Clinical outcomes and hemin use of patients with acute hepatic porphyria in the phase 3 ENVISION study who were not attack-free after 6 months of givosiran treatment

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Conclusions

- **Both patient groups had reduced attacks and other treatment-related improvements within the first 6 months of givosiran treatment**
- **Patients who were attack-free remained attack-free, did not require hemin treatment, and reported HRQoL improvements through month 36**
- **Patients who were not attack-free after the first 6 months of givosiran treatment experienced further reductions in attack frequency and hemin use, and improvements in HRQoL with long-term givosiran treatment**
- **The results suggest that the response to givosiran treatment helps to reduce chronic symptoms as well as AHP attack frequency and further clinical improvement is expected over time**

Introduction

- Acute hepatic porphyria (AHP) comprises a group of rare, chronic, multisystem disorders caused by defects in the heme biosynthesis pathway
- Patients with AHP may experience:
  - acute episodic attacks characterized by pain, neurological symptoms, and changes in mental status
  - chronic symptoms that impact daily activities and health-related quality of life (HRQoL)
  - long-term complications requiring proactive management
- Givosiran is an RNA interference therapy that prevents accumulation of δ-aminolevulinic acid (ALA) and porphobilinogen (PBG)
  - Approved in the USA, Brazil, Taiwan, and Canada for the treatment of adults with AHP, and in the EU, Switzerland, and Japan for the treatment of adults and adolescents (≥12 years of age) with AHP
- ENVISION (NCT03338816) was the pivotal phase 3, multicenter, randomized, double-blind (DB), placebo-controlled study of givosiran in AHP
  - Sustained reductions in annualized attack rate (AAR) with givosiran were observed[1,2]
  - 58% of patients who completed the study through month 36 were attack-free after the first 6 months of givosiran treatment and for the study duration[2]
- Evaluating changes in treatment burden, such as hemin administration, may offer additional insights into the treatment benefit of givosiran over time
- We examined long-term outcomes, including hemin use, in patients who were not attack-free after the first 6 months of givosiran treatment

Table 1. Demographics and baseline disease characteristics

Demographic/characteristic	Attack-free[a] (n=46)	Not attack-free[b] (n=33)	All patients treated with givosiran (N=79)
Age at screening, years			
Median (range)	41.5 (19.0-61.0)	36.0 (20.0-57.0)	38.0 (19.0-61.0)
Time since diagnosis, years			
Mean (SD)	9.43 (10.00)	10.32 (9.92)	9.80 (9.91)
Median (range)	5.63 (0.19-38.52)	7.31 (0.14-43.29)	6.64 (0.14-43.29)
Q1, Q3	2.05, 16.76	4.25, 12.97	2.25, 13.93
Age at diagnosis, years			
Mean (SD)	32.44 (11.39)	26.70 (9.03)	30.04 (10.79)
Median (range)	30.13 (6.26-58.07)	27.15 (5.00-46.09)	29.25 (5.00-58.07)
Q1, Q3	24.82, 41.51	21.50, 32.84	22.69, 36.55
Female, n (%)	39 (84.8)	31 (93.9)	70 (88.6)
Prior hemin prophylaxis regimen, n (%)	18 (39.1)	13 (39.4)	31 (39.2)
Prior chronic symptoms when not having attacks, n (%)	23 (50.0)	20 (60.6)	43 (54.4)
Prior chronic opioid use when not having attacks, n (%)	13 (28.3)	10 (30.3)	23 (29.1)
History of depression, n (%)	11 (23.9)	13 (39.4)	24 (30.4)
History of hypertension, n (%)	11 (23.9)	10 (30.3)	21 (26.6)
History of neuropathy, n (%)	18 (39.1)	13 (39.4)	31 (39.2)

The demographics and disease characteristics at the DB period baseline were summarized.
Baseline represents 6 months before randomization.
[a]Patients with 0 attacks after 6 months of givosiran treatment. [b]Patients with ≥1 attack after 6 months of givosiran treatment.
DB, double-blind; N, total number of patients included; n, patients included per subgroup; Q1, first quartile; Q3, third quartile; SD, standard deviation.

