Clinical outcomes and hemin use of patients with acute hepatic porphyria in the phase 3 ENVISION study who were not attack-free after 6 months of givosiran treatment

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Disclosures

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

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

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

Eliane Sardh received grant support and personal fees, paid to Karolinska Institutet, from Alnylam Pharmaceuticals.

Weiming Du and **Ilaria Olivetti** are employees of and own stock and stock options in Alnylam Pharmaceuticals.

Manisha Balwani has received grant support, consulting fees, advisory board fees, and lecture fees from Alnylam Pharmaceuticals; grant support from Disc Medicine and Mitsubishi Tanabe Pharma; and advisory board fees from Alexion, CRISPR Therapeutics, Disc Medicine, and Genzyme/Sanofi. 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.

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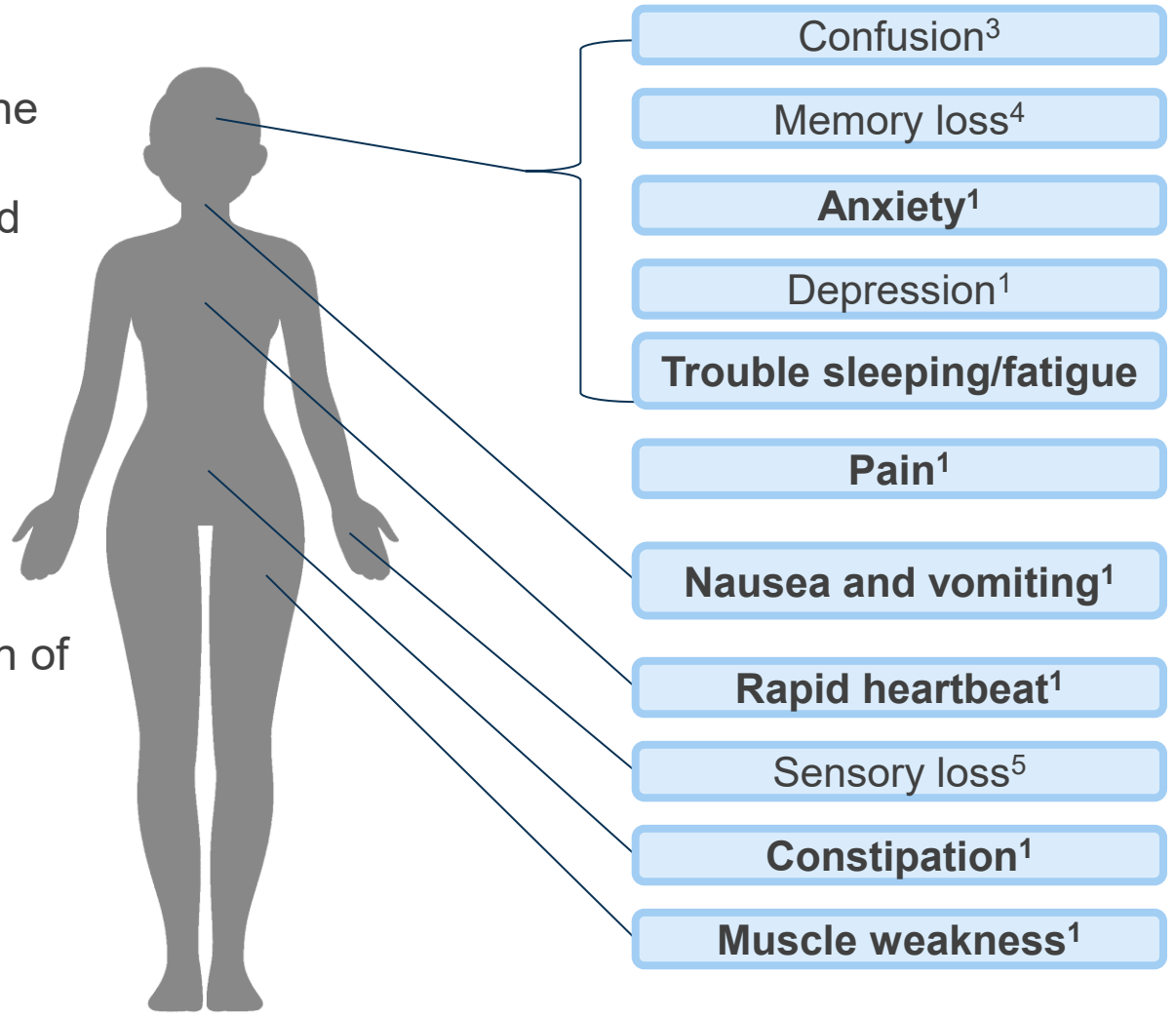
Background

- 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
  - long-term complications

- Givosiran is an RNAi therapy that reduces accumulation of ALA and PBG[2]
  - Approved in the USA, Brazil, Canada, Taiwan, Colombia*, and Mexico for the treatment of adults with AHP
  - Approved in the EU/EEA, UK, Switzerland, Israel, Japan, Argentina, Australia, Kuwait, and UAE for the treatment of adults and adolescents (≥12 years of age) with AHP



