease in eGFR, mostly at the start of treatment, that stabilized over the course of treatment (Figure 11). The onset of eGFR decreases generally occurred in the first 2 months of treatment with evidence of stabilization after 6 months of treatment.

Figure 11. Median of eGFR Test Results by Visit During Givosiran Treatment (All Givosiran Treated Set)

Abbreviations: eGFR: Estimated Glomerular Filtration Rate.

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1.11.3 Other AEs of interest

Injection-site reactions were reported in [redacted] patients ([redacted]%) and [redacted] [redacted]%) of the [redacted] total doses of givosiran administered, see Table 25. Signs and symptoms of ISRs reported in ≥5% of patients were injection site [redacted]. The majority of ISRs were non-serious AEs that were mild or moderate in severity and resolved without treatment interruption or discontinuation, with the exception of ISRs experienced by one patient.

Specifically, one patient in the placebo/givosiran 1.25 mg/kg group had recurrent ISRs that increased in severity from mild to severe during the OLE period. On Day 720, the patient had a serious ISR that was characterized by shaking chills, chest tightness, acute dyspnea, erythroderma of the face, neckline and upper arms, swelling of the hands, and an urticarial reaction on the left and right upper arms at the injection sites that occurred within the first 5 minutes after the injection. The patient was treated with dimetindene maleate and sodium chloride 0.9%, as well as cooling elements for swelling of the hands, and the event resolved in 3 hours. The event was considered definitely related to study drug and resulted in discontinuation of study drug and withdrawal from the study. The patient also was noted to have a concurrent elevation of blood homocysteine that was reported as a SAE.

Table 25. Injection Site Reactions in ≥2 Patients During Givosiran Treatment (All Givosiran Treated Set)

	Number (%) of Patients		
	Placebo/Givosiran [redacted]	Givosiran/Givosiran [redacted]	All Givosiran [redacted]
Number of patients with at least 1 ISR [a]	[redacted]	[redacted]	[redacted]
Total number of injections	[redacted]	[redacted]	[redacted]
Total number of injections complicated by ISRs	[redacted]	[redacted]	[redacted]
% of injections complicated by ISRs	[redacted]	[redacted]	[redacted]
ISR Signs and Symptoms [b]			
Injection site erythema	[redacted]	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]	[redacted]
Injection site pruritus	[redacted]	[redacted]	[redacted]
Injection site rash	[redacted]	[redacted]	[redacted]
Injection site swelling	[redacted]	[redacted]	[redacted]
Injection site bruising	[redacted]	[redacted]	[redacted]
Injection site discolouration	[redacted]	[redacted]	[redacted]
Injection site haematoma	[redacted]	[redacted]	[redacted]
Injection site induration	[redacted]	[redacted]	[redacted]

Abbreviations: AE=adverse event; CRF=case report form; DB=double-blind; HLT=high level term; ISR=injection site reaction; MedDRA=Medical Dictionary for Regulatory Activities; OLE=open-label extension; PY=patientyears

Notes: Placebo/givosiran includes patients who received placebo in DB period and givosiran in OLE, including data only post-givosiran treatment. Givosiran/givosiran includes patients who received givosiran in DB and OLE periods.

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Nausea was reported in [redacted]% of all patients, with [redacted]% in the placebo/givosiran group and [redacted]% in the givosiran/givosiran group. No nausea SAEs were reported. [redacted] nausea severe AEs were reported, [redacted] in the placebo/givosiran group and [redacted] in the givosiran/givosiran group.

Vomiting was reported in [redacted]% of all patients, with [redacted]% in the placebo/givosiran group and [redacted]% in the givosiran/givosiran group. Most events were mild or moderate in severity. [redacted] instances of severe AEs related to vomiting. No events of vomiting led to study drug interruption or discontinuation.

As acute hepatic porphyria patients have been found to have an increased risk of hepatocellular carcinoma, this is an AE of interest. During the 36-month follow-up, there were no reports of hepatocellular carcinoma.

The OLE period of the study was ongoing during the COVID-19 pandemic, however, no impact on the safety profile was observed due to the COVID-19. In total, there were [redacted] [redacted]%) patients who had AEs that mapped to the COVID-19 custom query. [redacted] of the patients had SAEs of COVID-19 pneumonia. [redacted] patients died due to COVID-19 and [redacted] of the events led to treatment discontinuation.

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PART B: Summary of Modelling Assumptions

9.1.2 List of all updated assumptions in the model and a justification for each assumption

Accompanying this document we are providing a revised version of our cost-effectiveness model (*CEM for the assessment of Givlaari (givosiran) for patients with AHP 15-03-22 v.1.0.xlsm*), which incorporates the updated assumptions described in Table 26.

Table 26. Givosiran cost-effectiveness model assumptions

Assumptions	Justification
Extrapolation of effect in givosiran arm: last observation (year 3 of OLE) carried forward up to year 5	In the latest analysis (up to Year 3), patients in the ENVISION OLE period not only maintained the improvement achieved in the double-blind period but showed continual improvement beyond the initial beneficial effect of givosiran in the double-blind period. A 5-year time point was selected as a reasonable extrapolation limit for this trend.
Piecewise approach for extrapolation of ToT curve	Givosiran ToT data are available up to Month 36, which allows more observed data points to be used to inform the probability of unplanned discontinuation in the givosiran arm. The updated model incorporates a piecewise approach proposed by the NICE Evidence Review Group, which uses the observed Kaplan–Meier curve for the period of available data followed by the best-fitting parametric model beyond the observation period (i.e. beyond Month 36).

OLE, open-label extension; ToT, time on treatment.

