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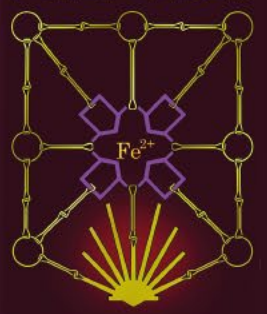

September 21-25, 2024

Pamplona (Spain)

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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

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Disclosures

Paolo Ventura received consultancy fees and honoraria from Alnylam Pharmaceuticals and Recordati Rare Disease

Encarna Guillen-Navarro 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

Bruce Wang is a scientific advisor to Alnylam Pharmaceuticals and Recordati Rare Diseases.

Weiming Du is an employee of and owns stock and stock options in Alnylam Pharmaceuticals

Ana Camejo was an employee of and shareholder in Alnylam Pharmaceuticals at the time of the study

Manish Thapar is a consultant and speaker for Alnylam Pharmaceuticals and has served as a consultant for Disc Medicine, Mitsubishi Tanabe, and Recordati Rare Diseases

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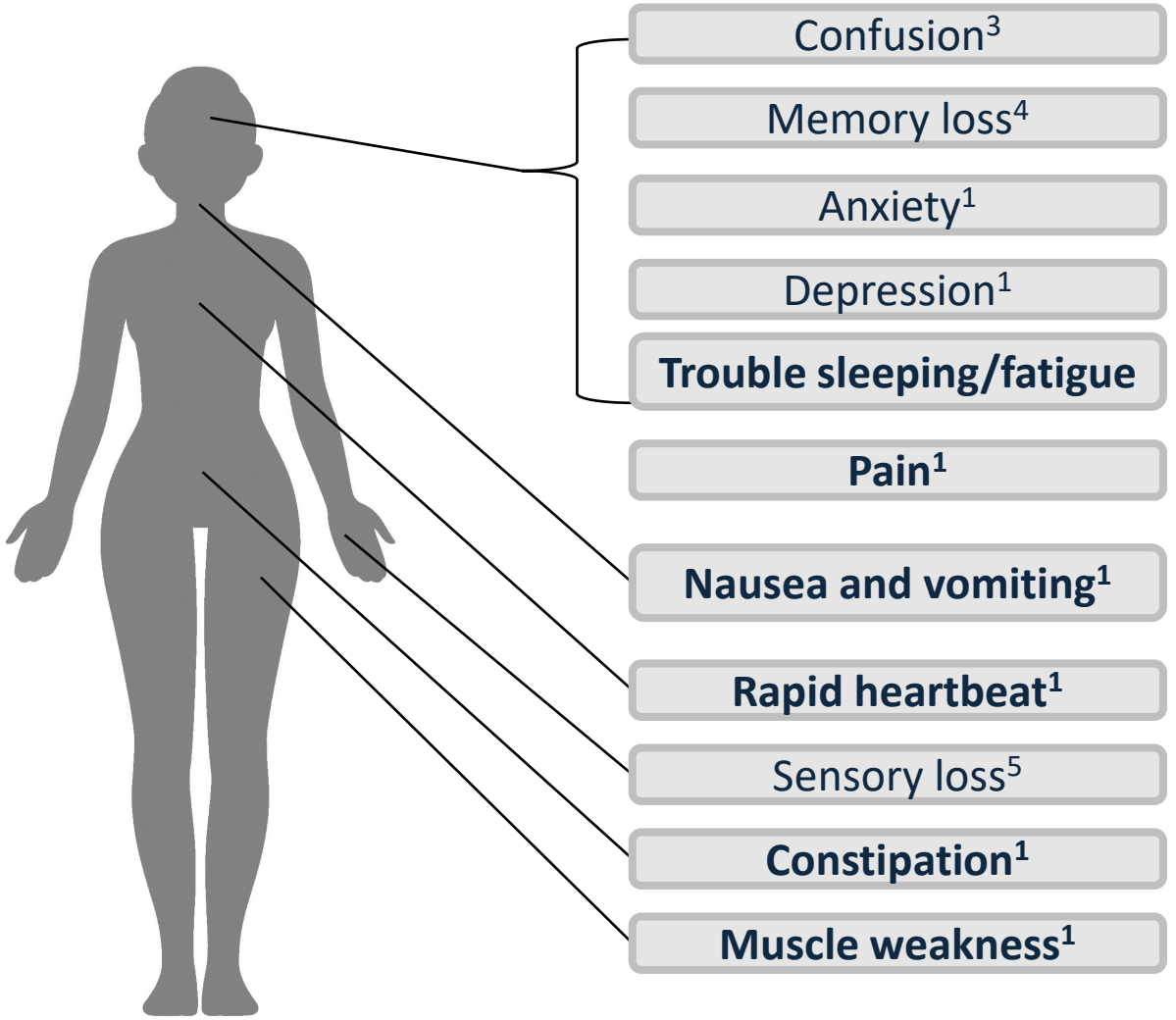
Background

