Disease Burden in Patients with Acute Hepatic Porphyria: Experience from the Phase 3 ENVISION Study

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Conclusions

- These data from ENVISION are consistent with prior natural history reports[4,10] showing the severe disease burden of AHP
- At baseline of ENVISION, patients had a high number of annual attacks, and a substantial proportion of patients presented with chronic symptoms, comorbidities, and concomitant medication use, including opioid use daily or on most days between attacks for 29% of patients
  - These baseline characteristics contributed to impaired physical and mental QoL and interference with normal functioning
- The relationship between time since diagnosis and AAR suggests patients may experience worsening disease and complications over time
- Givosiran reduced daily worst pain scores and analgesic use during and between attacks
- Earlier initiation of treatments such as givosiran—which prevent attacks and reduce chronic manifestations of AHP—may lead to improvement in patients' prognoses

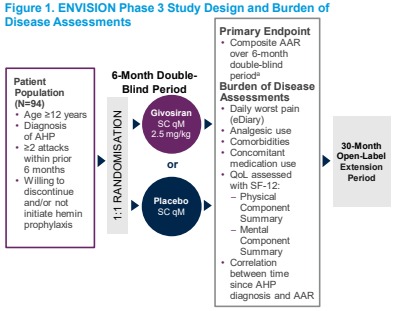
Introduction

- Acute hepatic porphyria (AHP) is a family of rare metabolic disorders caused by defects in heme biosynthesis enzymes,[1-3] and is characterised by disabling acute neurovisceral attacks and chronic symptoms (e.g., pain, nausea, and fatigue) between attacks[2,4,5]
- Standard of care for acute attacks is intravenous (IV) hemin, which is also used off-label for prophylaxis[4]
- Acute and chronic complications of hemin use include phlebitis, iron overload, venous thrombosis or obliteration, and central venous catheter complications
- Givosiran is a synthetic aminolevulinate synthase 1 (*ALAS1*)–directed small interfering RNA that is selectively delivered to the liver[6]
- In the phase 3 ENVISION study (NCT03338816), givosiran reduced the annualised attack rate (AAR) by 74% versus placebo in patients with acute intermittent porphyria during the double-blind period[7]
  - During the open-label extension period, 85% of patients continuing givosiran were attack-free at >15 to 18 months[8]
- ENVISION data are used to summarise the spectrum of disease burden associated with AHP

Methods

- ENVISION had two phases: a 6-month, double-blind, randomised, placebo-controlled period and a 30-month open-label extension period (**Figure 1**)
- This analysis assessed daily worst pain (eDiary) on a numeric rating scale from 0 (no pain) to 10 (worst pain imaginable), analgesic use, comorbidities, concomitant medication use, QoL as reported on the Short Form (12-item) Health Survey (SF-12), and AAR and its correlation to time since AHP diagnosis

Figure 1. ENVISION Phase 3 Study Design and Burden of Disease Assessments



AAR, annualised attack rate; AHP, acute hepatic porphyria; IV, intravenous; qM, every month; QoL, quality of life; SC, subcutaneous; SF-12, Short Form (12-item) Health Survey.
[a]Attacks requiring hospitalisation, urgent health care facility visit, or IV hemin use at home; composite AAR was calculated for each patient by dividing total number of porphyria attacks by total number of days in treatment period before multiplying by 365.25.

Results

- In total, 94 patients enrolled in ENVISION; their disease severity at baseline was severe (**Table 1**)

Table 1. Patient Characteristics and Chronic Symptoms at Baseline in ENVISION

Characteristic	Placebo (n=46)	Givosiran (n=48)	Total (N=94)
Age in years, median (range)	36.0 (20–60)	42.0 (19–65)	37.5 (19–65)
Years since diagnosis, mean (SD)[7]	8.3 (8.5)	11.1 (11.2)	9.7 (10.0)
Previous hemin prophylaxis, n (%)[7]	18 (39)	20 (42)	38 (40)
Historical AAR,[a] median (range)[7]	7.0 (0[b]–46)	8.0 (4–34)	8.0 (0[b]–46)
Prior chronic symptoms,[c] n (%)[7]	26 (57)	23 (48)	49 (52)
Prior chronic opioid use,[c] n (%)[7]	13 (28)	14 (29)	27 (29)
Average daily worst pain score, mean (SD)[d]	3.7 (2.2)	3.0 (2.3)	3.3 (2.3)

AAR, annualised attack rate; IV, intravenous; SD, standard deviation.
[a]Calculated as number of attacks requiring hospitalisation, urgent health care facility visit, or IV hemin use at home within 6 months before randomisation.
[b]One patient in placebo group did not meet inclusion criterion of ≥2 attacks requiring hospitalisation, urgent health care facility visit, or IV hemin use at home within 6 months before screening (patient had 2 attacks treated without IV hemin at home).
[c]Defined as chronic if patient reported occurrence as daily or on most days when patient was not having an attack.
[d]Collected with eDiary on days when patient was not having an attack.

