Disease Burden in Patients with Acute Hepatic Porphyria: Experience from the Phase 3 ENVISION Study

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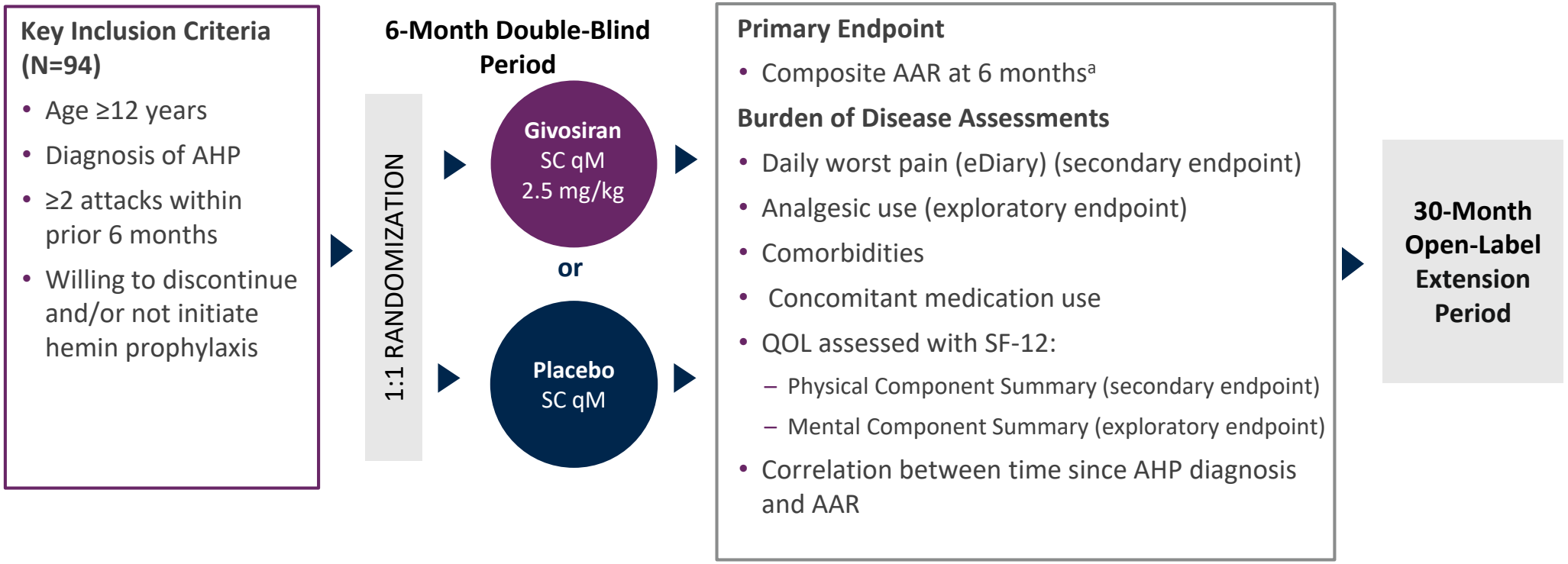
Introduction

- AHP is a family of rare metabolic disorders caused by defects in heme biosynthesis enzymes,[1–3] and is characterized by disabling acute neurovisceral attacks and chronic symptoms (e.g., pain, nausea, and fatigue) between attacks[2,4,5]
- Standard of care for acute attacks is IV hemin (also used off-label for prophylaxis)[4]
- Acute and chronic complications of hemin use include phlebitis, iron overload, venous thrombosis or obliteration, and central venous catheter complications[6–8]
- Givosiran, a synthetic *ALAS1*-directed small interfering RNA, is selectively delivered to the liver[9]
- In the phase 3 ENVISION study (NCT03338816), givosiran reduced the AAR by 74% versus placebo in patients with acute intermittent porphyria during the 6-month double-blind period[10]
  - During the open-label extension period, 85% of patients continuing givosiran were attack-free at >15 to 18 months[11]
- In this analysis we used data from ENVISION to summarize the spectrum of disease burden associated with AHP

AAR, annualized attack rate; AHP, acute hepatic porphyria; *ALAS-1*, aminolevulinate synthase; IV, intravenous

