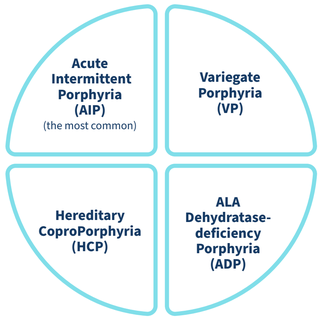
Long-term clinical outcomes of patients with acute hepatic porphyria who were not attack-free after 6 months of givosiran treatment: a subgroup analysis of the phase 3 ENVISION study

1 Introduction

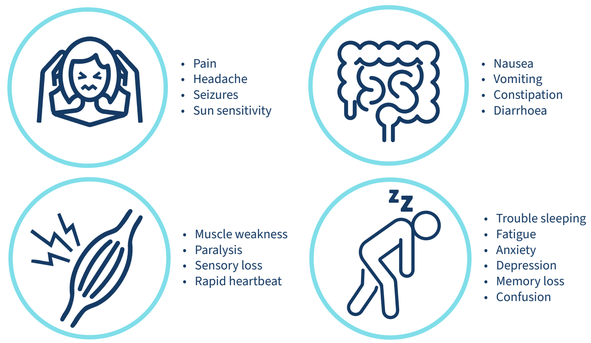
What is AHP?

- Acute hepatic porphyria (AHP) is a term for a group of four genetic diseases that affect the whole body and that if untreated, can get worse with time



- A build-up of delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) in the body can cause:
  - **Attacks**
    - Appear suddenly and last a short time
    - Severe and sometimes life-threatening symptoms
  - **Chronic symptoms**
    - Appear more slowly and can last a long time
    - Negatively affect day-to-day activities and quality of life

Symptoms of AHP



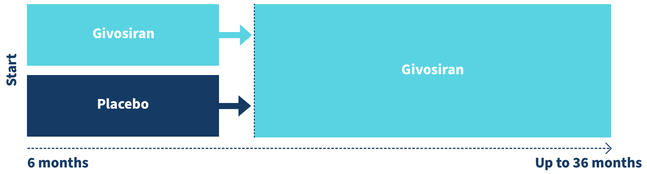
Not all symptoms of AHP shown

What is givosiran?

- A medicine that is used to treat adults with AHP that prevents the build-up of ALA and PBG in the body

What was the ENVISION study?

- ENVISION (NCT03338816) was a Phase 3 clinical study in patients with AHP that evaluated the:[1,2]
  - effects of givosiran compared with placebo
  - long-term effect and safety of givosiran treatment



- In the 1st 6 months (6M), patients treated with givosiran had fewer attacks than those on placebo
- **We investigated the long-term outcomes of patients who completed the study through to month 36 (36M)**

- Patients were grouped into:[1]

Attack Free: had no attacks after 6M of givosiran treatment (46 patients)

Not Attack Free: had at least 1 attack after 6M of givosiran treatment (33 patients)

All Patients: 'Attack Free' and 'Not Attack Free' groups combined (79 patients)

2 Methods and Results

Annualized attack rate

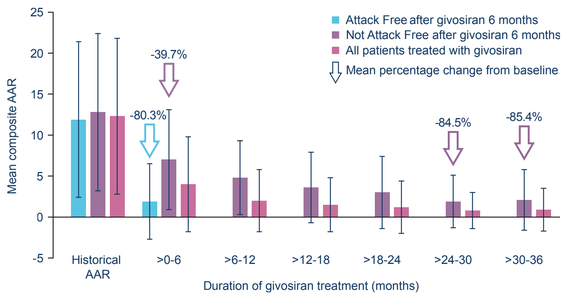
Methods

- Primary endpoint was annualized attack rate (AAR)
- AAR was the average number of attacks per person in a year that required any of the following:

Hospitalization | **Urgent care visit** | **Intravenous hemin at home**

- To calculate the effect of givosiran treatment, AARs were
  - calculated every 6M
  - compared to values before treatment

AAR decreased over time with givosiran treatment



- 1st 6M of treatment: all treated patients had reduced AAR (historical AAR vs >0-6M)
- Continued treatment: AAR decreased further over time in all groups (>6-12M and later)

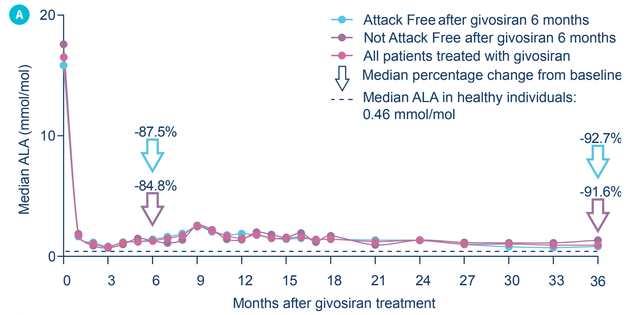
Of the Not Attack-Free group, the percentage of patients who were attack-free after the 1st 6M of treatment (during 6M treatment intervals) increased over time:
- 9% attack-free after >6-12M of treatment
- 79% after >30-36 M of treatment

