Impact of givosiran treatment on symptoms between acute attacks of acute hepatic porphyria as assessed by dimension-level analysis of EQ-5D data from the ENVISION study

Manish Thapar[1]; Bruce Wang[2]; Susana Monroy[3]; Weiming Du[4]; Teresa L Kauf[4]; Marianne T Sweetser[4]; Jamie L Weiss[4]; Paolo Ventura[5]; Manisha Balwani[6]

[1]Thomas Jefferson University, Philadelphia, PA, USA; [2]University of California, San Francisco, CA, USA; [3]Instituto Nacional de Pediatría, Mexico City, Mexico; [4]Alnylam Pharmaceuticals, Cambridge, MA, USA; [5]Internal Medicine Unit, University of Modena and Reggio Emilia, Modena, Italy; [6]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Poster number: 5046

For US HCPs Only
Scan to View Congress Material Presented

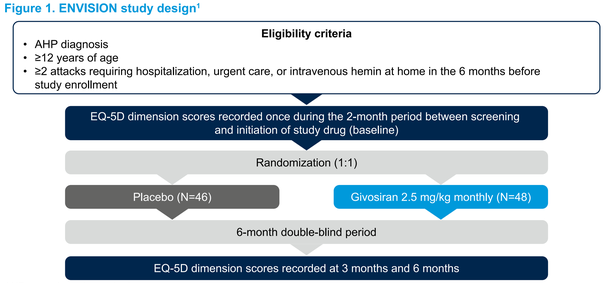
Conclusions

- **AHP symptoms occurring between attacks and their impact on HRQoL reflect the burden of disease beyond acute attacks**
- **This analysis builds on earlier findings from ENVISION[1,2] and suggests that givosiran is associated with improvements across EQ-5D dimensions, particularly pain/discomfort and anxiety/depression**
- **Additional research is needed to increase understanding of the impact of givosiran on AHP symptoms between attacks, including longer-term assessments**

Introduction

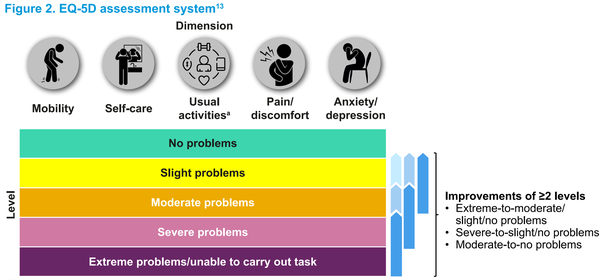
- Acute hepatic porphyria (AHP) are a group of rare, chronic, multisystem disorders of heme biosynthesis, characterized by acute attacks and long-term complications[3-5]
- Givosiran is a small interfering RNA which lowers *ALAS1* expression in the liver, thereby preventing accumulation of δ-aminolevulinic acid and porphobilinogen
- Givosiran is approved for the treatment of adults with AHP (in Brazil, Canada, and the USA)[6-8] and in adults and adolescents ≥12 years (in the European Economic Area, Japan, Switzerland, and the UK)[9-12]
- In the phase 3 ENVISION study (NCT03338816), patients with AHP and a history of acute attacks were randomized 1:1 to givosiran 2.5 mg/kg monthly as a subcutaneous injection or placebo[1]
- Compared with placebo in the 6-month double-blind period, givosiran treatment led to:
  - significant reductions in annualized attack rate (AAR)
  - significant reductions in pain scores
  - improvements in physical health as measured by the physical component summary of the 12-item short-form health survey, version 2 (SF-12)[1]
- Patients (aged ≥18 years) receiving givosiran also reported improvements in health-related quality of life (HRQoL) as measured using the visual analog scale element of the EQ-5D[2]
- We present a post hoc analysis to evaluate the effect of givosiran treatment and placebo on individual EQ-5D dimension levels[13] during the 6-month double-blind period[1]
  - These analyses identified the EQ-5D dimensions most affected by givosiran treatment (**Figures 1 and 2**)

Figure 1. ENVISION study design[1]



AHP, acute hepatic porphyria.

Figure 2. EQ-5D assessment system[13]



[a]The usual activities dimension asks respondents to evaluate the severity of problems in their usual activities, such as work, study, housework, family, or leisure activities.

Methods

- Patients completed the EQ-5D survey to record the impact of AHP on HRQoL on that day
- The EQ-5D was completed once during the 2-month period between screening and initiation of study drug (defined as baseline), then at 3 months and 6 months (6M) in the double-blind period (**Figure 1**: dark blue sections)
- The impact on HRQoL was evaluated (**Figure 2**) by examining the following measures for each EQ-5D dimension:
  - the change in dimension-level distributions between baseline and 6M
  - the proportion of patients reporting any improvement between baseline and 6M
  - the change in the proportion of patients reporting moderate-to-extreme problems between baseline and 6M
  - the difference between givosiran and placebo groups in the proportion of patients with moderate-to-extreme problems at baseline reporting a ≥2-level improvement from baseline to 6M, expressed as odds ratios
- Owing to the limited number of patients in some of the dimension levels at baseline and the post hoc nature of these analyses, all results are reported descriptively

