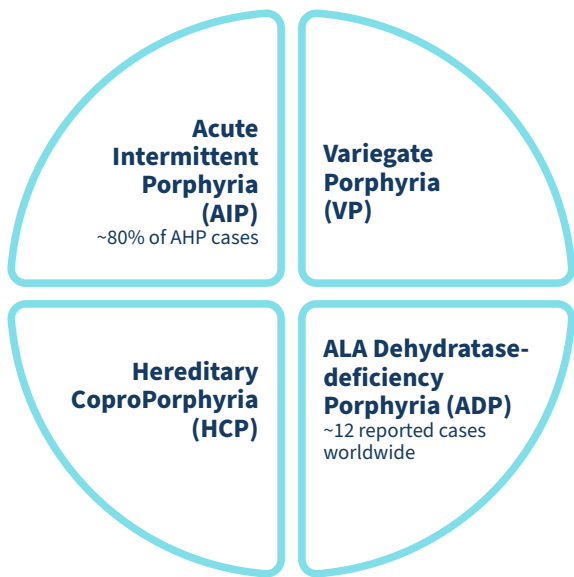


Long-term assessment of patients with acute hepatic porphyria who were not attack-free after 6 months of givosiran treatment: a post hoc subgroup analysis of the phase 3 ENVISION study¹

1 Introduction

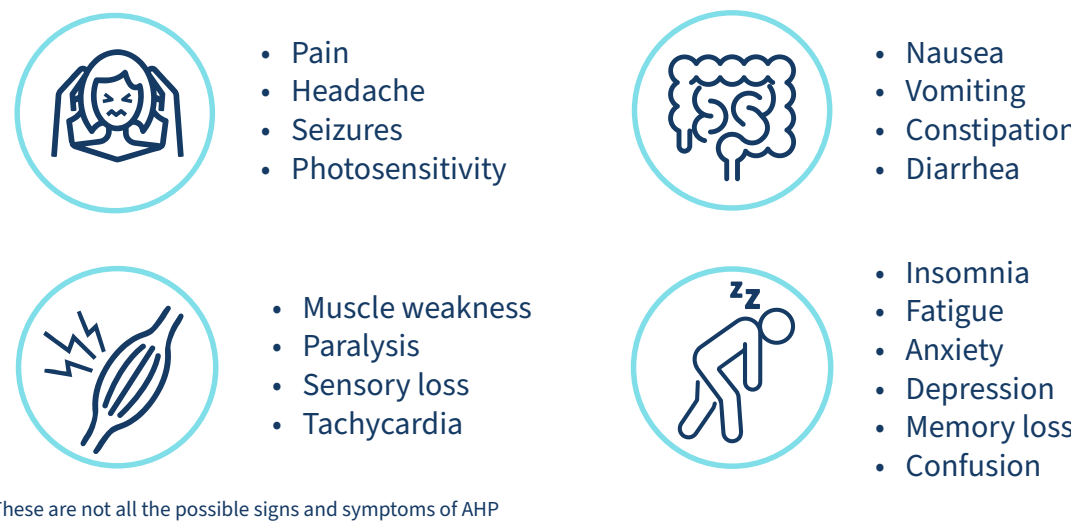
What is AHP?^{2,3}

- Acute hepatic porphyria (AHP) is a group of four rare, genetic, multisystemic disorders caused by defects in the heme biosynthesis pathway
- AHP can be potentially progressive with long-term complications



- A build-up of delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) in the body can cause:
 - Attacks**
 - Appear suddenly and are short lived
 - May be recurrent or non-recurrent
 - Severe and debilitating 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^{4,5}



What is givosiran?