9.2.1 Presentation of any updated input data used in the model and how they were obtained

Table 27 presents the updated inputs for the estimation of the probability of unplanned discontinuation, updated based on Month-36 OLE data. The updated transition matrices based on Month-36 OLE data are presented in section 9.2.1.7 below.

Table 27. Summary of variables applied in the model

ToT Exponential parameter	Value	Standard error	Lower value	Upper value	PSA distribution	Source
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	Cholesky	ENVISION DB + OLE
Shape	[redacted]	[redacted]		[redacted]	Cholesky	ENVISION DB + OLE
Scale	[redacted]	[redacted]		[redacted]	Cholesky	ENVISION DB + OLE

DB, double-blind (period); OLE, open-label extension; PSA, probabilistic sensitivity analysis; ToT, time on treatment.

9.2.1.7 Transition probabilities – Givosiran

Transition probabilities in the givosiran arm of the model are estimated from observations at 6 months during the double-blind period of ENVISION and at 6-month intervals up to Month 36 during the OLE period. By 6 months, most patients had improved to the Asymptomatic or Symptomatic categories (Table 28). Of the Severe patients at study

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start, all showed AAR reductions. Similar trends for continuing reductions in AAR were observed in the OLE period through Month 36 (Table 29 – Table 33).

Table 28. Number of givosiran patients transitioning between health states from baseline to Month 6, ENVISION double-blind period

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic					
Symptomatic					
Recurrent					
Severe					
Total					

Source: Alnylam, data on file.

Table 29. Number of givosiran patients transitioning between health states from Month 6 to Month 12, ENVISION OLE period.

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic					
Symptomatic					
Recurrent					
Severe					
Total					

Source: Alnylam, data on file. OLE, open-label extension.

Table 30. Number of givosiran patients transitioning between health states from Month 12 to Month 18, ENVISION OLE period.

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic					
Symptomatic					
Recurrent					
Severe					
Total					

Source: Alnylam, data on file. OLE, open-label extension.

Table 31. Number of givosiran patients transitioning between health states from Month 18 to Month 24, ENVISION OLE period.

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic					
Symptomatic					
Recurrent					
Severe					
Total					

Source: Alnylam, data on file. OLE, open-label extension.

Table 32. Number of givosiran patients transitioning between health states from Month 24 to Month 30, ENVISION OLE period.

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic					
Symptomatic					
Recurrent					
Severe					
Total					

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Source: Alnylam, data on file. OLE, open-label extension.

Table 33. Number of givosiran patients transitioning between health states from Month 30 to Month 36, ENVISION OLE period.

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe	Total
Asymptomatic					
Symptomatic					
Recurrent					
Severe					
Total					

Source: Alnylam, data on file. OLE, open-label extension.

These transition data from the ENVISION double-blind period and OLE were used to estimate givosiran transition probabilities in the first through the sixth Markov cycles (Table 34 – Table 39).

Table 34. Givosiran health-state transition probabilities in cycle 1, based on ENVISION double-blind Month-6 data

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe
Asymptomatic				
Symptomatic				
Recurrent				
Severe				

Table 35. Givosiran health-state transition probabilities in cycle 2, based on ENVISION OLE Month-6 to Month-12 data

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe
Asymptomatic				
Symptomatic				
Recurrent				
Severe				

OLE, open-label extension.

Table 36. Givosiran health-state transition probabilities in cycle 3, based on ENVISION OLE Month-12 to Month-18 data

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe
Asymptomatic				
Symptomatic				
Recurrent				
Severe				

OLE, open-label extension.

Table 37. Givosiran health-state transition probabilities in cycle 4, based on ENVISION OLE Month-18 to Month-24 data

From \ To	Asymptomatic	Symptomatic	Recurrent	Severe
Asymptomatic				
Symptomatic				
Recurrent				
Severe				

OLE, open-label extension.

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Table 38. Givosiran health-state transition probabilities in cycle 5, based on ENVISION OLE Month-24 to Month-30 data

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

OLE, open-label extension.

Table 39. Givosiran health-state transition probabilities in cycles 6 to 10, based on ENVISION OLE Month-30 to Month-36 data

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

OLE, open-label extension.

9.2.2.2.1 Treatment discontinuation

In the context of ENVISION, treatment discontinuation represents unplanned stopping of treatment due to any reason. In the revised model, the probability of unplanned discontinuation is estimated based on the additional evidence available up to 36 months in the OLE study. The treatment discontinuation is modeled via a piecewise method proposed by the NICE Evidence Review Group, using values from the Kaplan–Meier curve for observed data followed by the best-fitting parametric function to extrapolate beyond the observed data. This piecewise method generates a ToT curve that is used in the analysis to simulate the proportion of the cohort discontinuing treatment with givosiran at each cycle of the model. After discontinuation of givosiran treatment, patients assumed to experience the transition probabilities observed in the placebo arm of ENVISION.

Data on treatment discontinuation due to any reason in patients receiving givosiran were obtained from the ENVISION double-blind and OLE periods (final data cut, for 36 months, having been updated from the 18-month data available at the time of the original submission). Beyond the trial period, ToT was extrapolated by fitting parametric models to observed time-to-event data. Akaike information criterion (AIC) and Bayesian information criterion (BIC) estimators were used to evaluate the relative quality (i.e., fit) of the parametric models considered, namely: Exponential, Weibull, Gompertz, Log-Normal, and Log-Logistic (Table 40).

Table 40. Fit statistics of parametric models to givosiran time-on-treatment data

	AIC	BIC
Exponential	110.3856	112.9289
Weibull	111.8124	116.899
Gompertz	111.9856	117.0722
Log-Normal	111.6952	116.7817
Log-Logistic	111.8108	116.8973

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

Table 41 presents the parameters used to extrapolate ToT data over time with each of the tested parametric models. The CEA uses the Exponential model, which is the best-fitting model based on the sum of AIC and BIC (Table 40).