Bolded text are the most common symptoms experienced by patients with AHP

*Approved for the treatment of AHP in adults who have had >4 attacks requiring hospitalization, emergency care, or intravenous hemin administration in the previous year

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 study: overview

- The ENVISION study (NCT03338816) was the pivotal phase 3, international, multicenter trial that supported the approval of givosiran for AHP

- 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]

- Evaluating changes in treatment burden, such as the need for hemin administration, may offer additional insights into the treatment benefit over time

- 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;79:1150-581

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 enrollment

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

Overview of patient demographics and characteristics

- In total, 94 patients were randomized; 79 completed the study
  - 46 patients (58%) were attack free after >0-6 months of givosiran treatment
  - 33 patients (42%) were not attack free >0-6 months of givosiran treatment
- 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. Baseline represents 6 months before randomization
AAR, annualized attack rate

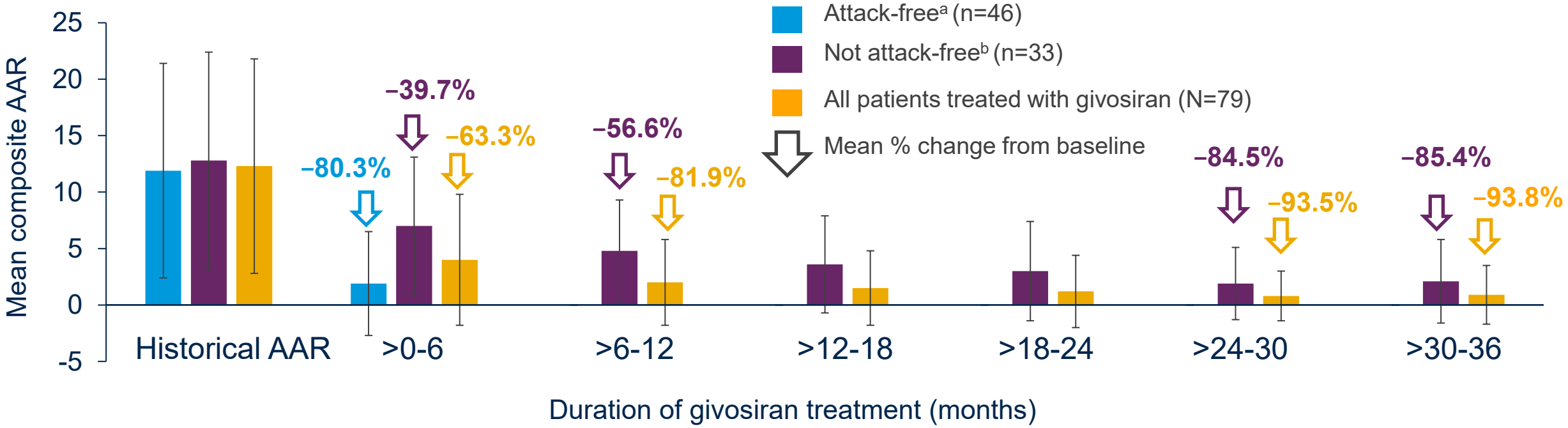
Baseline demographics and disease characteristics

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 (range)	41.5 (19.0-61.0)	36.0 (20.0-57.0)	38.0 (19.0-61.0)
Years since diagnosis 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. Baseline represents 6 months before randomization. [b]Patients with 0 attacks. [c]Patients with ≥1 attack
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 [96]):
  - 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