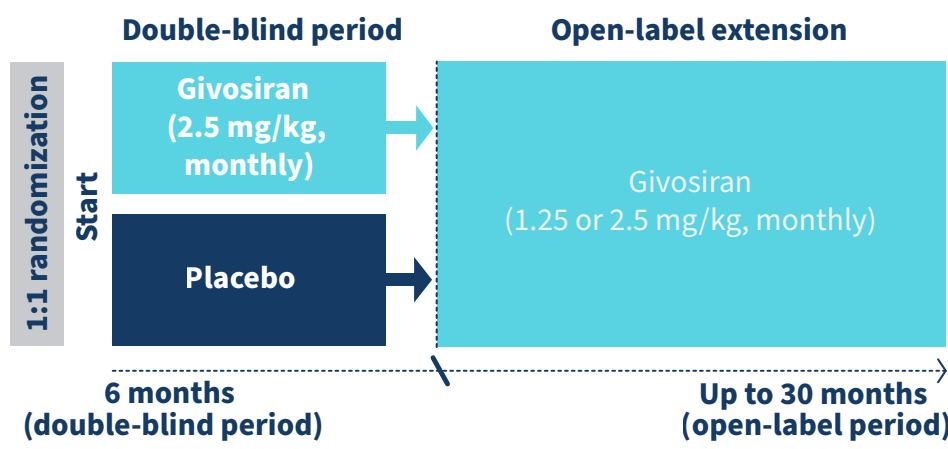
- An RNAi therapy that is used to treat adults with AHP⁶
- Please see the GIVLAARI full prescribing information for the FDA-approved product labeling⁵

What was the ENVISION study?

- ENVISION (NCT03338816) was a randomized, double-blind, placebo-controlled, multinational phase 3 study in adult patients with AHP (N=94), with a 30-month open-label extension (OLE) period (N=93)^{7,8}
- During the 6-month double-blind period, efficacy was measured as the rate of AHP attacks requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home
- Long-term efficacy and safety of givosiran treatment was evaluated through the OLE period

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



In the beginning of the open-label extension, patients were administered either 1.25 mg/kg or 2.5 mg/kg. Eventually, all patients were given 2.5 mg/kg.

What is this post hoc analysis?

- This descriptive post hoc subgroup analysis of patients who were either attack-free or not attack-free after 6 months of givosiran treatment describes the long-term outcomes up to month 36, which include¹:
 - annualized attack rate (AAR)
 - urinary ALA and PBG concentrations
 - EQ visual analog scale (EQ-VAS) score
 - 12-item short-form health survey (SF-12) version 2 physical component summary (PCS) score
- In a post hoc descriptive analysis composed of patients who had completed the double-blind and open-label periods, patients were grouped into:¹
 - Attack-Free:** had no attacks after 6 months of givosiran treatment (46 patients)
 - Not Attack-Free:** had at least 1 attack after 6 months of givosiran treatment (33 patients)
 - All Patients:** Attack-Free and Not Attack-Free groups combined (79 patients)

The listed endpoints were assessed as exploratory endpoints during the 36 month duration of the ENVISION study as part of the pre-specified analysis.

2 Methods

Annualized attack rate¹

Methods

- AAR was defined as the average number of attacks per person in a year that required any of the following:



- The AAR was calculated every 6 months to illustrate how the AAR changes throughout each 6-month period from the historical AAR baseline through to month 36
- Historical AAR was defined as the composite of porphyria attacks requiring hospitalization, an urgent healthcare visit, or intravenous hemin administration at home during the 6 months before randomization

ALA and PBG urine concentrations¹

Methods

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

Health-related quality of life (HRQoL)¹

HRQoL was measured using:

- EQ-VAS score
 - Rated on a scale of 0 to 100 (worst to best health you can imagine)⁹
 - An increase of more than 7-8 EQ-VAS points has been considered as 'clinically meaningful' in other chronic diseases^{9,10}



- SF-12 PCS score
 - General health, current effect of health on activities, and effect of physical health or pain on work or activities in the past 4 weeks were scored^{11,12}

3 Results

Baseline demographics and disease characteristics¹

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)
Age at diagnosis, years, mean (SD)	32.44 (11.39)	26.70 (9.03)	30.04 (10.79)
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)