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Table 41. Model parameters for parametric functions to extrapolate givosiran time on treatment curves

	Exponential	Weibull	Gompertz	Log-Normal	Log-Logistic
_cons	-5.231024	-5.981653	-5.519827	5.123843	4.783401
ln parameter		0.1976308		0.5021514	-0.2379529
Parameter		1.218512	0.017576	1.652272	0.7882398

9.2 Extrapolation of relative efficacy

Patients in the ENVISION OLE period through Month 36 not only maintained the improvement achieved in the double-blind period but showed continual improvement beyond the initial beneficial effect of givosiran for the entire 3 years in the latest analysis. This evidence shows that there is no indication of diminishing efficacy of givosiran treatment with prolonged use ([redacted]). On the contrary, the proportion of patients randomized to givosiran in ENVISION achieving Asymptomatic health status increased from [redacted]% at Month 6 to [redacted]% at Month 18 and [redacted]% at Month 36 [redacted]). The base-case analysis therefore extrapolates transitions up to 5 years, which was selected as a reasonable extrapolation limit for this trend. This extrapolation applies the last observed transitions from Month 30 to Month 36 (Table 39) to each model cycle from cycle 7 until cycle 10 (i.e. for 2 additional years beyond the last observed data at Year 3). After that point, the cohort is assumed to remain stable (i.e., no further transitions between alive AHP severity health states, though transitions to death occur). To be fully transparent, a scenario analysis has also been performed with no extrapolation beyond the 36 months of follow-up in the ENVISION double-blind and OLE periods.

[redacted]

DB, double-blind; Givo, givosiran; OLE, open-label extension; Pbo, placebo.

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[redacted]

OLE, open-label extension.

PART C: Summary of Updated Model Results

9.6.2 Base-case results

The base-case results (discounted) for givosiran compared with BSC in terms of life-years gained, QALYs, costs and ICER (per QALY) from the restricted societal perspective in Denmark are presented in Table 42. Givosiran compared with BSC yields a discounted ICER of DKK[redacted]/QALY.

Table 42. Base-case results

Per patient	Givosiran	BSC	Difference
Life-years gained			
Total	[redacted]	[redacted]	[redacted]
Asymptomatic	[redacted]	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
QALYs			
Total	[redacted]	[redacted]	[redacted]
Asymptomatic	[redacted]	[redacted]	[redacted]
Symptomatic	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]

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Per patient	Givosiran	BSC	Difference
Costs			
Total	[redacted]	[redacted]	[redacted]
Drug	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Chronic symptoms	[redacted]	[redacted]	[redacted]
Attacks	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
Opioid addiction	[redacted]	[redacted]	[redacted]
Transportation cost	[redacted]	[redacted]	[redacted]
Use of time	[redacted]	[redacted]	[redacted]
EOL	[redacted]	[redacted]	[redacted]
Incremental results	**Givosiran vs. BSC**		
ICER (per QALY)	[redacted]		

AE, adverse event; BSC, best supportive care; EOL, end of life; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

9.7.1 Scenario Analyses

Outcomes of various scenario analyses relative to the base case are summarised in Table 43. The detailled description of each scenario is reported in the originally submitted dossier, with the exception of Scenario 1 which has been updated and is described below. Moreover, following DMC's request, an updated version of the model was submitted in August 2021 which did not include caregiver disutility. Since the current base case therefore does not consider caregiver disutility, the related scenario analysis became irrelevant and it is not included in the Table below.

Table 43. Outcomes of scenario analyses relative to the base case

#	Scenario	Incremental Costs (DKK)	Incremental QALYs	ICER	% change
0	Base case	[redacted]	[redacted]	[redacted]	[redacted]
1	Givosiran efficacy: no recycling of effect past Year 3	[redacted]	[redacted]	[redacted]	[redacted]
2	BSC efficacy: DB ENVISION for cycle 1, then probability of disease worsening up to Year 5	[redacted]	[redacted]	[redacted]	[redacted]

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#	Scenario	Incremental Costs (DKK)	Incremental QALYs	ICER	% change
3	Mortality scenario analysis	[redacted]	[redacted]	[redacted]	[redacted]
4	Alternative assumption for prevalence of chronic conditions	[redacted]	[redacted]	[redacted]	[redacted]
5	Vial sharing for givosiran administration	[redacted]	[redacted]	[redacted]	[redacted]

BSC, best supportive care; DB, double-blind; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Scenario 1: Alternative extrapolation of Givosiran efficacy: no recycling beyong observation period (36 months)

In the base case, the model assumes that the transition probabilities observed in the ENVISION OLE period continue over time beyond the duration of the OLE period. A 5-year time point was selected as a reasonable extrapolation limit for this trend. After that point, the cohort is assumed to remain stable (i.e., no further transitions between AHP severity health states, though transitions to death occur). To address the uncertainty regarding extrapolation of treatment effects beyond observed data for givosiran, a scenario analysis was performed in which no recycling of effect is assumed beyond the observation period (i.e. beyond Year 3). From cycle 7 of the model patients on givosiran are assumed to remain stable unless they die.

PART D: Summary of Updated Budget Impact Results

9.3 Budget Impact Results

Based on the base case settings, the estimated budget impact of recommending givosiran as standard treatment in Denmark at PPP was DKK 8,004,619 in Year 1, decreasing to DKK 4,698,640 in Year 5, as shown in Table 44.