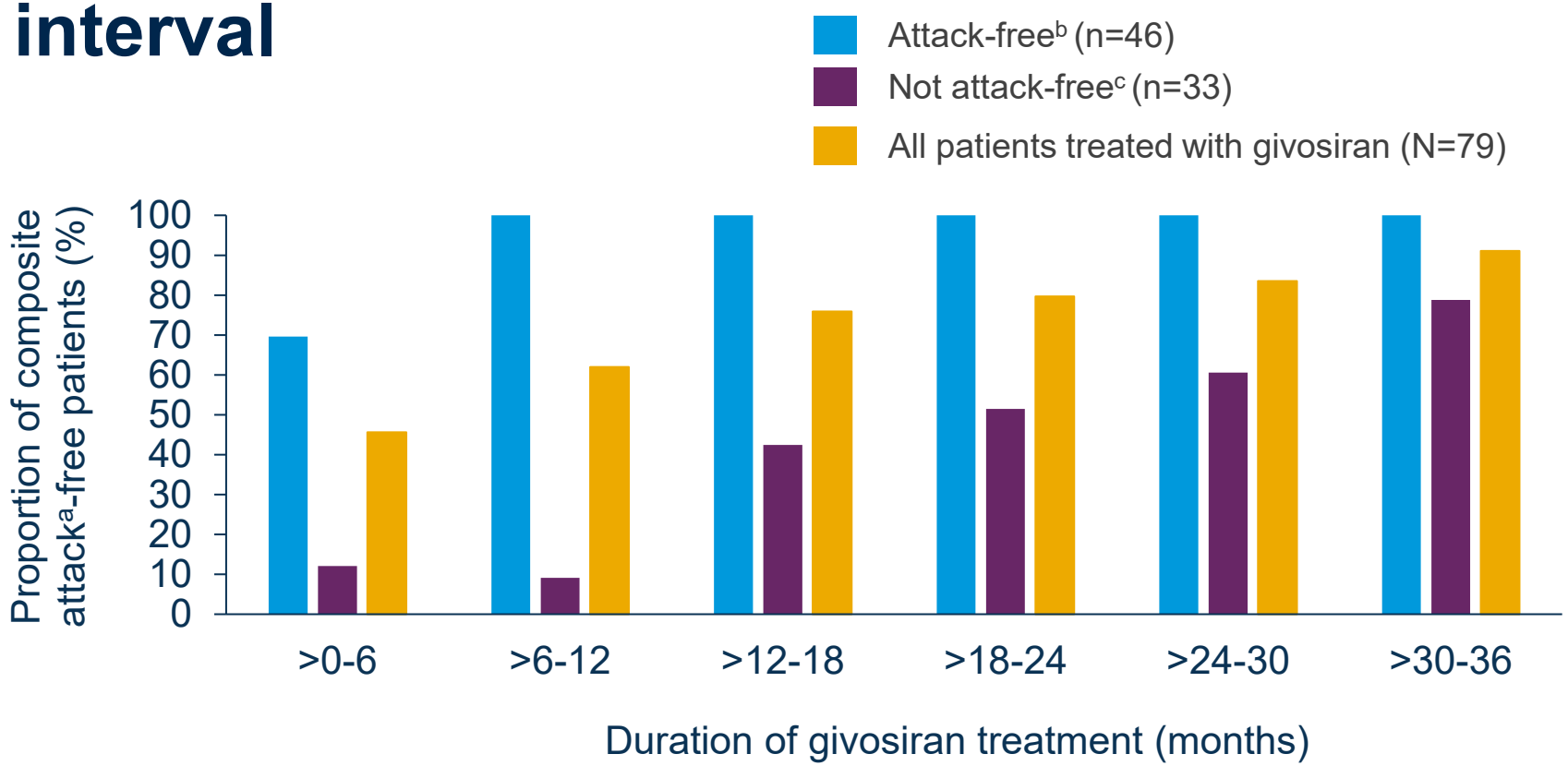
Composite AAR included attacks requiring hospitalization, urgent care, or intravenous hemin at home. Historical AAR was calculated based on the number of attacks requiring hospitalization, healthcare facility visit, or hemin use at home at baseline. Baseline represents 6 months before randomization. Error bars show standard deviations. Data on arrows show mean % change from baseline in mean composite AAR

[a]Patients with 0 attacks after 6 months of givosiran treatment. [b]Patients with ≥1 attack after 6 months of givosiran treatment

AAR, annualized attack rate; N, total number of patients included; n, patients included per subgroup; 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% attack-free after >30-36 months of treatment