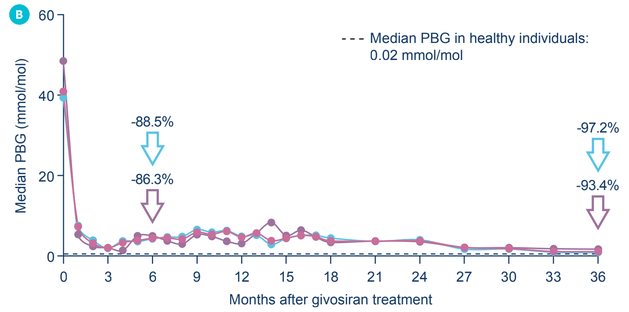
ALA and PBG urine concentrations

Methods

- To estimate effect of givosiran, concentrations of ALA and PBG in urine were:
  - measured throughout the study
  - compared to starting values

ALA and PBG concentration decreased over time with givosiran treatment



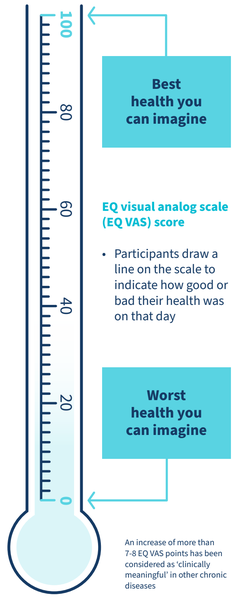


- ALA and PBG reductions were similar in the Not Attack Free and Attack Free groups

Health-related quality of life (HRQoL)

- Several surveys are used by medical professionals to evaluate health-related quality of life (HRQoL) in people
- These tools can estimate impact of disease on a person's life beyond their symptoms

HRQoL was measured using:



EQ visual analog scale (EQ VAS) score

- Participants draw a line on the scale to indicate how good or bad their health was on that day

An increase of more than 7-8 EQ VAS points has been considered as 'clinically meaningful' in other chronic diseases

12-item Short-Form Health Survey (SF-12) version 2 Physical Component Summary (PCS) score

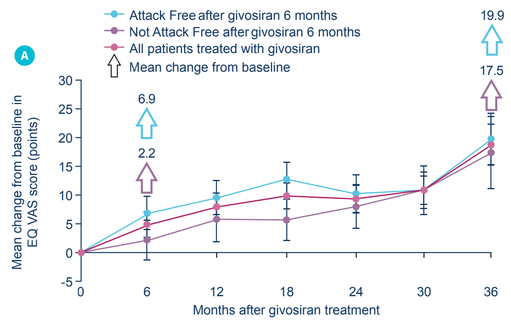
General health
Health (excellent → poor)

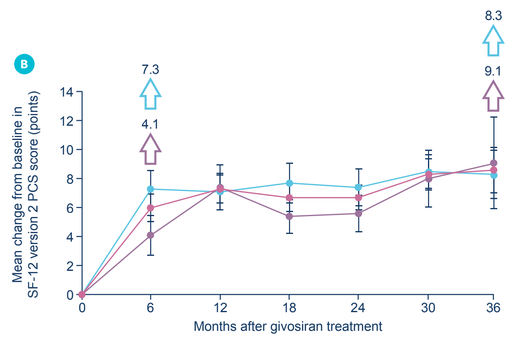
Current effect of health on activities
- Moderate-intensity activities, like pushing a vacuum cleaner or bowling (limited a lot → not at all)
- Climbing several flights of stairs (limited a lot → not at all)

Effect of physical health on work or activities in the past 4 weeks
- Limited the kind of work/ activities performed (all of the time → none of the time)
- Limited accomplishments (all of the time → none of the time)
- Pain interfered with normal work (extreme interference → no interference)

An increase in PCS score of 2-5 has been considered 'clinically meaningful' in other chronic diseases

HRQoL improved over time with givosiran treatment



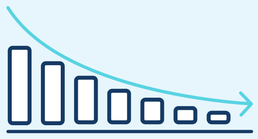


- HRQoL improved in all patients
  - After 6M of treatment (0M vs 6M)
  - After 36M of treatment (0M vs 36M)
    - At 36M, HRQoL improvements were similar in the Not Attack Free and Attack Free groups

3 Conclusions

- **Results indicate that long-term treatment with givosiran provides sustained clinical and HRQoL benefits to patients who remain attack-free and those who don't**

- Both patient groups had reduced attacks and other treatment-related improvements within the 1st 6M of givosiran treatment



Attack-Free group
- Remained attack-free
- HRQoL continued to improve until end of study

Not Attack-Free group
- Further reductions in number of attacks
- HRQoL improved with long-term treatment

Acknowledgements

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1. Balwani M et al. N Engl J Med 2020;382:2289-301. 2. Kuter DJ et al. J Hepatol 2023;79:1150-58.