1. Anderson KE, et al. Ann Intern Med. 2005;142(6):439–450; 2. Ramanujam VM, Anderson KE. Curr Protoc Hum Genet. 2015;86:17.20.1–17.20.26; 3. Bonkovsky HL, et al. Mol Genet Metab. 2019;128(3):213–218; 4. Gouya L, et al. Hepatology. 2020;71(5):1546–1558; 5. Simon A, et al. Patient. 2018;11(5):527–537; 6. Wang B, et al. Hepatol Commun. 2019;3:193–206; 7. Stein PE, et al. Br J Haematol. 2017;176:527–538; 8. Recordati Rare Disease Inc. US prescribing information: PANHEMATIN (hemin for injection). 2017; 9. Springer AD, Dowdy SF. Nucleic Acid Ther. 2018;28(3):109–118; 10. Balwani M, et al. N Engl J Med. 2020;382(24):2289–2301; 11. Kuter DJ, et al. Presented at: Annual Scientific Symposium of the Hemostasis and Thrombosis Research Society; March 10–12, 2021

ENVISION Phase 3 Study Design and Burden of Disease Assessments



AAR, annualized attack rate; AHP, acute hepatic porphyria; IV, intravenous; qM, every month; QOL, quality of life; SC, subcutaneous; SF-12, Short Form (12-item) Health Survey
[a]Attacks requiring hospitalization, urgent health care facility visit, or IV hemin use at home; composite AAR was calculated for each patient by dividing total number of porphyria attacks by total number of days in treatment period before multiplying by 365.25

Patient Characteristics and Chronic Symptoms at Baseline in ENVISION

Characteristic	Placebo (n=46)	Givosiran (n=48)	Total (N=94)
Age in years, median (range)	36.0 (20–60)	42.0 (19–65)	37.5 (19–65)
Years since diagnosis, mean (SD)[1]	8.3 (8.5)	11.1 (11.2)	9.7 (10.0)
Previous hemin prophylaxis, n (%)[1]	18 (39)	20 (42)	38 (40)
Historical AAR,[a] median (range)[1]	7.0 (0[b]–46)	8.0 (4–34)	8.0 (0[b]–46)
Prior chronic symptoms,[c] n (%)[1]	26 (57)	23 (48)	49 (52)
Prior chronic opioid use,[c] n (%)[1]	13 (28)	14 (29)	27 (29)
Average daily worst pain score, mean (SD)[d]	3.7 (2.2)	3.0 (2.3)	—[e]

AAR, annualized attack rate; IV, intravenous; SD, standard deviation
[a]Calculated as number of attacks requiring hospitalization, urgent health care facility visit, or IV hemin use at home within 6 months before randomization. [b]One patient in placebo group did not meet inclusion criterion of ≥2 attacks requiring hospitalization, urgent health care facility visit, or IV hemin use at home within 6 months before screening (patient had 2 attacks treated without IV hemin at home). [c]Defined as chronic if patient reported occurrence as daily or on most days when patient was not having an attack. [d]Collected with eDiary on days when patient was not having an attack. [e]Data not estimated
1. Balwani M, et al. N Engl J Med. 2020;382(24):2289–2301

ENVISION Patients Had Severe Disease Burden at Baseline

Patient Characteristics and Chronic Symptoms at Baseline

- Although 40% and 6% of patients were receiving prophylactic hemin and GnRH analogs, respectively, the median AAR in the 6 months prior to randomization was 8 (range: 0–46)
  - Attacks were treated with IV hemin at home (13%), at an urgent health care facility (49%), or at a hospital (37%)
- 52% experienced symptoms daily or on most days when not having an attack
- Severe disease burden was similarly evident among the 60% of patients who were not on hemin prophylaxis

Pain and Analgesic Use

- Patients required analgesics, including opioids, for chronic pain management
  - 29% of patients were using opioid analgesics daily or on most days between attacks[1]
  - 83% and 67% of patients treated with placebo and givosiran, respectively, received opioid analgesics during the double-blind period

AAR, annualized attack rate; GnRH, gonadotropin-releasing hormone; IV, intravenous

1. Balwani M, et al. N Engl J Med. 2020;382(24):2289–2301

A High Proportion of Patients Had Comorbidities at Baseline

Comorbidity, n (%)	Placebo (n=46)	Givosiran (n=48)	Total (N=94)
Neuropathy	16 (35)	20 (42)	36 (38)
Sensory	8 (17)	10 (21)	18 (19)
Motor	8 (17)	13 (27)	21 (22)
Autonomic	3 (7)	0	3 (3)
Hypertension	11 (24)	14 (29)	25 (27)
Compromised liver function			
Any history of liver disease	13 (28)	13 (27)	26 (28)
Elevated transaminase levels	18 (39)	17 (35)	35 (37)
Compromised kidney function			
Chronic kidney disease	9 (20)	8 (17)	17 (18)
eGFR <60 mL/min/1.73 m^2 (worst screen value)	18 (39)	14 (29)	32 (34)
Psychiatric disorders	18 (39)	26 (54)	44 (47)
Anxiety	9 (20)	13 (27)	22 (23)
Depression	8 (17)	17 (35)	25 (27)
Insomnia	8 (17)	9 (19)	17 (18)
Iron overload	15 (33)	16 (33)	31 (33)
Ferritin level (µg/L), median (quartile 1–quartile 3)	245 (44–662)	201 (53–875)	209 (48–719)

eGFR, estimated glomerular filtration rate

Concomitant Medication Use Was Consistent with AHP Symptoms and Common Comorbidities