Table 44. Expected budget impact of recommending givosiran

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommended (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients on givosiran treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recommended (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients on givosiran treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Response document for DMC

Concerning follow-up questions from the submission of the 36-month ENVISION OLE update, for the assessment of Givlaari™ (givosiran) for patients with acute hepatic porphyria

NOTE: This document contains confidential information not to be published.

Confidential data for redaction are highlighted in yellow.

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DMC Request

Alnylam Pharmaceuticals on the 18th of January received a request from the DMC to provide an updated application containing the most recent data from the ENVISON OLE to support the application of Givlaari™ (givosiran) for patients with acute hepatic porphyria (AHP). After a subsequent meeting on 31st January Alnylam and the DMC agreed that Alnylam would provide:

1. An updated cost-effectiveness model (CEM) incorporating 36-month data from the ENVISION open-label extension (OLE)
2. An abbreviated document providing a summary of 36-month data from the ENVISION OLE, a summary of changes to the model made to incorporate these data, and updated CEM results
3. Provisional agreement to provide the full 36-month CSR (dependent on availability and ability to share).

Alnylam provided the response to the DMC request on 25th March.

DMC Follow-up Questions

Following the submission of the updated application, Alnylam received a list of follow-up questions from the DMC on 5 April. This document provides Alnylam's response to the DMC's follow-up questions.

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DMC Follow-up Questions

Requests for additional data

No.	Subject/Element	DMC request
1	Endpoint data	In general, please provide illustrative graphs whenever possible for all endpoints.
2	Porphyria AAR (Section 1.1, Table 1)	Please provide the confidence interval for the overall reduction in annualized attack rate (AAR) from baseline (reported as [redacted]). In table 1, please use the same method to quantify the uncertainty (CI/SE/SEM).
3	SF12 domain scores (Tables 7 to 14)	It is very difficult to interpret the results, as a lot of the estimates appear to be identical. Please ensure that estimates are correct. If possible, please provide illustrative graphs to ease the interpretation of data.
4	PGIC	You state that data until 12 months have been collected. However, in earlier versions of the application, only data at 6 months have been provided. Please provide data at 12 months.
5	PPEQ (Figure 8)	The results at 6 months differ compared to earlier versions of the application (Figure 8). Please explain the reason for this.
6	Daily worst pain/worst fatigue/nausea	Only data at 6 months have been provided in earlier versions of the application (with the exception of the proportions of patients achieving a change > 2 points in daily worst pain). Please provide data at 12 months.
7	Opioid use	Only data at 6 months have been provided in earlier versions of the application. Please provide data at 12 months.
8	Caregiver support (Section 1.9, Table 16)	In the response letter dated 24/08/2021, you state that patients with AHP on average receive support for 639.6 hours yearly. How does this correspond to the values of [redacted] hours both at baseline and at later follow ups provided in the current response letter?

Statistical issues

No.	Subject/Element	DMC request
9	Porphyria AAR (Table 1)	Why is data from the patient with shorter than 36 months of data not included with the actual person time and number of attacks, corresponding to what has been observed?
10	SF-12 PCS & MCS (Tables 5 & 6)	How has the calculations been performed? Have they been based on a model? How has missing data been handled? Results should be reported as difference in mean value and 95% CI. The number of patients at each time point should be presented.
11	SF12 domain scores (Tables 7 to 14)	Results should be presented as mean and CI, and the number of patients at each time point should be presented.
12	Discontinuation (Table 27)	Please explain how this corresponds to the data.
0	Health-state transitions (Table 34)	Symptomatic sums up to [redacted] (should be [redacted]). There should be a transition probability from symptomatic to recurrent of the same size as from symptomatic to symptomatic.

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Health economic model

No.	Subject/Element	DMC request
14	EQ-5D utility data (Table 15)	We need full information on the available EQ-5D data from ENVISION. This includes information on the number of completed EQ-5D questionnaires, the timing of collected data. Despite potential problems in using EQ-5D data from ENVISION to estimate health state utilities, we still need the estimates divided by the model's health states.
15	Health-state transitions (Table 30)	There seems to be a discrepancy between the table containing number of givosiran patients transitioning between health states from Month 12 to Month 18 (ENVISION OLE period). The information in table 30 differs from earlier versions of your application. Please explain way this is the case.
16	Health-state transitions	The distribution of patients between health-states at month 18 differs from earlier versions of the application. Please explain the reason for this.

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Response to DMC follow-up questions

1. In general, please provide illustrative graphs whenever possible for all endpoints

All data within the scope of the initial DMC request have been presented in tables, in the most relevant form (number of patients, mean values, % change from baseline, etc.). Where graphs are readily available and will be informative, these have also been provided. The 36-month update includes a total of 44 tables. Producing additional graphs where these do not already exist, across all endpoints, would require considerable additional resources to specify, generate and quality check. Due to internal resource constraints, it has not been possible at this stage to provide additional graphs for illustrative purposes only.

2. Please provide the confidence interval for the overall reduction in annualized attack rate from baseline (reported as [redacted] %). In Table 1, please use the same method to quantify the uncertainty (confidence interval, standard error, SEM).

Statistical testing was not applied to the change from baseline in the annualized attack rate (AAR) for the porphyria attack composite endpoint up to 36 months. Statistical testing, including confidence intervals, was only applied for the formal endpoint up to 6 months.

3. It is very difficult to interpret the results of Tables 7 to 14, as a lot of the estimates appear to be identical. Please ensure that estimates are correct. If possible, please provide illustrative graphs to ease the interpretation of data.