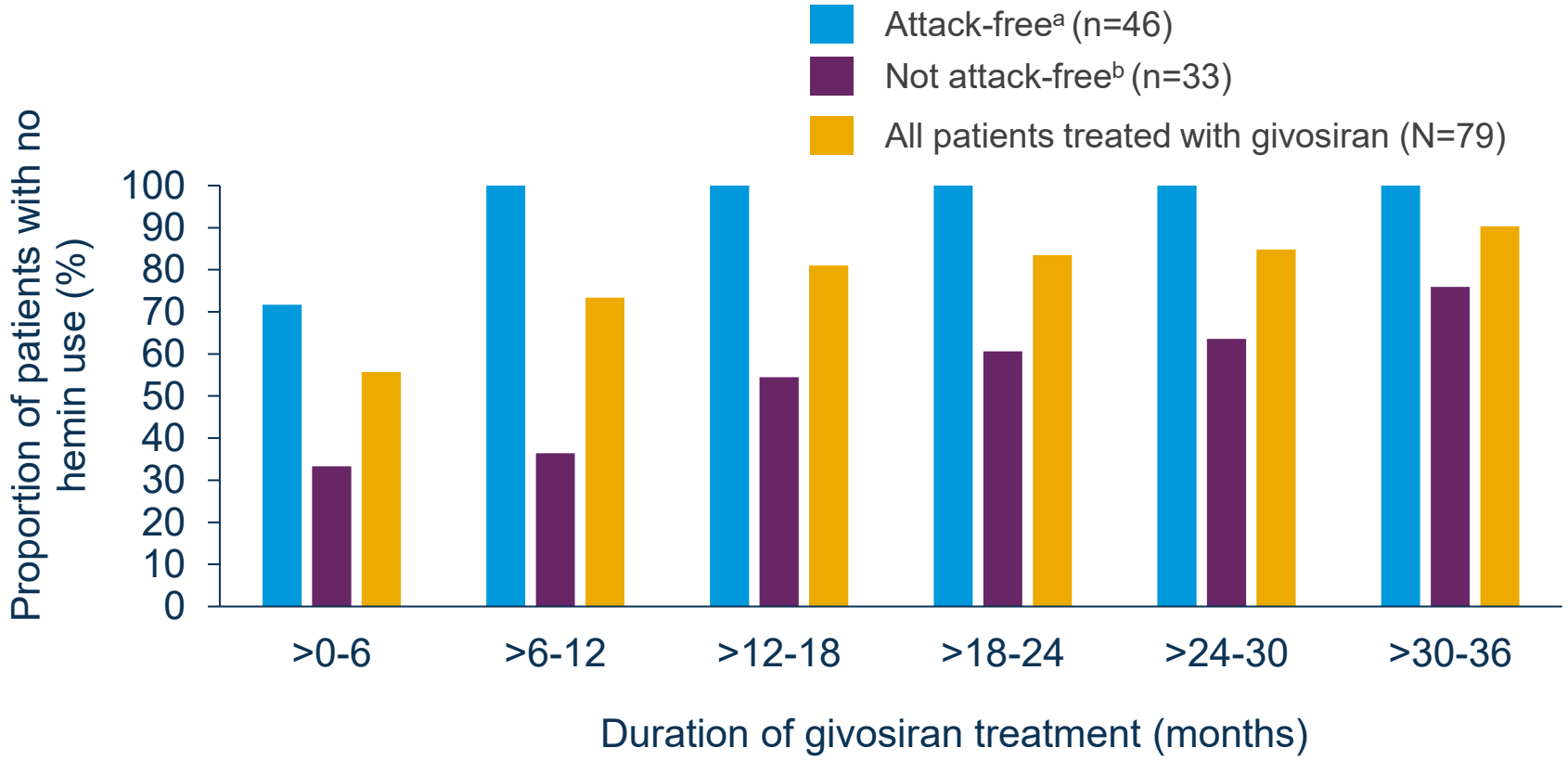


No. of patients:						
Attack-free[b]	32	46	46	46	46	46
Not attack-free[c]	4	3	14	17	20	26
Total	36	49	60	63	66	72

[a]Composite attacks included attacks requiring hospitalization, urgent care, or intravenous hemin at home. [b]Patients with 0 attacks after 6 months of givosiran treatment. [c]Patients with ≥1 attack after 6 months of givosiran treatment
N, total number of patients included; n, patients included per subgroup

The number of patients with no hemin use increased with each 6-month interval

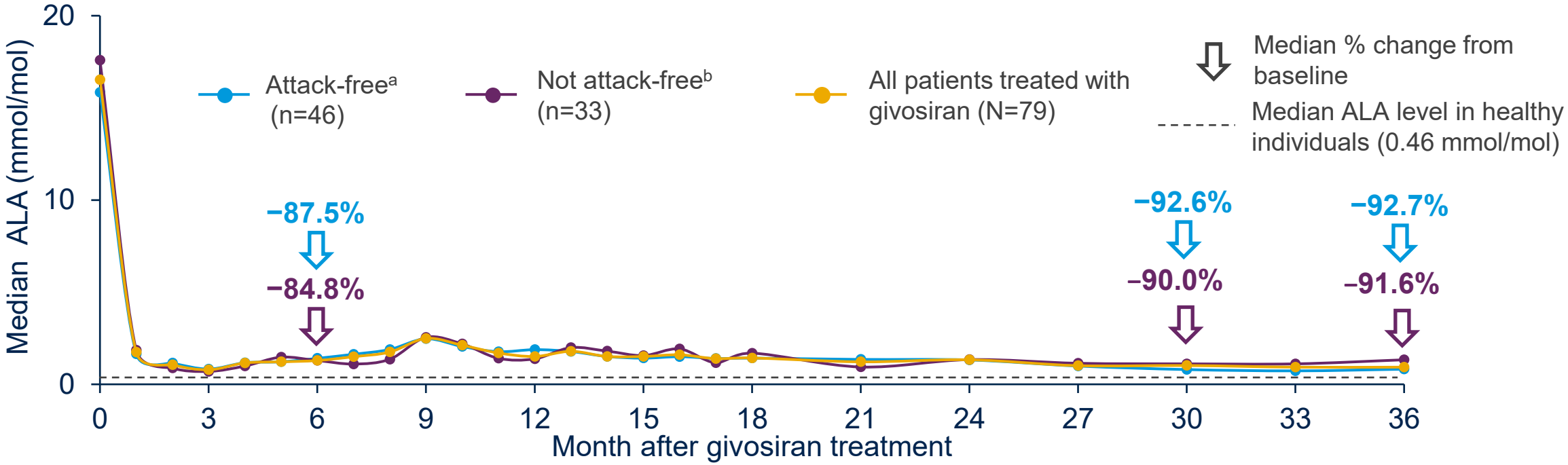
- Of the patients who were not attack-free after the first 6 months of treatment, the proportion of patients with no hemin use (during 6-month treatment intervals) increased over time:
  - 36% after >6-12 months of treatment
  - 76% after >30-36 months of treatment