- Acute hepatic porphyria (AHP) is a group of four rare, genetic, multisystemic disorders caused by defects in the heme biosynthesis pathway[1]
- Defects cause the accumulation of δ-aminolevulinic acid (ALA) and porphobilinogen (PBG)[2]
- Patients with AHP can experience:[1]
  - acute attacks
  - chronic symptoms
  - progressive elements
  - long-term complications
- Givosiran is an RNAi therapy that reduces accumulation of ALA and PBG[2]
  - Approved in the USA, Brazil, Taiwan, and Canada for the treatment of adults with AHP
  - Approved in the EU, Switzerland, and Japan for the treatment of adults and adolescents (≥12 years of age) with AHP



Symptoms **in bold** are those most commonly experienced by patients with AHP

AHP, acute hepatic porphyria; ALA, δ-aminolevulinic acid; PBG, porphobilinogen; RNAi, interfering RNA

1. Wang B *et al. Hepatol Commun* 2019;3:193-206; 2. Puy H et al. *Lancet* 2010;375:924-37; 3. Wheeden K *et al. Adv Ther* 2022;39:4330-45; 4. Simon A *et al. Patient* 2018;11:527–37; 5. Thandani *et al. BMJ* 2000;320:1647-51

ENVISION: overview

A multicentre, randomized, double-blind, placebo-controlled, phase 3 study (NCT03338816)

- In the ENVISION study, sustained reductions in annualized attack rate 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, and were not attack-free after the first 6-months of givosiran treatment

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

ENVISION: study design

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

1:1 randomization

6-month DB period

- Givosiran 2.5 mg/kg monthly
- Placebo

30-month OLE period

- Givosiran 1.25 mg/kg monthly, or 2.5 mg/kg monthly[a]

***Post hoc* descriptive analysis**

- Comprised patients who had 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

[a]The dose could be increased from 1.25 mg/kg to 2.5 mg/kg monthly or after month 13 in those who experienced inadequate control on the 1.25 mg/kg dose. Per a subsequent protocol amendment, the 1.25 mg/kg dose was increased to 2.5 mg/kg monthly in the remaining patients. AHP, acute hepatic porphyria; DB, double-blind; OLE, open-label extension

Baseline demographics and disease characteristics

- In total, 94 patients were randomized; 79 completed the study
  - 46 (58%) patients were attack-free
  - 33 (42%) patients were not attack free

- For patients who were not attack-free, mean composite AAR (attacks requiring hospitalization, urgent care, or intravenous hemin at home) after >0–6-months of givosiran treatment was 7.0 (range, 0.0-23.9)

The demographics and disease characteristics at the double-blind period baseline were summarized.
AAR, annualized attack rate