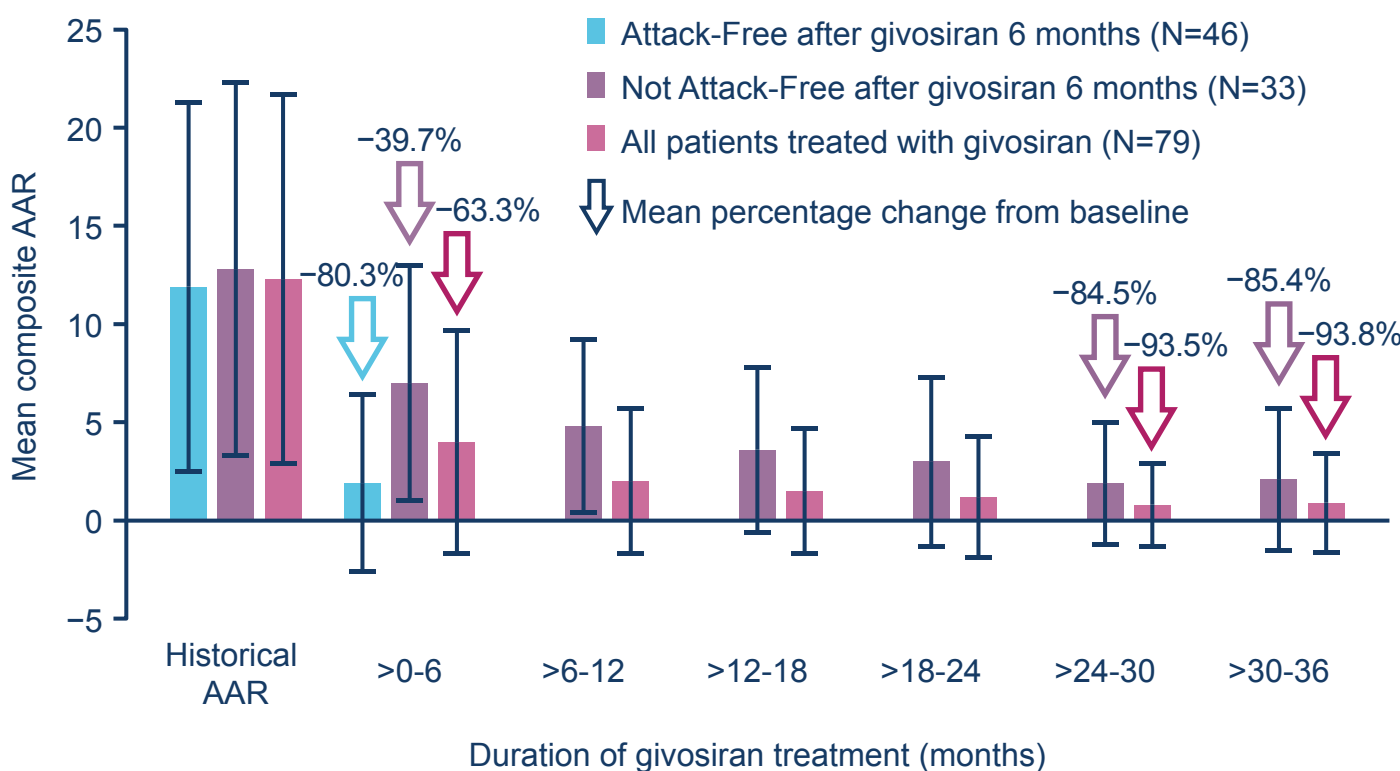
Annualized attack rate^{1,14}

The proportion of patients who became attack-free increased over time

- In the Not Attack-Free group, the percentage of patients who became attack-free changed from 9% (3/33 patients) after >6-12 months of treatment to 79% (26/33 patients) after >30-36 months of treatment
- In the Attack-Free group, all patients remained attack-free throughout the 36 months of the study