No. of patients:						
Attack-free[a]	33	46	46	46	46	43[c]
Not attack-free[b]	11	12	18	20	21	22[d]
Total	44	58	64	66	67	65[e]

[a]Patients with 0 attacks after 6 months of givosiran treatment. [b]Patients with ≥1 attack after 6 months of givosiran treatment. [c]Data were available for 43 patients. [d]Data were available for 29 patients. [e]Data were available for 72 patients
N, total number of patients included; n, patients included per subgroup

Median urinary ALA levels decreased over time

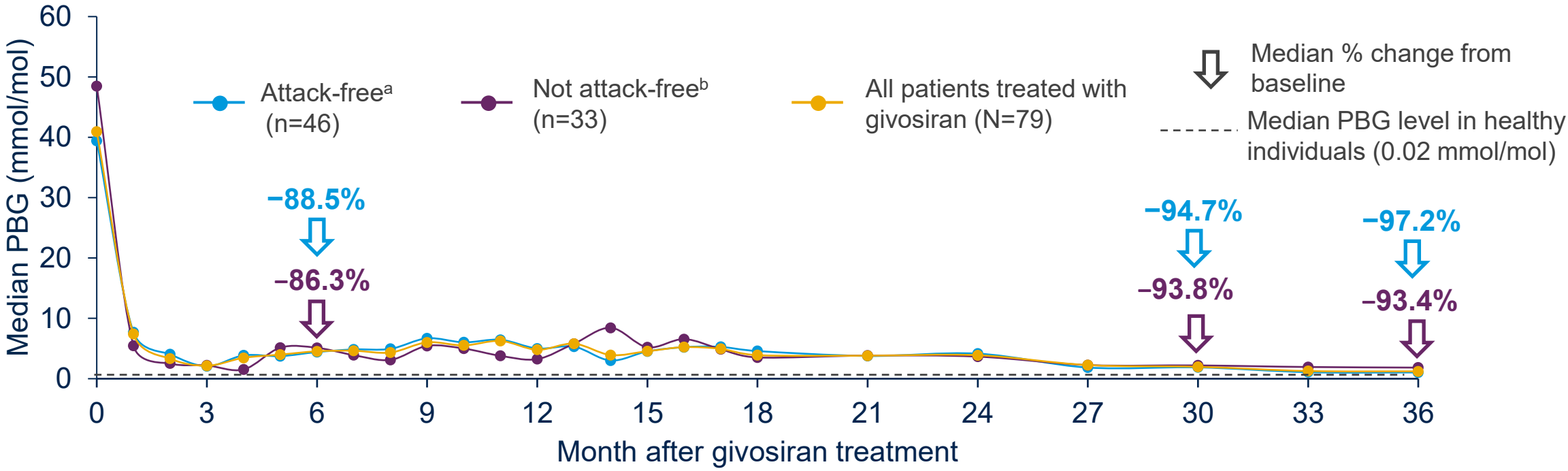


No of patients:

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**

Urinary levels of ALA were normalized to creatinine. Baseline represents 6 months before randomization. Data on arrows show median % change from baseline in median ALA levels.
[a]Patients with 0 attacks after 6 months of givosiran treatment. [b]Patients with ≥1 attack after 6 months of givosiran treatment. [c]Percentage median change from baseline
ALA, δ-aminolevulinic acid; N, total number of patients included; n, patients included per subgroup