The data for SF-12 summary scores (PCS and MCS) and domain scores (PF, RP, BP, GH, VT, SF, E, MH) were presented in the 36-month update as median change from baseline (with inter-quartile range) in Tables 7 to 14. Summary graphs have been provided in [redacted] to aid interpretation. These graphs include data for the 6-month period of placebo treatment for placebo/givosiran patients in the double-blind phase of the trial.

[redacted]

[redacted]

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[redacted]

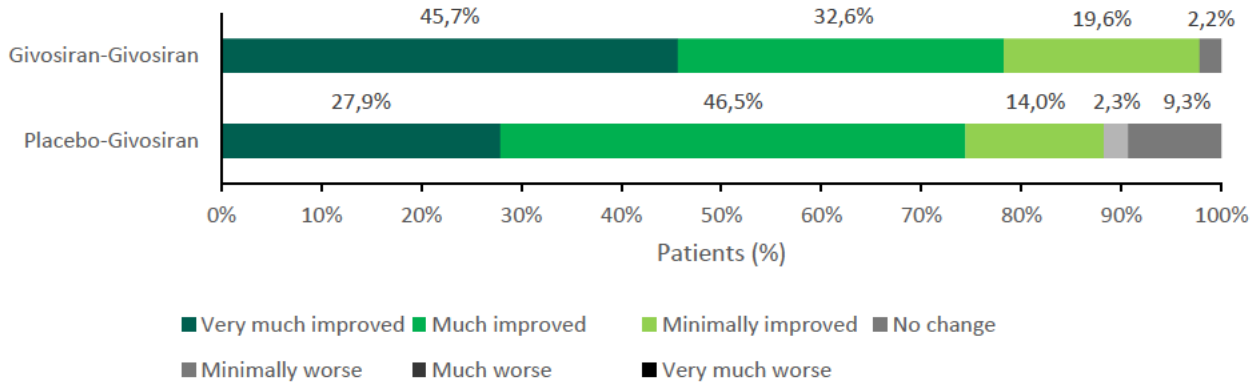
All tables for SF-12 domain scores have been quality checked. The SF-12 is a shorter, 12-item version of the SF-36. The SF-12 has two summary scores (PCS and MCS) and 8 domain scores (PF, RP, BP, GH, VT, SF, E, MH). The domain scores are reported in Tables 7 to 14 of the 36-month update. Although SF-12 domain scores have a potential range from 0 to 100, each domain score is calculated via an algorithm, from the responses from one or more of the 12 questions within the survey. Within the SF-12 survey, each question has a fixed number of categorical responses (from two up to six) [1, 2]. This in turn produces a limited number of final values for domain scores. This explains the presence of values in the table that appear numerically precise, but are the same across different groups/periods.

4. You state that PGIC data until 12 months have been collected. However, in earlier versions of the application, only data at 6 months have been provided. Please provide data at 12 months.

Data for patient global impression of change (PGIC) were only provided up to 6 months in the original 18-month submission. No further data cuts were provided in the 36-month update since PGIC data were not collected at 36 months.

At Month 12, using the PGIC instrument, 78.3% of givosiran-treated AHP patients and 74.4% of placebo crossover patients reported that their condition was 'Very much improved' or 'Much improved'. PGIC data are presented at 12 months in Figure 2 below.

Figure 2: PGIC at 12 months (Full Analysis Set)



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As explained in Part A of the 36-month response document, PGIC was not collected beyond month 12, as specified in the ENVISION trial protocol. Therefore, no further data can be provided beyond this time point.

5. PPEQ results at 6 months differ compared to earlier versions of the application (Figure 8). Please explain the reason for this.

The graph presented for the Porphyria Patent Experience Questionnaire (PPEQ) in Figure 8 of the 36-month update was revised to correct an error in the original submission. The first seven items in the PPEQ have a five-point change rating scale (much better, minimally better, no change, minimally worse, and much worse). The eighth item inquires about how often subjects felt the study drug was helping them to return back to a more normal life (always, most of the time, sometimes, rarely, and never). In the original submission, the graph for the last element of the PPEQ, "Study drug helping more normal life", reported the percentage of patients responding "Always" or 'Most of the time". In the revised graph in the 36-month update, only the percentage of patients responding "Always" is reported.

6. For daily worst pain/worst fatigue/nausea, only data at 6 months have been provided in earlier versions of the application (with the exception of the proportions of patients achieving a change > 2 points in daily worst pain). Please provide data at 12 months.

These data were only provided up to 6 months in the original 18-month submission. No further data were reported in the 36-month update as an extension of the reporting period was not specifically requested by the DMC following the original 18-month submission. Worst pain, worst fatigue and worst nausea were all reported using area-under-curve methods at 6 months, as part of the pre-specified statistical analysis plan for ENVISION. Calculating, reporting and quality checking 12-month data using the same methods would be a new, one-off analysis that would take a disproportionate amount of additional time and resources to complete.

7. For opioid use, only data at 6 months have been provided in earlier versions of the application. Please provide data at 12 months

Mean proportion of days with opioid use was only provided up to 6 months in the original 18-month submission. No further update was provided in the 36-month update. Opioid use data are presented through 6 months and 12 months in Table 1 below.

Table 1: Mean proportion of days with opioid use (All Givosiran Treated Set)

Mean (SD)	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)
Month 6	35.6 (39.3)	23.1 (34.7)
Month 12	30.4 (36.76)	22.3 (33.0)

As explained in Part A of the 36-month response document, opioid use data were not accurately captured after month 12, as they were recorded via electronic diaries that measured daily worst pain. Therefore, no data are presented beyond 12 months.

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8. In the response letter dated 24/08/2021, you state that patients with AHP on average receive caregiver support for 639.6 hours yearly. How does this correspond to the values of [redacted] hours both at baseline and at later follow ups provided in the current response letter?