Mean composite AAR decreased over time with givosiran treatment

- 1st 6 months of treatment: mean composite AAR was reduced in all groups relative to historical AAR
- After 1st 6 months of treatment: Attack-Free group had no attacks and Not Attack-Free group had reduced attacks over 36 months of givosiran treatment

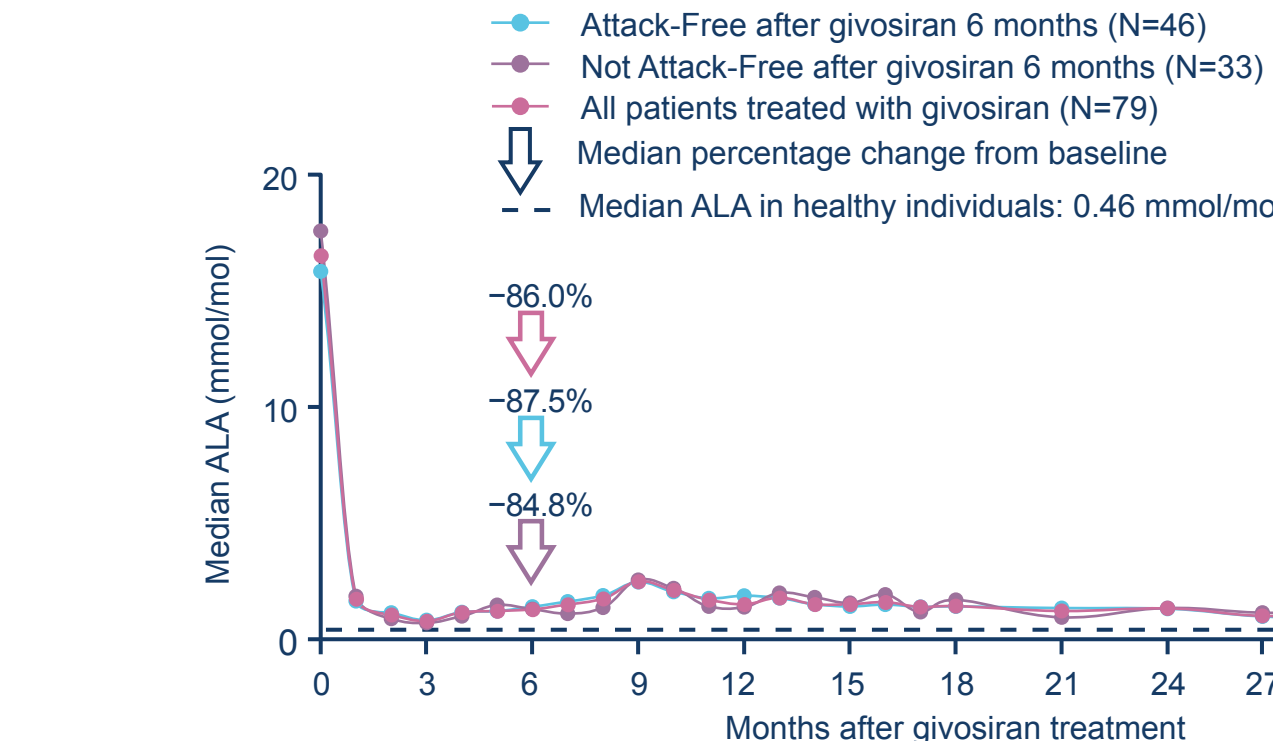


No. of patients:	Attack-free	Not attack-free	Total
Attack-free	46	33	79
Not attack-free	33	33	79
Total	79	79	79