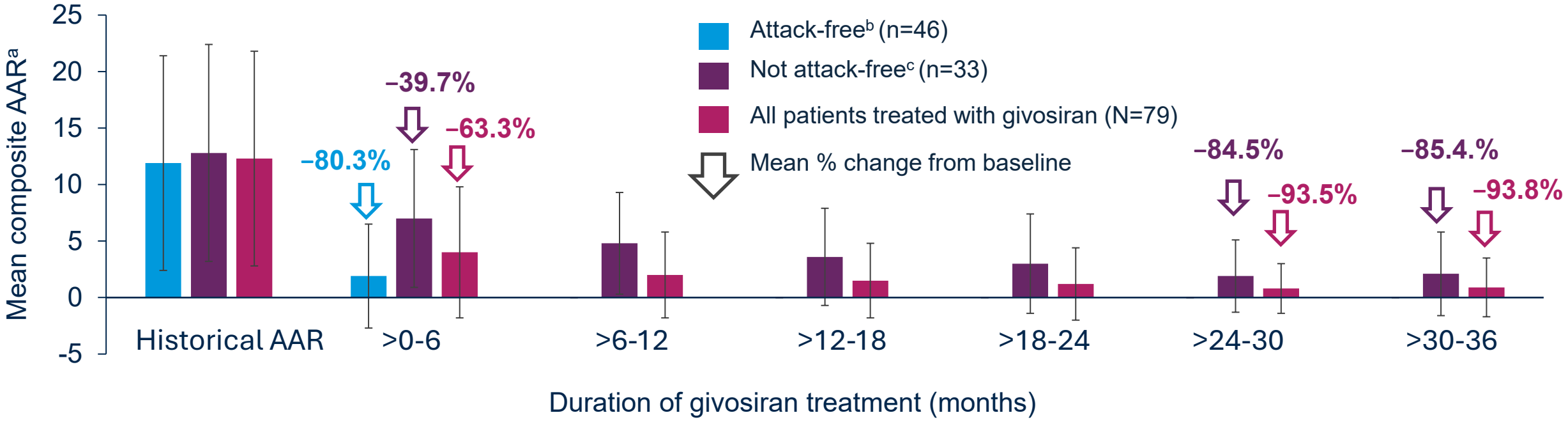
Baseline demographics and disease characteristics

Demographic/characteristic[a]	Attack-free[b] (n=46)	Not attack-free[c] (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)
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)

[a]The demographics and disease characteristics at the double-blind period baseline were summarized; [b]Patients with 0 attacks; [c]Patients with ≥1 attack after the first 6-months of givosiran treatment and for the study duration
Max, maximum; min, minimum; N, total number of patients included; n, patients included per subgroup; SD, standard deviation

Mean composite AAR per 6-month interval decreased over time for patients who were in the 'Not attack-free' group