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**

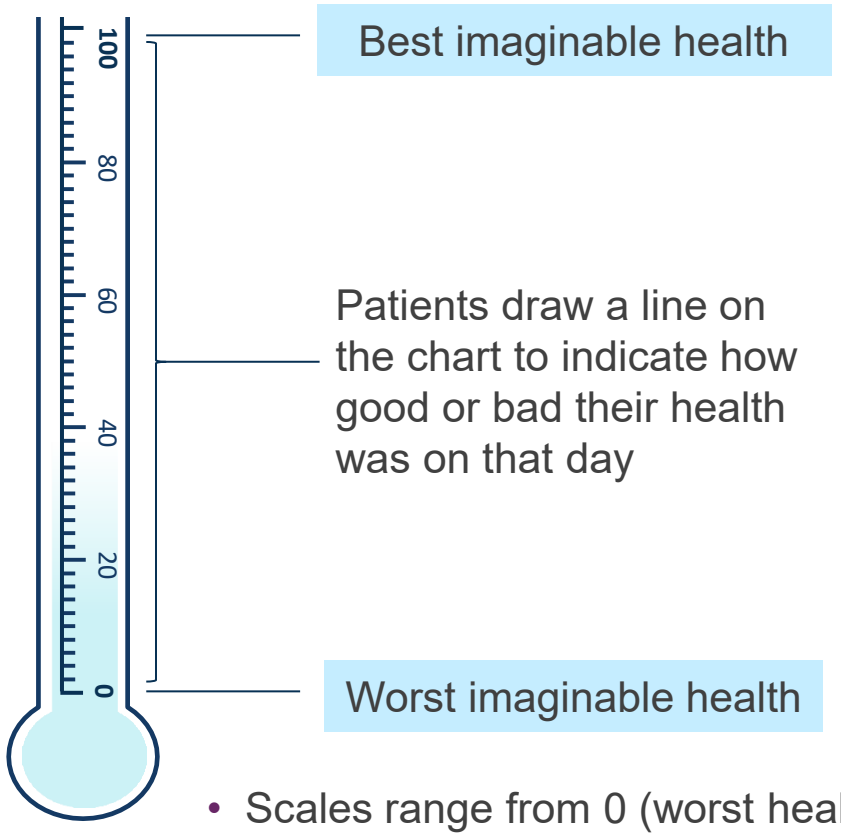
Urinary levels of PBG were normalized to creatinine. Baseline represents 6 months before randomization. Data on arrows show median % change from baseline in median PBG levels

[a]Patients with 0 attacks after 6 months of givosiran treatment. [b]Patients with ≥1 attack after 6 months of givosiran treatment. [c]Percentage median change from baseline

N, total number of patients included; n, patients included per subgroup; PBG, porphobilinogen

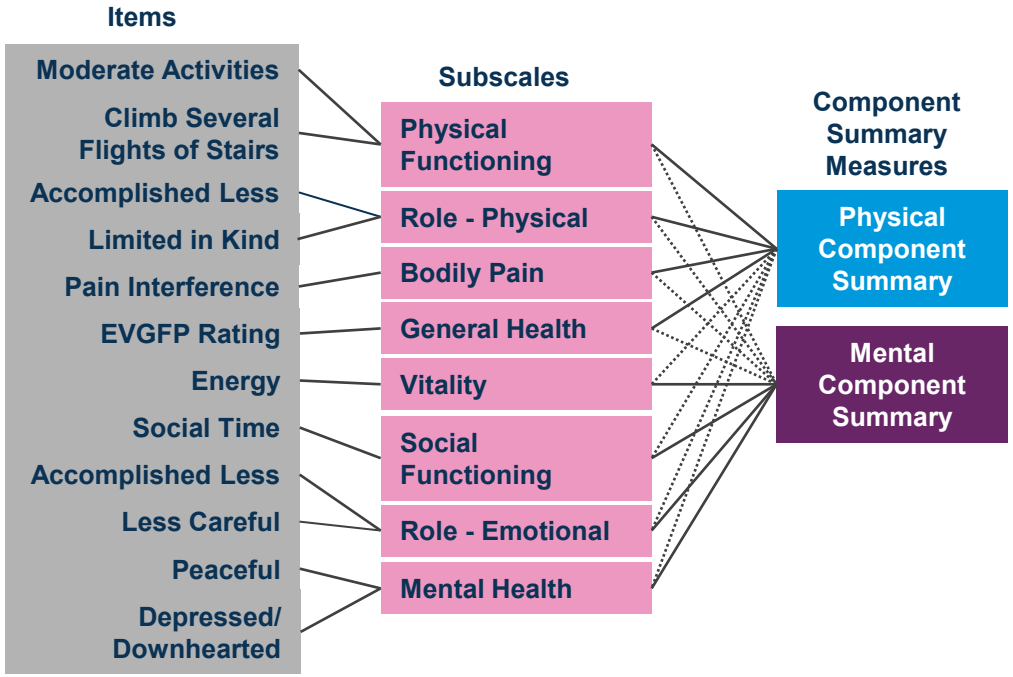
Health-Related Quality of Life (HRQoL) Tools in ENVISION Study

EQ VAS[1,2]



- Scales range from 0 (worst health) to 100 (best health)
- Estimates for clinically meaningful difference in EQ-VAS scores: ≥7-8 points

SF-12 health survey[1,3]