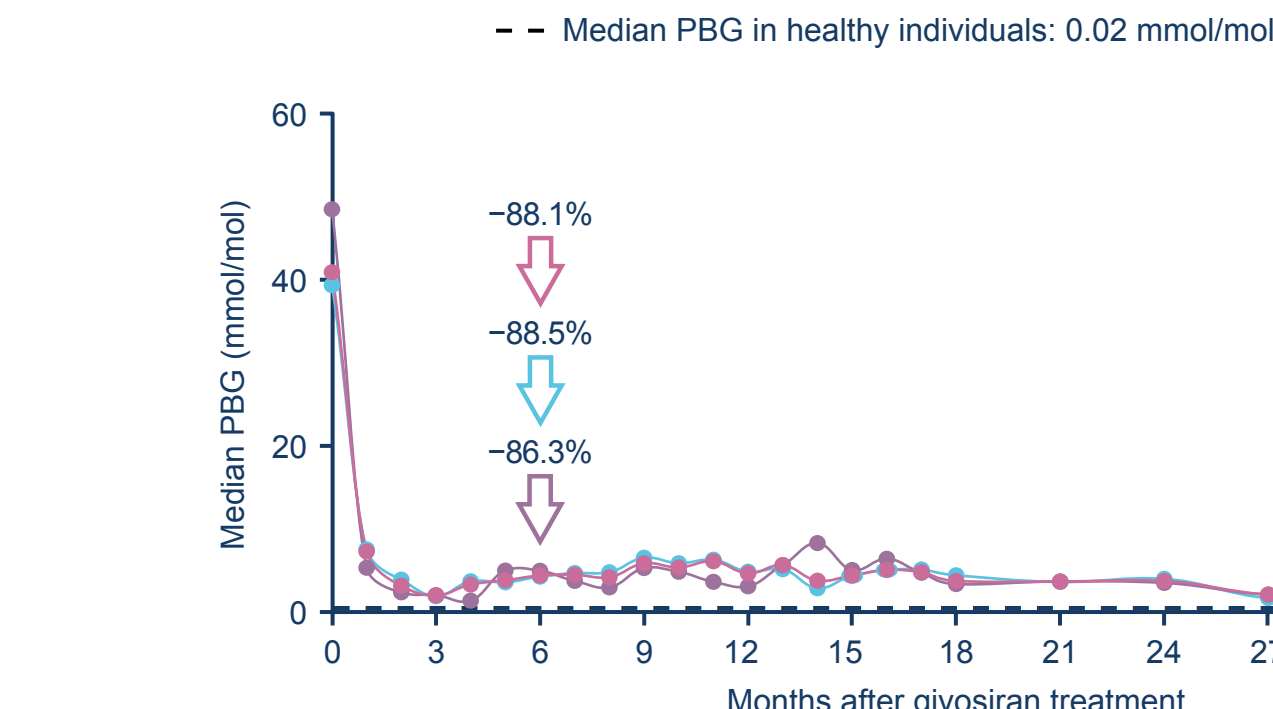
ALA and PBG urine concentrations¹

The reduction of median urinary ALA and PBG concentrations were sustained over time with givosiran treatment

- ALA and PBG reductions of >90% were observed through 36 months of givosiran treatment in the Not Attack-Free and Attack-Free groups*



No. of patients:	Attack-free	Not attack-free	Total
Attack-free	46	33	79
Not attack-free	33	33	79
Total	79	79	79