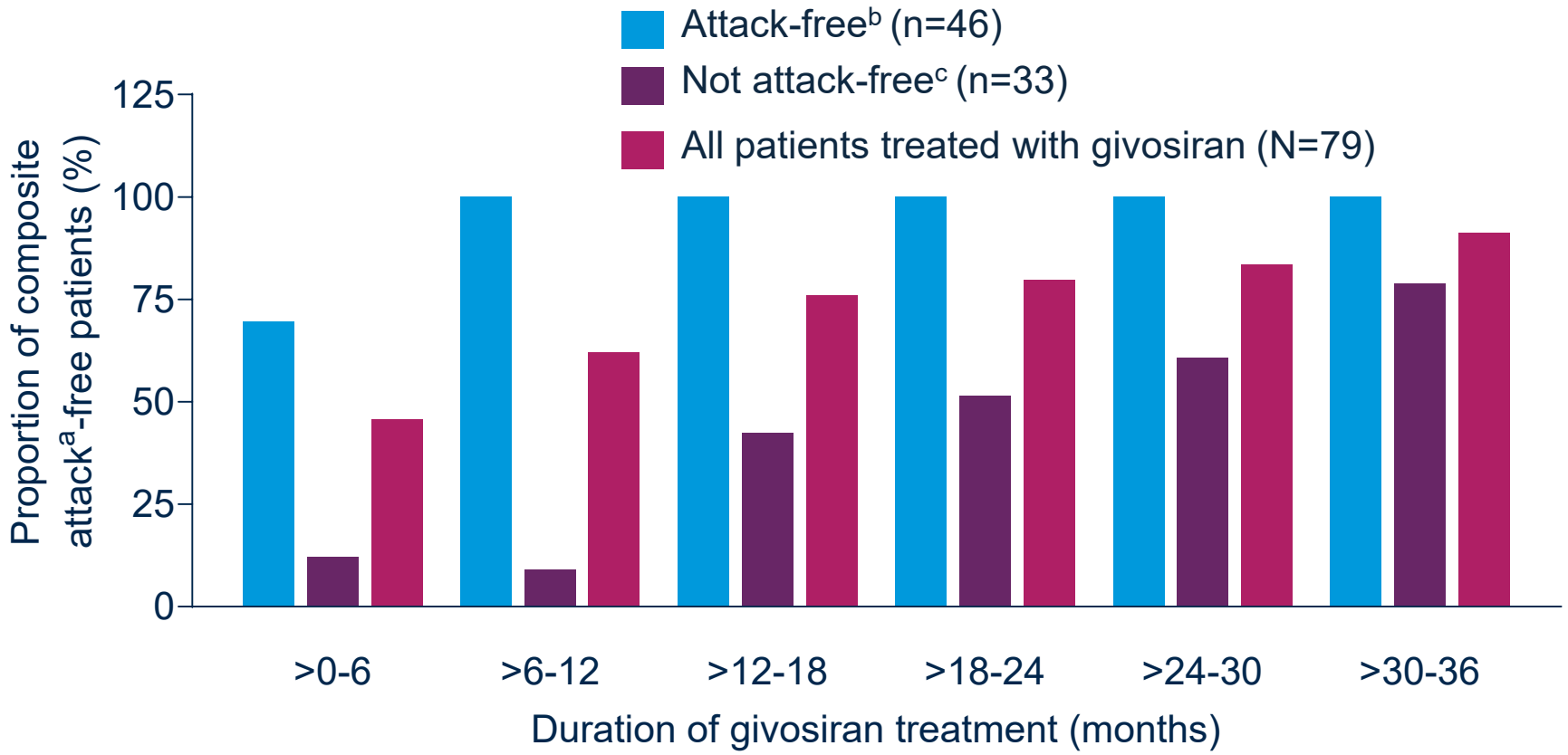
- Mean % reductions relative to historical composite AAR (mean [SD], 12.8 [9.6]):
  - −39.7% after >0-6-months of givosiran treatment
  - −85.4% after >30-36-months of givosiran treatment
- Patients who were attack-free remained attack-free throughout the 36-months of the study



AAR were attacks requiring hospitalization, urgent care, or intravenous hemin at home. Baseline represents 6-months before randomization. Error bars show SDs. Data on arrows show mean % change from baseline in mean composite AAR. [a]Composite attacks were attacks requiring hospitalization, urgent care, or intravenous hemin at home; [b]Patients with 0 attacks; [c]Patients with ≥1 attack after the first 6-month s of givosiran treatment and for the study duration. AAR, annualized attack rate; SD, standard deviation

Number of patients in the 'Not attack-free' group who became attack-free with continued treatment increased with each additional 6-month interval