The response letter of 24/08/2021 discusses average caregiver time per year, which was calculated from the baseline mean weekly caregiver hours reported. The 36-month update reported median weekly caregiver hours. Because of significant right skew in the distribution of caregiver hours, mean weekly hours at baseline takes a positive value, while the median remains [redacted]—the majority of patients received [redacted] hours of assistance from caregivers, but a significant minority reported positive values. Mean weekly caregiver hours, at baseline and 3-monthly intervals, are reported in [redacted] below.

[redacted]

Mean (SD)	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)
Baseline	[redacted]	[redacted]
Month 3	[redacted]	[redacted]
Month 6	[redacted]	[redacted]
Month 9	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
Month 24	[redacted]	[redacted]
Month 30	[redacted]	[redacted]
Month 36	[redacted]	[redacted]

9. For Table 1, why is data from the patient with shorter than 36 months of data not included with the actual person time and number of attacks, corresponding to what has been observed?

In the 36-month update, Table 1 included a footnote explaining that one patient (Patient [redacted] with a follow-up duration after taking givosiran <85 days was excluded from the analysis. This patient was a crossover patient who withdrew from the trial. The ENVISION statistical analysis plan specified that, to avoid unstable estimation from limited duration of follow-up, the AAR would only be calculated for patients with at least 85 days of follow-up during the OLE period. One patient (Patient [redacted]) met this criterion and so was excluded from the AAR analysis per the SAP.

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10. How have the calculations been performed for SF-12 PCS & MCS? Have they been based on a model? How has missing data been handled? Results should be reported as difference in mean value and 95% CI. The number of patients at each time point should be presented.

The SF-12 questionnaire is a reduced form of the full SF-36 health survey, developed to reduce respondent burden. The SF-12 has twelve survey items that are used to produce two summary scores (PCS and MCS), representing physical and mental health, and 8 domain scores (PF, RP, BP, GH, VT, SF, E, MH). The steps involved in the calculation of the PCS and MCS summary scores have been described for the original version of the SF-12 by Ware et al [3] and published resources are available that can calculate scores [4]. A later version of the SF-12, the SF-12v2, was used in the ENVISION trial. The calculation of PCS and MCS summary scores for SF-12v2 follow the same essential steps, but use a revised scoring algorithm. The calculated SF-12 scores (e.g., PCS and MCS) for ENVISION were obtained using PRO CoRE 1.3 Smart Measurement® System software with the 2009 U.S. general population t-scores applied. The detailed scoring algorithm is proprietary to QualityMetric, who own the intellectual property of the SF-12v2 health survey. Any survey with a missing value for individual items is classified as missing overall in PCS and MCS summary scores.

In the 36-month update, mean change from baseline in PCS summary scores was reported in Figure 6, with median baseline values and change from baseline reported in Table 5. For MCS, median baseline values and change from baseline were reported in Table 6.

Mean values for PCS and MCS are provided in [redacted] and [redacted] below. Confidence intervals were not calculated for these data, since this was not specified within the statistical analysis plan for the ENVISION trial. Producing this analysis at this late stage would take considerable additional time and resources.

[redacted]

Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Baseline for Givosiran Treatment	Mean	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
3 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
6 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
12 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
18 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]

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Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
24 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
30 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
36 months of treatment	Mean difference		[redacted]	[redacted]
	SD		[redacted]	[redacted]
	n		[redacted]	[redacted]

Note: *, only includes Givo/givo data.

[redacted]

Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Baseline for Givosiran Treatment	Mean	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
3 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
6 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
12 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
18 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
24 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
30 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]

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Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
36 months of treatment	Mean difference		[redacted]	[redacted]
	SD		[redacted]	[redacted]
	n		[redacted]	[redacted]

Note: *, only includes Givo/givo data.

11. Results for SF-12 domain scores should be presented as mean and confidence interval, and the number of patients at each time point should be presented.

In the 36-month update, SF-12 domain scores were reported as median change from baseline. Mean difference in SF-12 scores are provided in [redacted] below, in summary graphs to aid interpretability, in line with Question 3 above. These graphs include data for the 6-month period of placebo treatment for placebo/givosiran patients in the double-blind phase of the trial.

[redacted]

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Mean difference, standard deviation and number of patients responding are provided for each of the SF-12 domains in Table 5 toTable 12 below. Confidence intervals were not calculated for these data, since this was not specified within the statistical analysis plan for the ENVISION trial. Producing this analysis at this late stage would take considerable additional time and resources to complete.

Table 5: Change from Baseline in Physical Functioning score of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Baseline for Givosiran Treatment	Mean	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
3 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
6 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
12 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
18 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
24 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]

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Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
30 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
36 months of treatment	Mean difference		[redacted]	[redacted]
	SD		[redacted]	[redacted]
	n		[redacted]	[redacted]

Note: *, only includes Givo/givo data.

Table 6: Change from Baseline in Role Physical score of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Baseline for Givosiran Treatment	Mean	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
3 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
6 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
12 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
18 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
24 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
30 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
36 months of treatment	Mean difference		[redacted]	[redacted]
	SD		[redacted]	[redacted]
	n		[redacted]	[redacted]

Note: *, only includes Givo/givo data.

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Table 7: Change from Baseline in Bodily Pain score of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Baseline for Givosiran Treatment	Mean	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
3 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
6 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
12 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
18 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
24 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
30 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
36 months of treatment	Mean difference		[redacted]	[redacted]
	SD		[redacted]	[redacted]
	n		[redacted]	[redacted]

Note: *, only includes Givo/givo data.