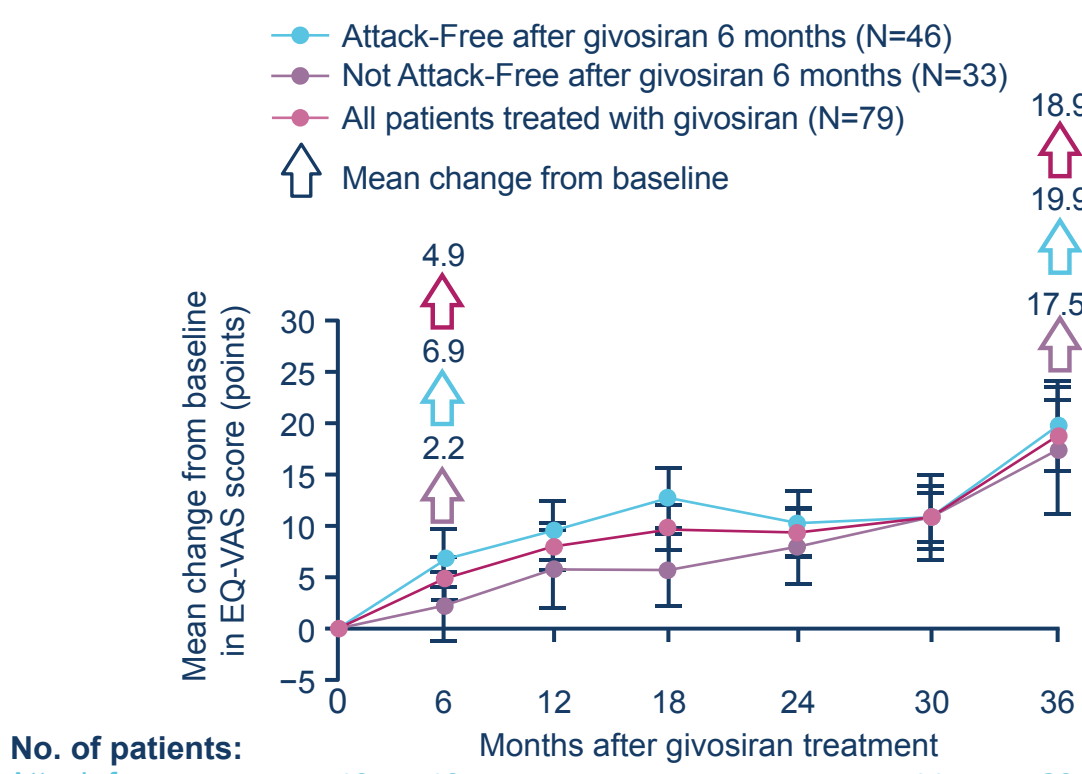
No. of patients:	Attack-free	Not attack-free	Total
Attack-free	46	33	79
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Total	79	79	79

*Baseline was redefined relative to the first dose of givosiran for patients receiving placebo in the DB period and analysis visits mapped based on redefined baseline.