Medication, n (%)	Placebo (n=46)	Givosiran (n=48)	Total (N=94)
Antidepressants			
Benzodiazepine derivatives	10 (22)	10 (21)	20 (21)
Benzodiazepine-related drugs	3 (7)	4 (8)	7 (7)
Other antidepressants	4 (9)	9 (19)	13 (14)
Selective serotonin reuptake inhibitors	2 (4)	4 (8)	6 (6)
Antihypertensives			
Angiotensin-converting enzyme inhibitors	2 (4)	1 (2)	3 (3)
Angiotensin II receptor antagonists	3 (7)	2 (4)	5 (5)
Beta-blockers, nonselective	1 (2)	3 (6)	4 (4)
Beta-blockers, selective	5 (11)	7 (15)	12 (13)
Alpha- and beta-blockers	2 (4)	0	2 (2)
Antiemetics			
5-HT3 receptor antagonists	12 (26)	12 (25)	24 (26)
Other antiemetics	5 (11)	5 (10)	10 (11)
Analgesics			
Natural opium alkaloids	27 (59)	23 (48)	50 (53)
Fentanyl	5 (11)	1 (2)	6 (6)
Fentanyl citrate	0	2 (4)	2 (2)
Opioid/non opioid combinations	2 (4)	5 (10)	7 (7)
Opium alkaloid derivatives	2 (4)	0	2 (2)
Other opioids	8 (17)	6 (13)	14 (15)
Other analgesics and antipyretics	10 (22)	13 (27)	23 (24)
Propionic acid derivatives	9 (20)	10 (21)	19 (20)
Salicylic acid and derivatives	2 (4)	1 (2)	3 (3)
Tramadol	9 (20)	5 (10)	14 (15)
Gonadotropin-releasing hormone analogs	3 (7)	3 (6)	6 (6)

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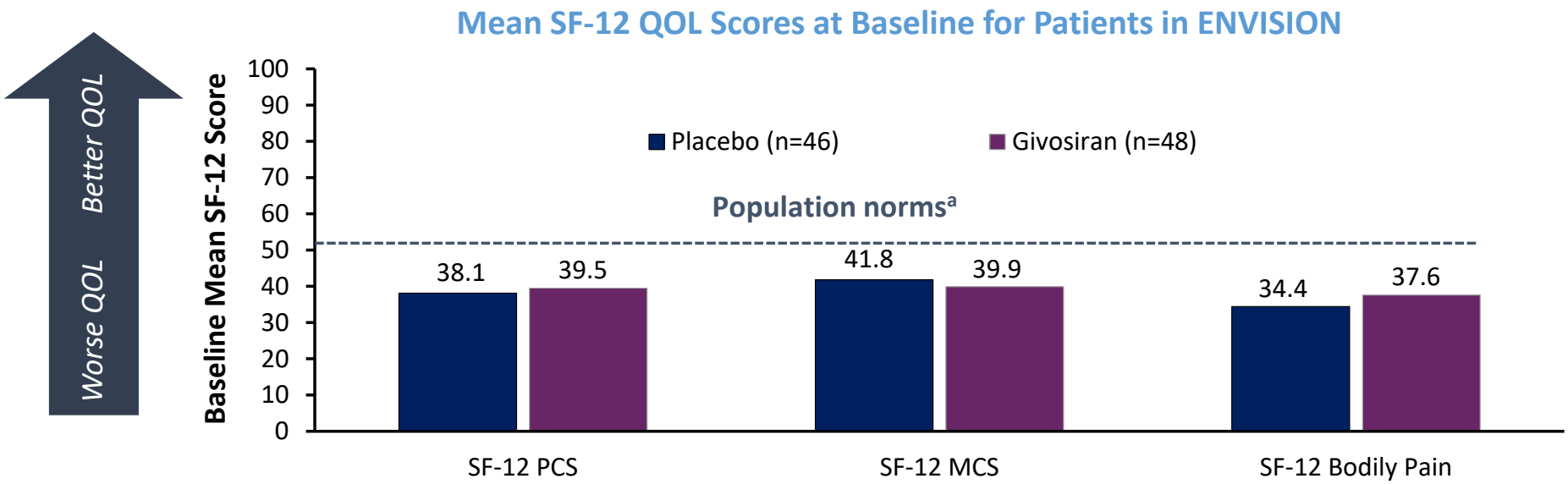
5-HT3, 5-hydroxytryptamine; AHP, acute hepatic porphyria