- Although 40% and 6% of them were receiving prophylactic hemin and gonadotropin-releasing hormone analogues, respectively, patients reported a median (range) of 8 (0–46) annualised attacks within the 6 months before randomisation
  - These attacks were treated with IV hemin at home (13%), at an urgent health care facility (49%), or at a hospital (37%)
- Overall, 52% experienced symptoms daily or on most days when they were not having an attack
- Severe disease burden—median historical AAR of 7.0; chronic symptoms (59% of patients) and chronic opioid use (23%) when not having attacks—was similarly evident among the 60% of patients who were not on hemin prophylaxis

Pain and Analgesic Use

- Patients required analgesics, including opioids, for chronic pain management
  - 29% of patients were using opioid analgesics daily or on most days between attacks[7] (**Table 1**)
  - 88% and 67% of patients treated with placebo and givosiran, respectively, received opioid analgesics during the double-blind period

Comorbidities and Concomitant Medications

- A high proportion of patients had comorbidities at baseline (**Table 2**)
- One third of patients had iron overload; for all patients, median (quartile 1–quartile 3) ferritin level was 209 (48–719) µg/L (normal levels are 13–150 µg/L for females and 30–400 µg/L for males)

Table 2. Comorbidities at Baseline for Patients in ENVISION

Comorbidity, n (%)	Placebo (n=46)	Givosiran (n=48)	Total (N=94)
Neuropathy	16 (35)	20 (42)	36 (38)
Sensory	8 (17)	10 (21)	18 (19)
Motor	8 (17)	13 (27)	21 (22)
Autonomic	3 (7)	0	3 (3)
Hypertension	11 (24)	14 (29)	25 (27)
Compromised liver function			
Any history of liver disease	13 (28)	13 (27)	26 (28)
Elevated transaminase levels	18 (39)	17 (35)	35 (37)
Compromised kidney function			
Chronic kidney disease	9 (20)	8 (17)	17 (18)
eGFR <60 mL/min/1.73 m² (worst screen value)	18 (39)	14 (29)	32 (34)
Psychiatric disorders	18 (39)	26 (54)	44 (47)
Anxiety	9 (20)	13 (27)	22 (23)
Depression	8 (17)	17 (35)	25 (27)
Insomnia	8 (17)	9 (19)	17 (18)
Iron overload	15 (33)	16 (33)	31 (33)
Ferritin level (µg/L), median (quartile 1–quartile 3)	245 (44–662)	201 (53–875)	209 (48–719)

eGFR, estimated glomerular filtration rate.

- Concomitant medication use was consistent with AHP symptoms and common comorbidities, with a high proportion of patients taking antidepressants, antihypertensives, opioids, and antiemetics (**Table 3**)

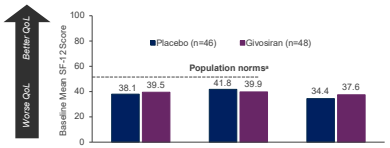
Table 3. Concomitant Medication Use at Baseline for Patients in ENVISION

