Long-term clinical outcomes of patients with acute hepatic porphyria who were not attack-free after 6 months of givosiran treatment in a subgroup analysis of the phase 3 ENVISION study

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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 not attack-free after the first 6 months of treatment experienced further attack reductions and quality of life improvements with long-term givosiran treatment**
- **Patients who were attack-free remained attack-free and report health-related quality of life (HRQoL) improvements through month 36**
- **Results of this analysis indicate that long-term givosiran treatment provides sustained benefits for patients in both groups**

Introduction and objectives

- Acute hepatic porphyria (AHP) is a group of rare, chronic, multisystem disorders characterized by acute attacks, chronic symptoms, progressive elements, and long-term complications requiring proactive management
- Patients with AHP may experience:
  - episodic acute attacks, including symptoms such as severe abdominal pain, nausea, vomiting, tachycardia, hypertension, constipation, muscle weakness, and changes in mental status
  - chronic symptoms (e.g. pain and fatigue) that impact daily activities and HRQoL
- Givosiran is an RNA interference therapy that prevents accumulation of δ-aminolevulinic acid (ALA) and porphobilinogen (PBG) and is approved is 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) is a multicentre, randomized, double-blind (DB), placebo-controlled, phase 3 study, in which 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]
- We examined long-term outcomes in patients who were not attack-free after the first 6 months of givosiran treatment

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 enrolment
- 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

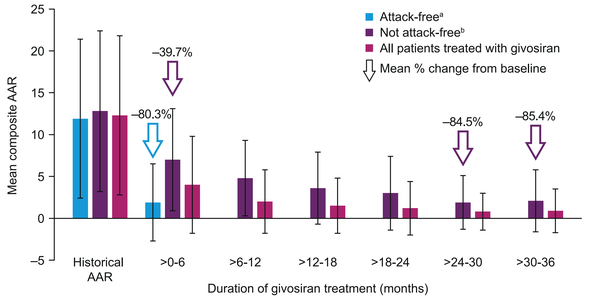
- In total, 94 patients were randomized and 79 of these completed the ENVISION study (46 [58%] were attack-free and 33 [42%] were not attack-free)
- Mean composite AAR (attacks requiring hospitalization, urgent care, or intravenous hemin at home) was 7.0 (range, 0.0-23.9) after >0-6 months of givosiran treatment for patients who 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 per 6-month interval decreased over time for patients who were not attack-free (**Figure 1**)
  - 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
- Patients who were attack-free remained attack-free throughout the 36 months of the study (**Figure 1**)
- Median urinary ALA and PBG levels decreased over time (**Figure 2**)
  - Median percentage reductions from baseline in ALA levels:
    - 87.5% after 6 months and 92.7% after 36 months in patients who were attack-free
    - 84.8% after 6 months and 91.6% after 36 months in patients who were not attack-free
  - Median percentage reductions from baseline in PBG levels:
    - 88.5% after 6 months and 97.2% after 36 months in patients who were attack-free
    - 86.3% after 6 months and 93.4% after 36 months in patients who were not attack-free

Table 1. Baseline demographics and disease characteristics

Demographic/characteristic	Attack-free n=46	Not attack-free n=33	All patients treated with givosiran N=79
Age at screening, years			
Median (min, max)	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 (min, max)	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 (min, max)	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
Sex, n (%)			
Female	39 (84.8)	31 (93.9)	70 (88.6)
Prior hemin prophylaxis regimen, n (%)			
Yes	18 (39.1)	13 (39.4)	31 (39.2)
No	28 (60.9)	20 (60.6)	48 (60.8)
Prior chronic symptoms when not having attacks, n (%)			
Yes	23 (50.0)	20 (60.6)	43 (54.4)
No	23 (50.0)	13 (39.4)	36 (45.6)
Prior chronic opioid use when not having attacks, n (%)			
Yes	13 (28.3)	10 (30.3)	23 (29.1)
No	33 (71.7)	23 (69.7)	56 (70.9)
History of depression, n (%)			
Yes	11 (23.9)	13 (39.4)	24 (30.4)
No	35 (76.1)	20 (60.6)	55 (69.6)
History of hypertension, n (%)			
Yes	11 (23.9)	10 (30.3)	21 (26.6)
No	35 (76.1)	23 (69.7)	58 (73.4)
History of neuropathy, n (%)			
Yes	18 (39.1)	13 (39.4)	31 (39.2)
No	28 (60.9)	20 (60.6)	48 (60.8)

Baseline represents 6 months before randomization.
max, maximum; min, minimum; N, total number of patients included; n, patients included per subgroup; Q1, first quartile; Q3, third quartile; SD, standard deviation.