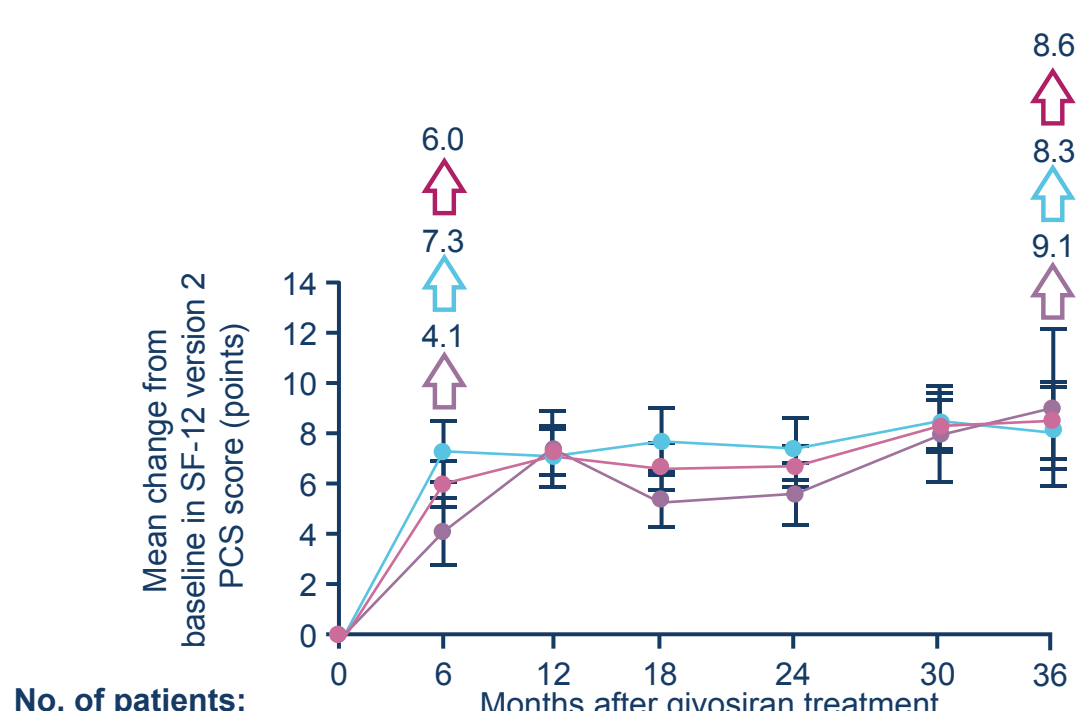
Health-related quality of life (HRQoL)¹

HRQoL scores increased over time with givosiran treatment

- HRQoL scores increased in all patients*
- After 6 months of treatment (0 months vs 6 months)
 - After 36 months of treatment (0 months vs 36 months)
 - At 36 months, EQ-VAS and SF-12 PCS score increases of >17.5 and >8, respectively, were observed in the Not Attack-Free and Attack-Free groups



No. of patients:	Attack-free	Not attack-free	Total
Attack-free	46	33	79
Not attack-free	33	33	79
Total	79	79	79



No. of patients:	Attack-free	Not attack-free	Total
Attack-free	46	33	79
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*Baseline was redefined relative to the first dose of givosiran for patients receiving placebo in the DB period and analysis visits mapped based on redefined baseline.

Safety¹

- In the 6-month double-blind placebo-controlled period of ENVISION, at least 1 adverse event was experienced in 90% of patients treated with givosiran (n=48) and 80% of patients receiving placebo (n=46)¹
- During this period, the most frequently occurring adverse events in patients treated with givosiran were nausea and injection site reactions
- Throughout the 36-month study period of ENVISION, including the 30-month OLE, 97% of the 94 patients treated with givosiran experienced any adverse event⁸
- The most frequently reported adverse events occurring in ≥20% of patients were injection site reactions, nausea, fatigue, nasopharyngitis, headache, urinary tract infection, and upper respiratory tract infection
- Hepatic and renal adverse events were reported in 18 (19%) and 21 (22%) patients, respectively
- Increased blood homocysteine was reported in 15 (16%) patients; 2 of these events were considered serious
- Pancreatitis was reported in 1 patient

Patients with ≥1 event, n (%)	All patients treated with givosiran (N=94)
Serious AE	37 (39)
Severe AE	35 (37)
AE leading to treatment discontinuation	6 (6)
AE leading to study withdrawal	4 (4)
Death	0

Study Limitations¹

- This post-hoc analysis was exploratory in nature and no formal statistical testing was planned for this analysis and, therefore, no statistical conclusions can be drawn
 - This analysis was not designed to evaluate the differences between and within group
 - Safety was not assessed in this post hoc analysis
- The study is limited by the relatively small number of patients in the study population
- For each outcome, there is a drop in patient numbers from 30 months to 36 months, as the data presented are only available for how long the patients were on givosiran therapy
- SF-12
 - Includes concepts that may not be relevant for the target population (ie, general health, moderate activities, climbing stairs)
 - The domains of bodily pain, social functioning, role limitations due to physical problems, and general health contribute more to the total PCS score
- EQ-VAS¹³
 - Includes measurement properties that were assessed for a broadly defined population
 - Self-completion may introduce possibly confounding effects

4 Summary

- In patients who remained attack-free and those who did not remain attack-free after 6 months of givosiran treatment, the data from the 36-month ENVISION post hoc analysis suggest decreased AAR, decreased urinary ALA/PBG concentrations, and increased SF-12 PCS and EQ-VAS scores with givosiran treatment through to the end of study¹



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