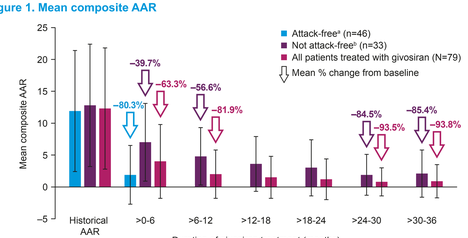
Methods

- Eligibility criteria:
  - AHP diagnosis
  - ≥12 years of age
  - ≥2 attacks requiring hospitalization, urgent care, or intravenous hemin at home during the 6 months before study enrollment
- Patients were randomized (1:1) to givosiran or placebo for 6 months in a DB period followed by a 30-month open-label extension (OLE) period, in which all patients received givosiran
- This *post hoc* descriptive analysis comprised patients who completed the DB and OLE periods
- Subgroups were defined based on attack frequency after the first 6 months of givosiran treatment
  - Attack-free: patients with 0 attacks
  - Not attack-free: patients with ≥1 attack

Results

- 94 patients were randomized and 79 of these completed the ENVISION study
  - 46 (58.2%) were attack-free
  - 33 (41.8%) were not attack-free
- Median age at screening (**Table 1**):
  - 41.5 years for patients who were attack-free
  - 36.0 years for patients who were not attack-free
- Mean composite AAR (attacks requiring hospitalization, urgent care, or intravenous hemin at home) was 7.0 (range, 0.0-23.9) during >0-6 months for patients who were not attack-free
- Mean composite AAR per 6-month interval decreased over time for patients who were not attack-free (**Figure 1**)

Figure 1. Mean composite AAR

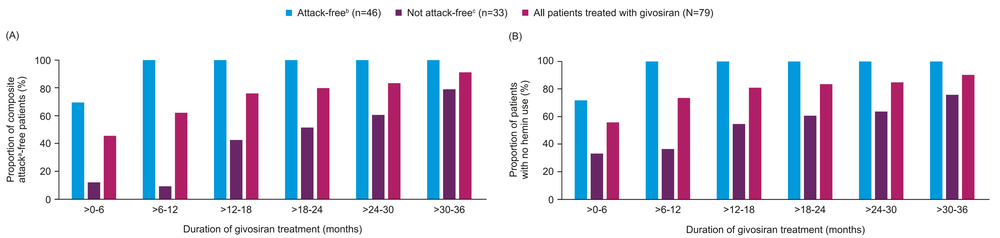


Attack-free,[a] n	46	46	46	46	46	46	23
Mean change from baseline, %		−80.3	−100.0			−100.0	−100.0
Not attack-free,[b] n	33	33	33	33	33	33	17
Mean change from baseline, %		−39.7	−56.6			−84.5	−85.4
Total, n	79	79	79	79	79	79	40
Mean change from baseline, %		−63.3	−81.9			−93.5	−93.8

Composite AAR included attacks requiring hospitalization, urgent care, or intravenous hemin at home. Historical AAR was calculated based on the number of attacks requiring hospitalization, healthcare facility visit, or hemin use at home at baseline. Baseline represents 6 months before randomization. Error bars show standard deviations. Data on arrows show mean % change from baseline in mean composite AAR.
[a]Patients with 0 attacks after 6 months of givosiran treatment. [b]Patients with ≥1 attack after 6 months of givosiran treatment.
AAR, annualized attack rate; N, total number of patients included; n, patients included per subgroup.

- Mean percentage reductions relative to historical composite AAR (mean [standard deviation], 12.8 [9.6]):
  - 39.7% after >0-6 months of givosiran treatment
  - 85.4% after >30-36 months of givosiran treatment
- The proportion of patients who became attack-free increased over time (**Figure 2A**)
  - Patients who were attack-free after 6 months of givosiran treatment remained attack-free throughout the study
- The proportion of patients with no hemin use per 6-month interval increased over time (**Figure 2B**)
  - All attack-free patients had discontinued hemin use after >6-12 months of givosiran treatment
  - Among patients who were not attack-free:
    - 33.3% (11/33) were not using hemin after >0-6 months of givosiran treatment
    - 75.9% (22/29) were not using hemin after >30-36 months of givosiran treatment

Figure 2. Proportions of (A) patients who became attack-free and (B) patients with no hemin use at each 6-month interval