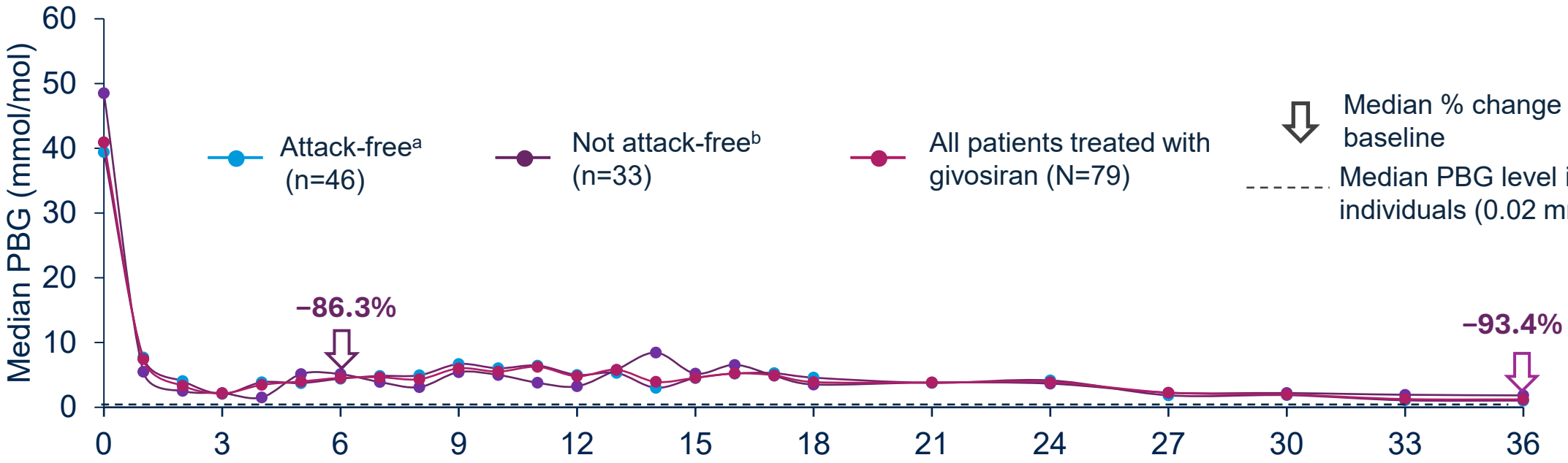
- Not attack-free group:
  - 9% attack-free after >6-12-months of treatment
  - 79% after >30-36-months of treatment



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

[a]Composite attacks were attacks requiring hospitalization, urgent care, or intravenous hemin at home; [b]Patients with 0 attacks; [c]Patients with ≥1 attack after the first 6-months of givosiran treatment and for the study duration

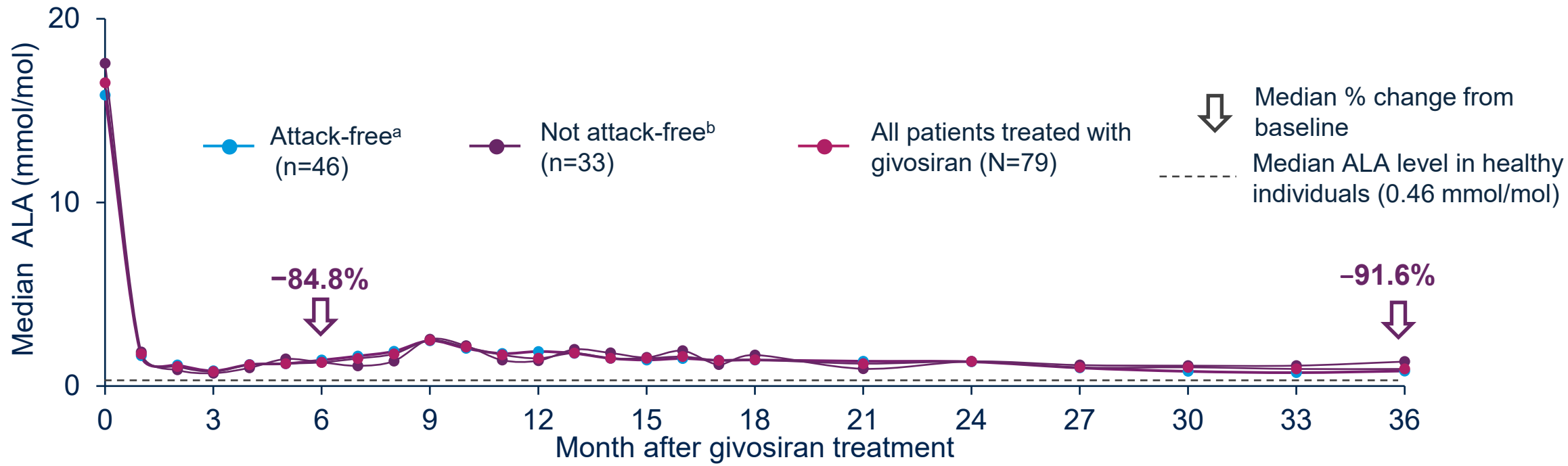
Median urinary PBG levels decreased over time