Table 8: Change from Baseline in General Health score of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Baseline for Givosiran Treatment	Mean	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
3 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]

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Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
6 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
12 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
18 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
24 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
30 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
36 months of treatment	Mean difference		[redacted]	[redacted]
	SD		[redacted]	[redacted]
	n		[redacted]	[redacted]

Note: *, only includes Givo/givo data.

Table 9: Change from Baseline in Vitality score of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Baseline for Givosiran Treatment	Mean	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
3 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
6 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
12 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
18 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]

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Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
24 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
30 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
36 months of treatment	Mean difference		[redacted]	[redacted]
	SD		[redacted]	[redacted]
	n		[redacted]	[redacted]

Note: *, only includes Givo/givo data.

Table 10: Change from Baseline in Social Functioning score of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Baseline for Givosiran Treatment	Mean	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
3 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
6 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
12 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
18 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
24 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
30 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
36 months of treatment	Mean difference		[redacted]	[redacted]
	SD		[redacted]	[redacted]
	n		[redacted]	[redacted]

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Note: *, only includes Givo/givo data.

Table 11: Change from Baseline in Role Emotional score of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Baseline for Givosiran Treatment	Mean	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
3 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
6 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
12 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
18 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
24 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
30 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
36 months of treatment	Mean difference		[redacted]	[redacted]
	SD		[redacted]	[redacted]
	n		[redacted]	[redacted]

Note: *, only includes Givo/givo data.

Table 12: Change from Baseline in Mental Health score of the SF-12 During Givosiran Treatment (All Givosiran Treated Set)

Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
Baseline for Givosiran Treatment	Mean	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
3 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]

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Period	Parameter	Placebo/ Givosiran (N=46)	Givosiran/ Givosiran (N=48)	All Givosiran (N=94)
6 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
12 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
18 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
24 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
30 months of treatment	Mean difference	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]
	n	[redacted]	[redacted]	[redacted]
36 months of treatment	Mean difference		[redacted]	[redacted]
	SD		[redacted]	[redacted]
	n		[redacted]	[redacted]

Note: *, only includes Givo/givo data.

12. Please explain how Table 27 corresponds to the data.

Treatment discontinuation is included in the economic model, using a piecewise method for extrapolation proposed by the NICE Evidence Review Group. Values from the Kaplan–Meier curve are used up to the end of the observed data, and thereafter time on treatment is extrapolated using the best-fitting of 5 commonly used parametric functions. This method generates a time-on-treatment curve that is used in the economic analysis to simulate the proportion of the cohort discontinuing treatment with givosiran at each cycle of the model.

The exponential function was found to be the best-fitting curve based on objective statistical criteria (AIC and BIC) and was therefore selected for the extrapolation. The 36-month update reported the updated values used for the parametrization of the exponential function, used to extrapolate time on treatment beyond the period observed in ENVISION, for use in the economic model. The standard error, plus upper and lower values, used for probabilistic and deterministic sensitivity analysis respectively, were also included in the table. These data are repeated in Table 13 below.

Table 13: Summary of variables applied in the model

ToT Exponential parameter	Value	Standard error	Lower value	Upper value	PSA distribution	Source
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	Cholesky	ENVISION DB + OLE

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ToT Exponential parameter	Value	Standard error	Lower value	Upper value	PSA distribution	Source
Shape	[redacted]	[redacted]		[redacted]	Cholesky	ENVISION DB + OLE
Scale	[redacted]	[redacted]		[redacted]	Cholesky	ENVISION DB + OLE

DB, double-blind (period); OLE, open-label extension; PSA, probabilistic sensitivity analysis; ToT, time on treatment.

13. Table 34, "Symptomatic" sums up to [redacted] (should be [redacted]). There should be a transition probability from "Symptomatic" to "Recurrent" of the same size as from "Symptomatic" to "Symptomatic".

In the 36-month update, Table 34 included a typographical error. The transition probability from "Symptomatic" to "Recurrent" should read [redacted], rather than [redacted]. A corrected version of the table is provided below.

Table 14. Givosiran health-state transition probabilities in cycle 1, based on ENVISION double-blind Month-6 data

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

The typographical error was confined to the submission document for the 36-month update - the transition probabilities implemented in the economic modelling were correct and remain unchanged.

14. We need full information on the available EQ-5D data from ENVISION. This includes information on the number of completed EQ-5D questionnaires, the timing of collected data. Despite potential problems in using EQ-5D data from ENVISION to estimate health state utilities, we still need the estimates divided by the model's health states.

Information on the number of completed EQ-5D questionnaires and the timing of data collection has already been provided. In the 36-month update, change from baseline in EQ-5D VAS scores over time, including the number of patients at each time point, was presented. These data are repeated in Figure 4 below.

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The 36-month update also provided mean EQ-5D utility scores at baseline and 6-monthly intervals up to 36 months, including the number of patients at each time point. These data are repeated in Table 15 below. Individual utility scores were calculated using the Danish EQ-5D-5L tariff [5]. For both VAS and utility scores, data are included for the 6-month period of placebo treatment for placebo/givosiran patients in the double-blind phase of the trial.

Table 15: Mean EQ-5D index values at baseline and Months 6, 12, 18, 24, 30 and 36 by treatment arm

Time point	EQ-5D utility								
	Givosiran-Givosiran			Placebo			All patients		
	n	Mean	SE	n*	Mean	SE	n	Mean	SE
Baseline†									
Month 6†									
Month 12†					N/A‡				
Month 18†					N/A‡				
Month 24†					N/A‡				
Month 30†					N/A‡				
Month 36†					N/A‡				

*In line with other analyses performed for the model, two placebo patients were excluded for protocol deviation
†Danish EQ-5D tariff; for each patient, the EQ-5D measurement at a given time-point is considered and the average utility across observations at that time point is then calculated.
‡ No observations are available for placebo during the open-label extension since all patients switched to givosiran.