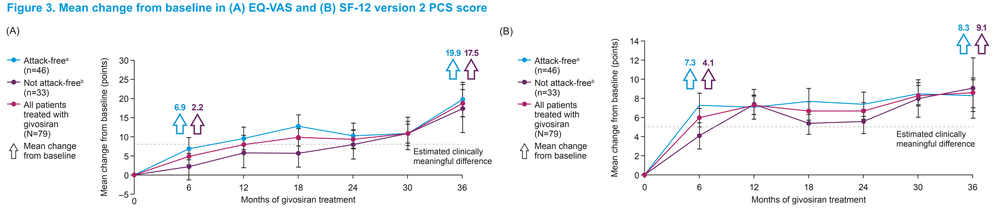


No. of patients:						
Attack-free[b]	32	46	46	46	46	46
Not attack-free[c]	4	3	14	17	20	26
Total	36	49	60	63	66	72

No. of patients:						
Attack-free[b]	33	46	46	46	46	43[d]
Not attack-free[c]	11	12	18	20	21	22[e]
Total	44	58	64	66	67	65[f]

[a]Composite attacks included attacks requiring hospitalization, urgent care, or intravenous hemin at home. [b]Patients with 0 attacks after 6 months of givosiran treatment. [c]Patients with ≥1 attack after 6 months of givosiran treatment. [d]Data were available for 43 patients. [e]Data were available for 29 patients. [f]Data were available for 72 patients.
N, total number of patients included; n, patients included per subgroup.

Figure 3. Mean change from baseline in (A) EQ-VAS and (B) SF-12 version 2 PCS score



Attack-free,[a] n	46	46	46	46	44	44	23
Mean EQ-VAS score±SEM	68.1±3.2	75.0±2.5	77.7±2.6	80.9±2.4	79.2±2.6	79.2±2.3	87.1±2.6
Mean change from baseline±SEM		6.9±3.0				10.9±3.3	19.9±4.6
Not attack-free,[b] n	33	33	32	31	31	29	17
Mean EQ-VAS score±SEM	62.0±3.9	64.2±3.2	68.3±3.8	66.9±3.3	71.1±3.4	72.7±3.6	76.8±3.1
Mean change from baseline±SEM		2.2±3.5				10.9±4.4	17.5±6.4
Total, n	79	79	78	77	75	73	40
Mean EQ-VAS score±SEM	65.6±2.5	70.5±2.1	73.6±2.2	75.3±2.1	75.8±2.1	76.6±2.0	82.7±2.1
Mean change from baseline±SEM		4.9±2.3				10.9±2.6	18.9±3.7

Attack-free,[a] n	46	45	46	45	45	44	23
Mean SF-12 PCS score±SEM	40.5±1.3	47.7±1.5	47.6±1.4	48.4±1.4	47.6±1.5	48.9±1.5	49.3±2.1
Mean change from baseline±SEM		7.3±1.3				8.5±1.2	8.3±1.7
Not attack-free,[b] n	33	33	33	32	30	29	17
Mean SF-12 PCS score±SEM	38.1±1.8	42.2±1.8	45.5±1.9	43.8±1.7	44.2±2.0	46.3±1.8	46.7±2.4
Mean change from baseline±SEM		4.1±1.4				8.0±2.0	9.1±3.2
Total, n	79	78	79	77	75	73	40
Mean SF-12 PCS score±SEM	39.5±1.1	45.4±1.2	46.7±1.1	46.5±1.1	46.2±1.2	47.9±1.1	48.2±1.6
Mean change from baseline±SEM		6.0±1.0				8.3±1.1	8.6±1.6

The EQ-VAS assesses a patient's global impression of their overall health on a visual analog scale that ranges from 0 (worst possible health) to 100 (best possible health). Scores on the PCS of the SF-12 range from 0 (worst functioning) to 100 (best functioning). Estimates for the clinically meaningful difference are ≥7 to 8 points for EQ-VAS and 2 to 5 points for SF-12. Baseline represents 6 months before randomization. Error bars show SEM. Data on arrows show absolute mean change from baseline in EQ-VAS and SF-12 score points.
[a]Patients with 0 attacks after 6 months of givosiran treatment. [b]Patients with ≥1 attack after 6 months of givosiran treatment.
N, total number of patients included; n, patients included per subgroup; PCS, Physical Component Summary; SEM, standard error of the mean; SF-12, 12-item Short Form Health Survey.