Results

- The trial included 94 patients (givosiran, n=48; placebo, n=46)
- Baseline characteristics were well balanced across treatment groups (**Table 1**)
- Most patients were women (89%); mean (standard deviation) age was 39 (11.4) years
- At baseline, 52% of patients reported prior chronic symptoms (symptoms of porphyria when not having an attack daily or on most days before the study)
- The median (range) historical AAR was 8.0 (0.0, 46.0)
- EQ-5D dimension-level distributions for both groups were similar at baseline (**Figure 3**)
  - At baseline, over 60% of patients reported problems (defined as patients who reported 'slight problems' or worse [**Figure 2**]) with:
    - anxiety/depression (placebo, 69.6%; givosiran, 61.7%)
    - pain/discomfort (placebo, 78.3%; givosiran, 72.9%)
    - usual activities (placebo, 60.9%; givosiran, 66.0%)
  - The least affected dimensions were mobility (placebo, 39.1%; givosiran, 35.4%) and self-care (placebo, 17.4%; givosiran, 17.0%)
- At 6M, over 30% of patients who received givosiran reported improvements (defined as ≥1 level) in the most affected EQ-5D dimensions at baseline, which was slightly higher than with placebo in each case (**Figure 4**):
  - usual activities (givosiran, 31.9%; placebo, 28.3%)
  - pain/discomfort (givosiran, 33.3%; placebo, 26.1%)
  - anxiety/depression (givosiran, 31.9%; placebo, 28.3%)

Table 1. Baseline characteristics and demographics

Characteristic/demographic	Placebo (N=46)	Givosiran (N=48)	Overall (N=94)
Age at screening, years, mean (SD)	37 (10.5)	40 (12.1)	39 (11.4)
Female, n (%)	41 (89)	43 (90)	84 (89)
Years since diagnosis, median (range)	6.1 (0.1, 38.5)	7.0 (0.2, 43.3)	6.5 (0.1, 43.3)
History of hemin prophylaxis, n (%)	18 (39)	20 (42)	38 (40)
Historical AAR, median (range)	7.0 (0.0, 46.0)	8.0 (4.0, 34.0)	8.0 (0.0, 46.0)
History of symptoms between attacks,[a] n (%)	26 (57)	23 (48)	49 (52)
Urinary ALA,[b,c] mmol/mol			
Mean (SD)	17.3 (10.8)	19.7 (16.6)	18.5 (14.1)
Range	0.7, 42.7	1.8, 88.9	0.7, 88.9
Urinary PBG,[b,d] mmol/mol			
Mean (SD)	45.4 (24.5)	49.0 (34.4)	47.2 (29.9)
Range	0.4, 106.5	0.4, 150.0	0.4, 150.0

[a]Defined as symptoms of porphyria when not having an attack daily or on most days before the study. [b]Creatinine normalized. [c]Median ALA in healthy individuals: 0.46 mmol/mol. [d]Median PBG in healthy individuals: 0.02 mmol/mol.
AAR, annualized attack rate; ALA, δ-aminolevulinic acid; PBG, porphobilinogen; SD, standard deviation.

- The proportion of patients receiving givosiran reporting moderate-to-extreme problems was lower at 6M than at baseline for usual activities, pain/discomfort, and anxiety/depression (**Table 2**)
  - The numerical reduction in the proportion of patients receiving givosiran who reported moderate-to-extreme problems was more pronounced than in those receiving placebo for both pain/discomfort and anxiety/depression (**Table 2**)
- At 6M, the odds of reporting an improvement of ≥2 levels in patients with moderate-to-extreme problems at baseline was higher in the givosiran group than in the placebo group across all three dimensions assessed (odds ratio: 2.0-2.5) (**Figure 5**)

Figure 3. EQ-5D level distribution at baseline

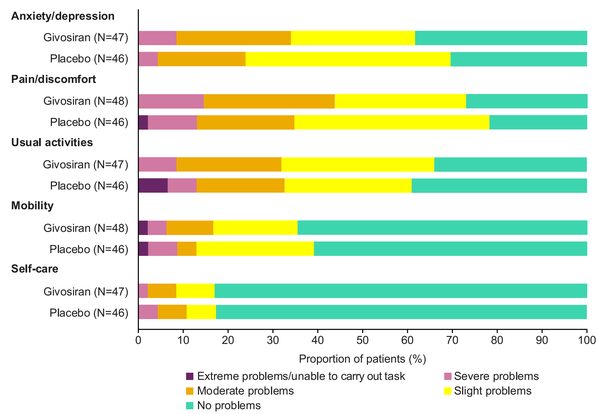
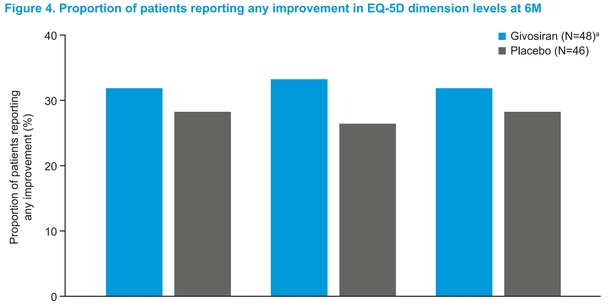