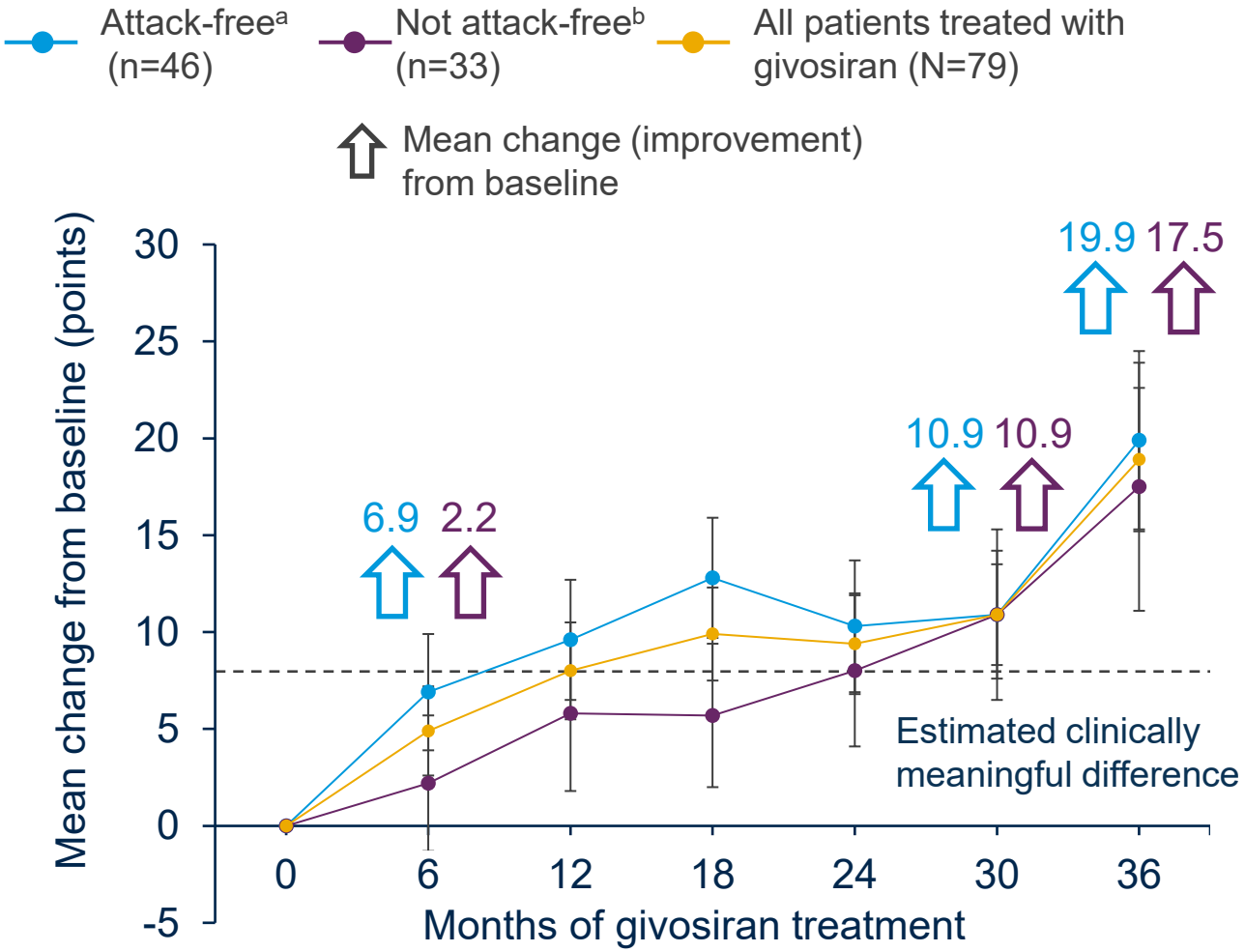


- Scores range from 0-100 and higher scores indicate better health/functioning
- Estimates for clinically meaningful difference in SF-12 scores: ≥2-5 points

EQ-VAS, EQ-visual analogue scale; EVGFP, excellent-very good-good-fair-poor health; HRQoL, health-related quality of life; SF-12, short-form 12

1. Kuter DJ *et al*. *J Hepatol* 2023;79:1150-581; 2. EuroQol Group. EQ-5D-5L User Guide. Available from: https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-5l/. Accessed October 2025.
3. Ware JE *et al*. *Medical Care* 1996;34:220–233