Medication, n (%)	Placebo (n=46)	Givosiran (n=48)	Total (N=94)
Antidepressants			
Benzodiazepine derivatives	10 (22)	10 (21)	20 (21)
Benzodiazepine-related drugs	3 (7)	4 (8)	7 (7)
Other antidepressants	4 (9)	9 (19)	13 (14)
Selective serotonin reuptake inhibitors	2 (4)	4 (8)	6 (6)
Antihypertensives			
Angiotensin-converting enzyme inhibitors	2 (4)	1 (2)	3 (3)
Angiotensin II receptor antagonists	3 (7)	2 (4)	5 (5)
Beta-blockers, nonselective	1 (2)	3 (6)	4 (4)
Beta-blockers, selective	5 (11)	7 (15)	12 (13)
Alpha- and beta-blockers	2 (4)	0	2 (2)
Antiemetics			
5-hydroxytryptamine (5-HT3) receptor antagonists	12 (26)	12 (25)	24 (26)
Other antiemetics	5 (11)	5 (10)	10 (11)
Analgesics			
Natural opium alkaloids	27 (59)	23 (48)	50 (53)
Fentanyl	5 (11)	1 (2)	6 (6)
Fentanyl citrate	0	2 (4)	2 (2)
Opioid/non-opioid combinations	2 (4)	5 (10)	7 (7)
Opium alkaloid derivatives	2 (4)	0	2 (2)
Other opioids	8 (17)	6 (13)	14 (15)
Other analgesics and antipyretics	10 (22)	13 (27)	23 (24)
Propionic acid derivatives	9 (20)	10 (21)	19 (20)
Salicylic acid and derivatives	2 (4)	1 (2)	3 (3)
Tramadol	9 (20)	5 (10)	14 (15)
Gonadotropin-releasing hormone analogues	3 (7)	3 (6)	6 (6)

Quality of Life

- Patients had poor QoL as evidenced by baseline mean SF-12 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores (**Figure 2**)
  - These baseline values are substantially lower than population norms and lower than mean scores of patients post myocardial infarction[9]
- Consistent with baseline pain scores and analgesic use, baseline mean SF-12 Bodily Pain scores were low, suggesting interference with normal functioning

Figure 2. Mean SF-12 QoL Scores at Baseline for Patients in ENVISION

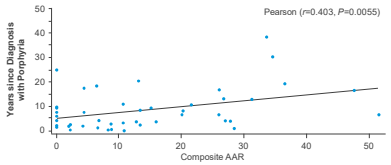


MCS, Mental Component Summary; PCS, Physical Component Summary; QoL, quality of life; SF-12, Short Form (12-item) Health Survey.
[a]Norms reported in a random sample of 2301 adults residing in The Netherlands.[9]

Disease Burden and Correlation with Time since Diagnosis

- Worsening of AHP likely occurs in the absence of effective disease-modifying treatment
  - During the 6-month double-blind period, a moderate linear correlation (Pearson r=0.403, P=0.0055) between longer time since AHP diagnosis and higher AAR was observed in the placebo group (**Figure 3**)

Figure 3. Correlation between Years since AHP Diagnosis and AAR in Placebo Recipients (n=46) during 6-Month Double-Blind Period of ENVISION

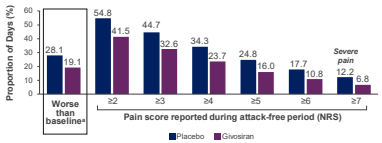


AAR, annualised attack rate; AHP, acute hepatic porphyria.

Treatment Benefits of Givosiran

- Givosiran reduced daily worst pain scores and use of analgesics during and between attacks (**Figures 4 and 5**)
  - Compared with placebo recipients, givosiran recipients had fewer days with daily worst pain scores above baseline and almost 50% fewer days with severe pain (respectively, 7% and 12% of days with scores ≥7)

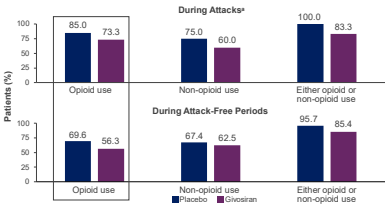
Figure 4. Givosiran Reduced Daily Worst Pain Scores during Attack-Free Periods



NRS, numeric rating scale.
[a]Baseline pain score is mean score from 4 to 7 days before first dose of study drug when patient is not experiencing an attack.

- During the 6-month double-blind period, opioid use was reduced in givosiran recipients compared with placebo recipients, with larger reductions observed during attack-free periods (**Figure 5**)

Figure 5. Givosiran Reduced Analgesic Use during and between Attacks



[a]All investigator-adjudicated attacks are included.

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Abbreviations: AAR, annualised attack rate; AHP, acute hepatic porphyria; ALA, delta-aminolevulinic acid; *ALAS1*, delta-aminolevulinic acid synthase 1; eGFR, estimated glomerular filtration rate; IV, intravenous; NRS, numeric rating scale; PBG, porphobilinogen; PCS, Physical Component Summary; qM, every month; QoL, quality of life; SC, subcutaneous; SD, standard deviation; SF-12, Short Form (12-item) Health Survey.

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