No. of patients:													
Attack free[a]	46	46	46	46	45	45	45	43	43	45	45	22	24
% change[c]			**−88.5**								**−94.7**		**−97.2**
Not attack free[b]	33	32	31	33	31	32	33	32	31	32	31	16	16
% change[c]			**−86.3**								**−93.8**		**−93.4**
Total	79	78	77	79	76	77	78	75	74	77	76	38	40
% change[c]			**−88.1**								**−94.6**		**−95.9**

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. Data on arrows show median % change from baseline in PBG levels. [a]Patients with 0 attacks; [b]Patients with ≥1 attack after the first 6-months of givosiran treatment and for the study duration; [c]Percentage change from baseline. DB, double blind, N, total number of patients included; n, patients included per subgroup; OLE, open-label extension; PBG, porphobilinogen

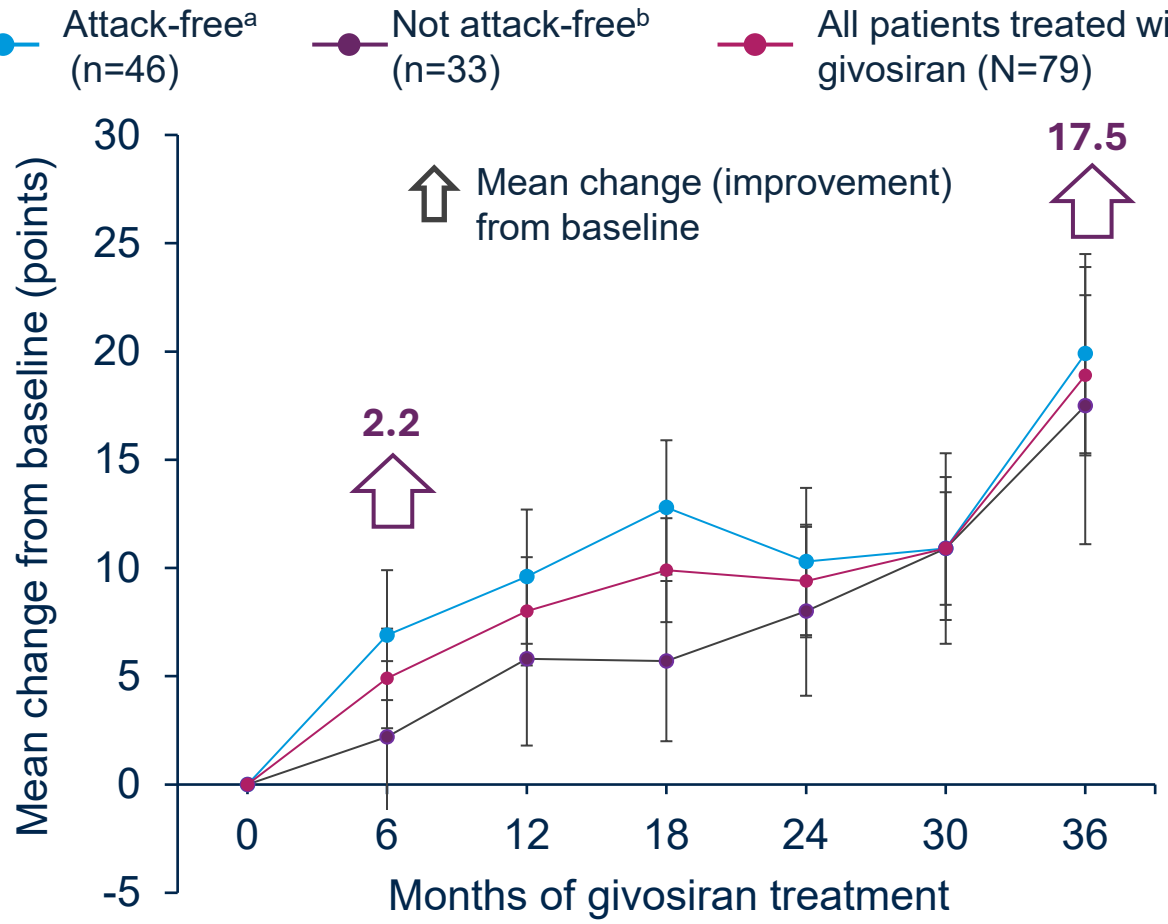
Median urinary ALA levels decreased over time