EQ-VAS Scores improved in both groups



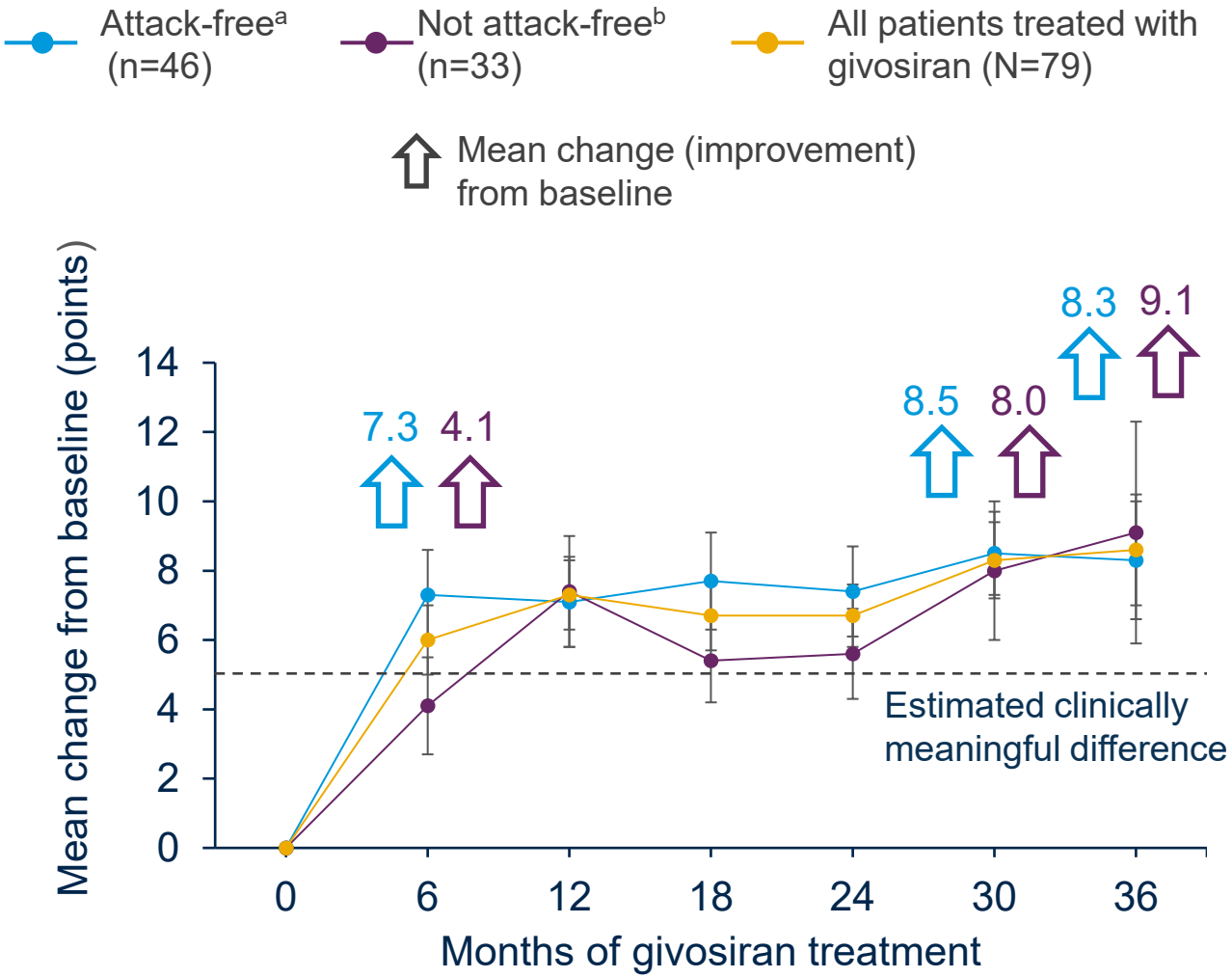
Change from baseline, mean ±SEM (n)	Attack-free[a] (n=46)	Not attack-free[b] (n=33)	All patients treated with givosiran (N=79)
Baseline	68.1±3.2 (46)	62.0±3.9 (33)	65.6±2.5 (79)
After 6 months of treatment	6.9±3.0 (46)	2.2±3.5 (33)	4.9±2.3 (79)
After 30 months of treatment	10.9±3.3 (44)	10.9±4.4 (29)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

The EQ-VAS assesses a patient's global impression of their overall health on a visual analog scale which ranges from 0 (worst possible health) to 100 (best possible health). **Estimates for the clinically meaningful difference are ≥7 to 8 points and are shown by the dotted line.** Baseline represents 6 months before randomization. Error bars show SEM. Data on arrows show absolute mean change from baseline in EQ-VAS

[a]Patients with 0 attacks after 6 months of givosiran treatment. [b]Patients with ≥1 attack after 6 months of givosiran treatment

N, total number of patients included; n, patients included in each subgroup; 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)

Scores on the PCS of the SF-12 range from 0 (worst functioning) to 100 (best functioning). **Estimates for the clinically meaningful difference are ≥2 to 5 points and are shown by the dotted line**. Baseline represents 6 months before randomization. Error bars show SEM. Data on arrows show absolute mean change from baseline in SF-12 score points

[a]Patients with 0 attacks after 6 months of givosiran treatment. [b]Patients with ≥1 attack after 6 months of givosiran treatment

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

ENVISION: summary of *post hoc* analysis results

- In this *post hoc* analysis of the phase 3 study of givosiran, both patient groups had reduced attacks and other treatment-related improvements within the first 6 months of givosiran treatment
- Patients who were attack-free after the first 6 months of givosiran treatment remained attack-free, did not require hemin treatment and reported HRQoL improvements through month 36
- Patients who were not attack-free after the first 6 months of givosiran treatment experienced further reductions in attacks and hemin use, and improvements in HRQoL with long-term givosiran treatment

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

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