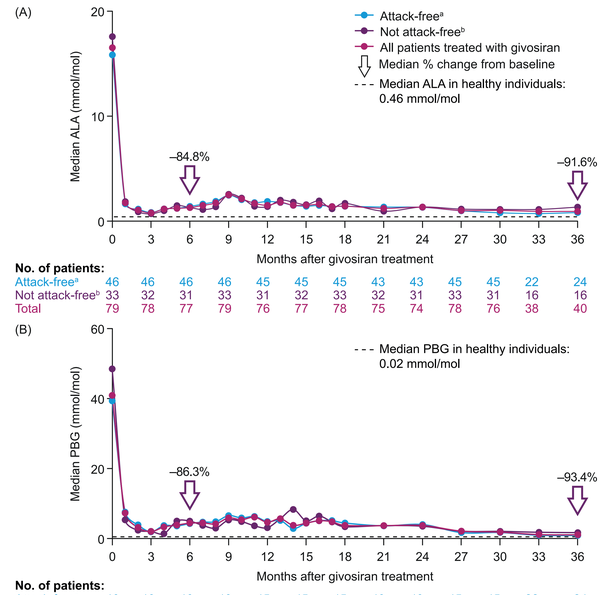
Figure 1. Mean composite AAR



Months of treatment	Attack-free[a] n=46	Not attack-free[b] n=33	All patients treated with givosiran N=79
Mean change from baseline, % (n)			
After >0-6	−80.3 (46)	−39.7 (33)	−63.3 (79)
After >24-30	−100.0 (46)	−84.5 (33)	−93.5 (79)
After >30-36	−100.0 (23)	−85.4 (17)	−93.8 (40)

AAR were attacks requiring hospitalization, urgent care, or intravenous hemin at home. 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. [b]Patients with ≥1 attack.
AAR, annualized attack rate; N, total number of patients included; n, patients included per subgroup.

Figure 2. Urinary (A) ALA and (B) PBG levels

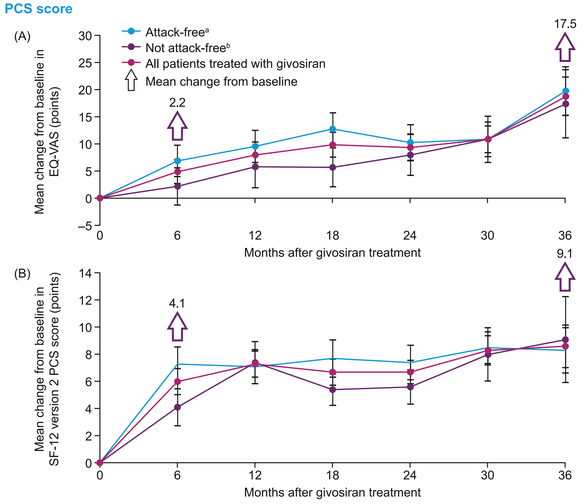


	Attack-free[a] n=46	Not attack-free[b] n=33	All patients treated with givosiran N=79
Median change from baseline, % (n)			
ALA			
After 6 months of treatment	−87.5 (46)	−84.8 (31)	−86.0 (77)
After 30 months of treatment	−92.6 (45)	−90.0 (31)	−92.3 (76)
After 36 months of treatment	−92.7 (24)	−91.6 (16)	−92.7 (40)
PBG			
After 6 months of treatment	−88.5 (46)	−86.3 (31)	−88.1 (77)
After 30 months of treatment	−94.7 (45)	−93.8 (31)	−94.6 (76)
After 36 months of treatment	−97.2 (24)	−93.4 (16)	−95.9 (40)

Baseline is shown at 0 months and it represents 6 months before randomization. Data on arrows show median % change from baseline in median ALA and PBG levels.
[a]Patients with 0 attacks. [b]Patients with ≥1 attack.
ALA, δ-aminolevulinic acid; N, total number of patients included; n, patients included per subgroup; PBG, porphobilinogen.

- HRQoL, measured using EuroQol visual analogue scale (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**)
    - 6.9 points after 6 months and 19.9 points after 36 months in patients who were attack-free
    - 2.2 points after 6 months and 17.5 points after 36 months in patients who were not attack-free
  - Mean change from baseline in SF-12 version 2 PCS scores improved over time (**Figure 3B**)
    - 7.3 points at 6 months and 8.3 points at 36 months in patients who were attack-free
    - 4.1 points at 6 months and 9.1 points at 36 months in patients who were not attack-free

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



	Attack-free[a] n=46	Not attack-free[b] n=33	All patients treated with givosiran N=79
Mean change from baseline±SEM (n)			
EQ-VAS score			
Baseline	68.1±3.2 (46)	62.0±3.9 (33)	65.6±2.5 (79)
After 6 months of treatment	6.9±3.0 (46)	2.2±3.5 (33)	4.9±2.3 (79)
After 30 months of treatment	10.9±3.3 (44)	10.9±4.4 (29)	10.9±2.6 (73)
After 36 months of treatment	19.9±4.6 (23)	17.5±6.4 (17)	18.9±3.7 (40)
SF-12 PCS score			
Baseline	40.5±1.3 (46)	38.1±1.8 (33)	39.5±1.1 (79)
After 6 months of treatment	7.3±1.3 (45)	4.1±1.4 (33)	6.0±1.0 (78)
After 30 months of treatment	8.5±1.2 (44)	8.0±2.0 (29)	8.3±1.1 (73)
After 36 months of treatment	8.3±1.7 (23)	9.1±3.2 (17)	8.6±1.6 (40)

Error bars show SEM. Baseline is shown at 0 months and it represents 6 months before randomization. Data on arrows show absolute mean change from baseline in EQ-VAS and SF-12 score points. Estimates for the clinically meaningful difference are ≥7 to 8 points for EQ-VAS and 2 to 5 points for SF-12.
[a]Patients with 0 attacks. [b]Patients with ≥1 attack.
EQ-VAS, EuroQol visual analogue scale; 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.

References

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