No. of patients:													
Attack free[a]	46	46	46	46	45	45	45	43	43	45	45	22	24
% change[c]			**−87.5**								**−92.6**		**−92.7**
Not attack free[b]	33	32	31	33	31	32	33	32	31	33	31	16	16
% change[c]			**−84.8**								**−90.0**		**−91.6**
Total	79	78	77	79	76	77	78	75	74	78	76	38	40
% change[c]			**−86.0**								**−92.3**		**−92.7**

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. Data on arrows show median % change from baseline in median ALA levels. [a]Patients with 0 attacks; [b]Patients with ≥1 attack after the first 6-months of givosiran treatment and for the study duration. [c]Percentage median change from baseline. ALA, δ-aminolevulinic acid; DB, double blind; N, total number of patients included; n, patients included per subgroup; OLE, open-label extension

EQ-VAS scores improved in both groups

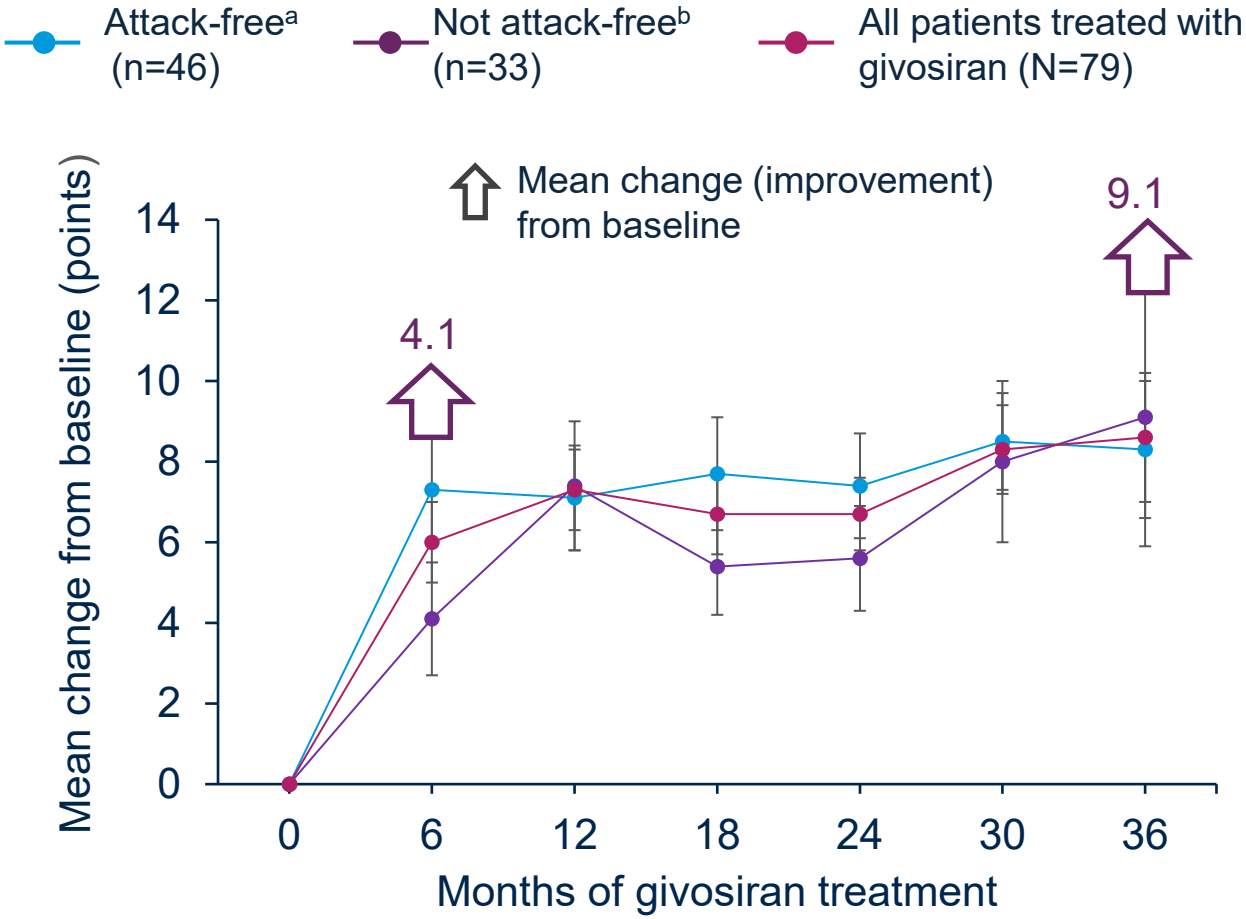


Change from baseline, mean±SEM (n)	Attack-free[a] (n=46)	Not attack-free[b] (n=33)	All patients treated with givosiran (N=79)
Baseline	68.1±3.2 (46)	62.0±3.9 (33)	65.6±2.5 (79)
After 6-months of treatment	6.9±3.0 (46)	2.2±3.5 (33)	4.9±2.3 (79)
After 30-months of treatment	10.9±3.3 (44)	10.9±4.4 (29)	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)

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. 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. **Estimates for the clinically meaningful difference are ≥7 to 8 points for EQ-VAS.** [a]Patients with 0 attacks; [b]Patients with ≥1 attack after the first 6-months of givosiran treatment and for the study duration