The EQ-5D data from ENVISION was not used to estimate health state utility values (HSUV) for economic modelling. EQ-5D utility values did not correlate with AAR in ENVISION and there were numerous other logistical obstacles to using data from the trial to derive utility estimates. A full explanation of these issues was provided in the original

submission. For these reasons, an alternative approach was used to derive HSUV. Long-term HRQoL decrements associated with pain, neurological and psychiatric symptoms were obtained from the literature and then applied to the proportion of the cohort with these conditions in every health state, based on prevalence data from a long-term dataset that recorded the occurrence of chronic conditions of AHP over a 50-year period from 1960 to 2015 [6]. This approach to estimating HSUV was considered more accurate and representative of how patients may truly develop complications due to the disease over a lifetime.

In response to the DMC's request, Alnylam has conducted further analysis of the EQ-5D data from ENVISION, specifically mean EQ-5D index values by health state, for different time points, which is provided in Table 16 below.

Table 16. Mean EQ-5D index values at each time point until latest follow-up (36 months) by health state in the double-blind period and OLE of ENVISION

Health state	EQ-5D utility								
	Givosiran-Givosiran			Placebo-Givosiran‡			All patients		
	n	Mean	SE	n*	Mean	SE	n	Mean	SE
Baseline†									
Asymptomatic	No observations								
Symptomatic	[redacted]								
Recurrent	[redacted]								
Severe	[redacted]								
6 Months†									
Asymptomatic	[redacted]								
Symptomatic	[redacted]								
Recurrent	[redacted]								
Severe	[redacted]								
12 Months†									
Asymptomatic	[redacted]								
Symptomatic	[redacted]								
Recurrent	[redacted]								
Severe	[redacted]								
18 Months†									
Asymptomatic	[redacted]								
Symptomatic	[redacted]								

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Health state	EQ-5D utility								
	Givosiran-Givosiran			Placebo-Givosiran‡			All patients		
	n	Mean	SE	n*	Mean	SE	n	Mean	SE
Recurrent	[redacted]								
Severe					[redacted]				
24 Months†									
Asymptomatic	[redacted]								
Symptomatic	[redacted]								
Recurrent	[redacted]								
Severe					[redacted]				
30 Months†									
Asymptomatic	[redacted]								
Symptomatic	[redacted]								
Recurrent	[redacted]								
Severe					[redacted]				
36 Months†									
Asymptomatic	[redacted]								
Symptomatic	[redacted]								
Recurrent	[redacted]								
Severe					[redacted]				

Source: Alnylam, ENVISION data on file

EQ-5D: EuroQol 5-dimensions; n: number of patients who completed the questionnaire; SE: standard error

*In line with other analyses performed for the model, two placebo patients were excluded for protocol deviation

†Danish EQ-5D tariff; for each patient, the EQ-5D measurement at given time-point is considered; patients are classified by health state based on AAR at the time-point of interest, and the average utility across observations for patients in each health state is then calculated. From month 12, data are based on the open label extension (OLE) of ENVISION

‡ Placebo patients switched to givosiran in ENVISION OLE and therefore from month 12 observations are in placebo-givosiran sequence.

15. There seems to be a discrepancy between the table containing number of givosiran patients transitioning between health states from Month 12 to Month 18 (ENVISION OLE period). The information in Table 30 differs from earlier versions of your application. Please explain way this is the case.

The data presented for the Month 12 to Month 18 period in the original 18-month submission do not match to the data for the same period in the 36-month update. The data within the 18-month submission were not fully mature—

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not all patients had reached 18 months of follow up at the time of the data-cut used for the submission. In the subsequent 36-month update, all data were mature for the Month 12 to Month 18 period and the additional follow-up time included for some patients generates differences in the calculation of AARs. The transition probabilities used in the economic model, presented in Table 30 of the 36-month update, are estimated from AARs in the ENVISION trial and were updated in line with the maturing of data between the original 18-month submission and subsequent 36-month update.

16. The distribution of patients between health-states at Month 18 differs from earlier versions of the application. Please explain the reason for this.

The distribution of patients between health states at Month 18 in the economic model does not match between the original 18-month submission and the 36-month update. As explained above in Question 15, the data within the 18-month submission were not fully mature for the Month 12 to Month 18 period. In the 36-month update, the data for this period were mature. The distribution of patients between health states at Month 18 in the economic model is determined by the transition probabilities in prior periods. In the 36-month update, the transition probabilities in the model were revised in line with the maturing data and changes in AAR for the period from Month 12 to Month 18 in the ENVISION trial.

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References

1. Ware, J., M. Kosinski, and S.D. Keller, *A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity.* Med Care, 1996. **34**(3): p. 220-33.
2. QualityMetric. *The SF12v2 Health Survey*. [cited 2022 25 May]; Available from: https://www.qualitymetric.com/health-surveys-old/the-sf-12v2-health-survey/.
3. Ware, J., M. Kosinski, and S. Keller, *SF-12: How to Score the SF-12 Physical and Mental Health Summary Scales.* 1998.
4. OrthoToolKit. *SF-12 online calculator*. [cited 2022 25 May]; Available from: https://orthotoolkit.com/sf-12/.
5. Jensen, C.E., et al., *The Danish EQ-5D-5L Value Set: a Hybrid Model Using cTTO and DCE Data.* Appl Health Econ Health Policy, 2021. **19**(4): p. 579-591.
6. Neeleman, R.A., et al., *Medical and financial burden of acute intermittent porphyria.* J Inherit Metab Dis, 2018. **41**(5): p. 809-817.

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