- Median urinary ALA and PBG levels decreased over time (**Table 2**)
  - Median percentage reductions from baseline in ALA levels:
    - Attack-free: 87.5% at 6 months and 92.7% at 36 months
    - Not attack-free: 84.8% at 6 months and 91.6% at 36 months
  - Median percentage reductions from baseline in PBG levels:
    - Attack-free: 88.5% at 6 months and 97.2% at 36 months
    - Not attack-free: 86.3% at 6 months and 93.4% at 36 months
- HRQoL, measured using EQ-VAS scores and 12-item Short Form Health Survey (SF-12) version 2 Physical Component Summary (PCS) scores, improved in both groups
  - Mean change from baseline in EQ-VAS scores improved over time (**Figure 3A**)
    - Attack free: 6.9 points at 6 months and 19.9 points at 36 months
    - Not attack-free: 2.2 points at 6 months and 17.5 points at 36 months
  - Mean change from baseline in SF-12 version 2 PCS scores improved over time (**Figure 3B**)
    - Attack-free: 7.3 points at 6 months and 8.3 points at 36 months
    - Not attack-free: 4.1 points at 6 months and 9.1 points at 36 months

Table 2. Urinary ALA and PBG levels

Months of treatment	Attack-free[a] (n=46)	Not attack-free[b] (n=33)	All patients treated with givosiran (N=79)
Baseline ALA, mmol/mol, median (range)	15.84 (1.39-82.00)	17.58 (2.35-88.85)	16.52 (1.39-88.85)
ALA, mmol/mol, median (median % change from baseline)			
After 6 months of treatment	1.41 (−87.5)	1.29 (−84.8)	1.29 (−86.0)
After 30 months of treatment	0.80 (−92.6)	1.11 (−90.0)	1.02 (−92.3)
After 36 months of treatment	0.82 (−92.7)	1.33 (−91.6)	0.93 (−92.7)
Baseline PBG, mmol/mol, median (range)	39.41 (2.99-147.17)	48.50 (0.44-150.00)	40.94 (0.44-150.00)
PBG, mmol/mol, median (median % change from baseline)			
After 6 months of treatment	4.42 (−88.5)	5.12 (−86.3)	4.54 (−88.1)
After 30 months of treatment	1.88 (−94.7)	2.20 (−93.8)	1.97 (−94.6)
After 36 months of treatment	1.04 (−97.2)	1.84 (−93.4)	1.22 (−95.9)

Urinary levels of ALA and PBG were normalized to creatinine. Median ALA in healthy individuals: 0.46 mmol/mol. Median PBG in healthy individuals: 0.02 mmol/mol. Baseline represents 6 months before randomization. For patients who received placebo in the DB period and givosiran in OLE period, the data only included post givosiran treatment with baseline redefined relative to the first dose of givosiran and analysis visits mapped based on redefined baseline.
[a]Patients with 0 attacks after 6 months of givosiran treatment. [b]Patients with ≥1 attack after 6 months of givosiran treatment.
ALA, δ-aminolevulinic acid; DB, double-blind; N, total number of patients included; n, patients included per subgroup; OLE, open-label extension; PBG, porphobilinogen.

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DISCLOSURES

MT is a consultant for Alnylam Pharmaceuticals and has served as a consultant for Disc Medicine, Mitsubishi Tanabe, and Recordati Rare Diseases. **PV** has received consultancy fees and honoraria from Alnylam Pharmaceuticals and Recordati Rare Diseases. **EG-N** has received grants/research support, paid to the Fundación para la Formación e Investigación Biosanitaria-FFIS, from Alnylam Pharmaceuticals and consulting fees from Alnylam Pharmaceuticals, BioMarin, and UCB. **BW** is a scientific adviser to Alnylam Pharmaceuticals and Recordati Rare Diseases. **ES** has received grant support and personal fees, paid to Karolinska Institutet, from Alnylam Pharmaceuticals. **WD** and **IO** are employees of and own stock and stock options in Alnylam Pharmaceuticals. **MB** has received grant support, consulting fees, advisory board fees, and lecture fees from Alnylam Pharmaceuticals; grant support from Disc Medicine and Mitsubishi Tanabe Pharma; and advisory board fees from Alexion, CRISPR Therapeutics, Disc Medicine, and Genzyme/Sanofi. In addition, Mount Sinai faculty are named coinventors with Alnylam on a patent related to the development of givosiran, the study drug. The Icahn School of Medicine at Mount Sinai receives payments related to this patent from Alnylam, and a portion of these payments are also distributed to faculty and other coinventors.

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