EQ-VAS, EuroQol visual analogue scale; DB, double blind; N, total number of patients included; n, patients included in each subgroup; OLE, open-label extension; SEM, standard error of the mean

SF-12 version 2 PCS scores improved in both groups



Change from baseline, mean±SEM (n)	Attack-free[a] (n=46)	Not attack-free[b] (n=33)	All patients treated with givosiran (N=79)
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)

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. 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 SF-12 score points. **Estimates for the clinically meaningful difference are 2 to 5 points for SF-12.** [a]Patients with 0 attacks; [b]Patients with ≥1 attack after the first 6-months of givosiran treatment and for the study duration

DB, Double blind, N, total number of patients included; n, patients included in each subgroup; OLE, open-label extension; PCS, Physical Component Summary; SEM, standard error of the mean; SF-12, 12-item Short Form Health survey

ENVISION: summary of *post hoc* analyses

- 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 HRQoL life improvements with long-term givosiran treatment
- Patients who were attack-free remained attack-free and report HRQoL improvements through month 36

Results of this analysis indicate that long-term givosiran treatment provides sustained improvements in health outcomes for patients, regardless of attack status

HRQoL, health-related quality-of-life

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the ENVISION study

For US HCPs only;
scan to view interactive Infographic of ENVISION *post hoc* study data

HCP, healthcare professional