Figure 4. Proportion of patients reporting any improvement in EQ-5D dimension levels at 6M



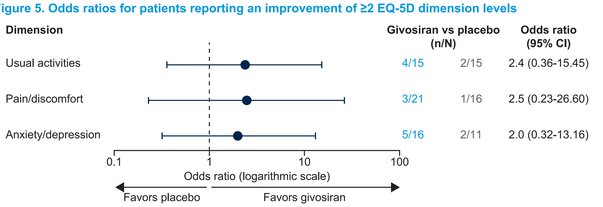
[a]N=47 for usual activities, and anxiety/depression.
6M, 6 months.

Table 2. Change from baseline to 6M in proportion of patients reporting moderate-to-extreme problems

EQ-5D dimension	Usual activities		Pain/discomfort		Anxiety/depression	
Treatment group	Givosiran	Placebo	Givosiran	Placebo	Givosiran	Placebo
Patients reporting moderate-to-extreme problems at baseline (n)	15	15	21	16	16	11
Patients reporting moderate-to-extreme problems at 6M (n)	14	14	15	15	11	12
Change in EQ-5D-5L reporting from baseline to 6M, n (%)	−1 (−6.7)	−1 (−6.7)	−6 (−28.6)	−1 (−6.3)	−5 (−31.3)	1 (9.1)

6M, 6 months.

Figure 5. Odds ratios for patients reporting an improvement of ≥2 EQ-5D dimension levels



CI, confidence interval; N, number of patients with moderate-to-extreme problems at baseline; n, number of patients reporting improvement of ≥2 levels at 6 months.

Strengths and limitations

- This is the first study to provide dimension-level data on the impact of givosiran treatment on HRQoL in patients with AHP
- HRQoL was an exploratory outcome in the ENVISION study; therefore, no formal statistical analysis was conducted
- The number of patients reporting a ≥2 level improvement in dimension scores was limited

REFERENCES

1. Balwani M *et al. N Engl J Med* 2020;382:2289-301.
2. Kuter DJ *et al. J Hepatol* 2023;79:1150-8.
3. Anderson KE *et al. Am J Med Sci* 2021;362:113-21.
4. Puy H *et al. Lancet* 2010;375:924-37.
5. Wang B *et al. Hepatol Commun* 2019;3:193-206.
6. United States Food and Drug Administration. 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021219s000lbl.pdf (Accessed October 7, 2024)
7. Alnylam Pharmaceuticals. 2020. Available from: https://investors.alnylam.com/sites/default/files/GIVLAARI-Brazil-Approval-Press-Release.pdf (Accessed October 22, 2024)
8. Health Canada. 2020. Available from: https://dhpp.hpfb-dgpsa.ca/review-documents/resource/RDS00828 (Accessed October 22, 2024)
9. EMA. 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf (Accessed October 22, 2024)
10. Alnylam Japan Co., Ltd. 2021. Available from: https://www.alnylam.jp/sites/default/files/news-articles/Japan_Givo_Approval_Press_Release_0.pdf (Accessed October 22, 2024)
11. Swissmedic. 2021. Available from: https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/new-medicines/givlaari-injektionsloesung-givosiranum.html (Accessed October 22, 2024)
12. NICE. 2021. Available from: https://www.nice.org.uk/guidance/hst16 (Accessed October 22, 2024)
13. Herdman M *et al. Qual Life Res* 2011;20:1727-36.

FUNDING

This study was sponsored by Alnylam Pharmaceuticals. Under the direction of the authors, medical writing support was provided by Matthew Long PhD and Ian Williams PhD of PharmaGenesis Cardiff, Cardiff, UK, and was funded by Alnylam Pharmaceuticals.

DISCLOSURES

MT is a consultant and speaker for Alnylam Pharmaceuticals and has served as a consultant for Disc Medicine, Mitsubishi Tanabe, and Recordati Rare Diseases. **BW** is a scientific adviser to Alnylam Pharmaceuticals and Recordati Rare Diseases. **SM** has received advisory board and speaker fees from Alnylam Pharmaceuticals. **WD**, **TLK**, **MTS**, and **JLW** are employees of and own stock and stock options in Alnylam Pharmaceuticals. **PV** has received consultancy fees and honoraria from Alnylam Pharmaceuticals and Recordati Rare Diseases. **MB** has received grant support, consulting fees, advisory board fees, and lecture fees from Alnylam Pharmaceuticals; advisory board fees from Recordati Rare Diseases; grant support and advisory board fees from Mitsubishi Tanabe; and advisory board fees from Alexion, Genzyme/Sanofi, and Takeda. In addition, Mount Sinai faculty are named co-inventors 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 co-inventors.

ACKNOWLEDGMENTS

The authors would like to thank the patients who participated in this study and their families.

Presented at the American Association for the Study of Liver Diseases (AASLD) 75th Liver Meeting 2024, November 15-19, 2024, San Diego, CA, USA