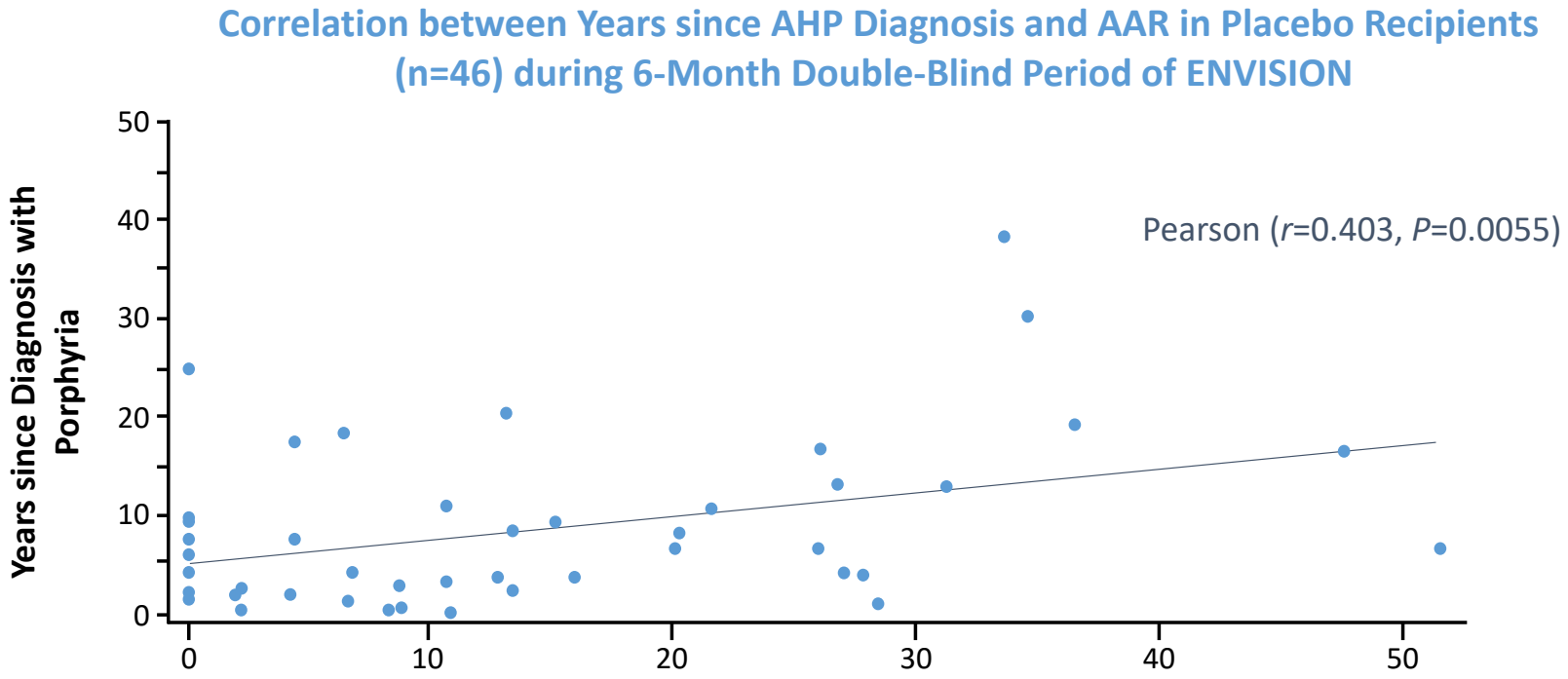
Patients Had Poor QOL as Evidenced by Baseline Mean SF-12 PCS and MCS Scores

- Baseline values were substantially lower than population norms and lower than mean scores of patients post myocardial infarction[1]
- Consistent with baseline pain scores and analgesic use, baseline mean SF-12 Bodily Pain scores were low, suggesting interference with normal functioning



MCS, Mental Component Summary; PCS, Physical Component Summary; QOL, quality of life; SF-12, Short Form (12-item) Health Survey
[a]Norms reported in a random sample of 2301 adults residing in the Netherlands
1. Mols F, et al. Qual Life Res. 2009;18(4):403–414

Correlation between Years since AHP Diagnosis and AAR in Placebo Patients

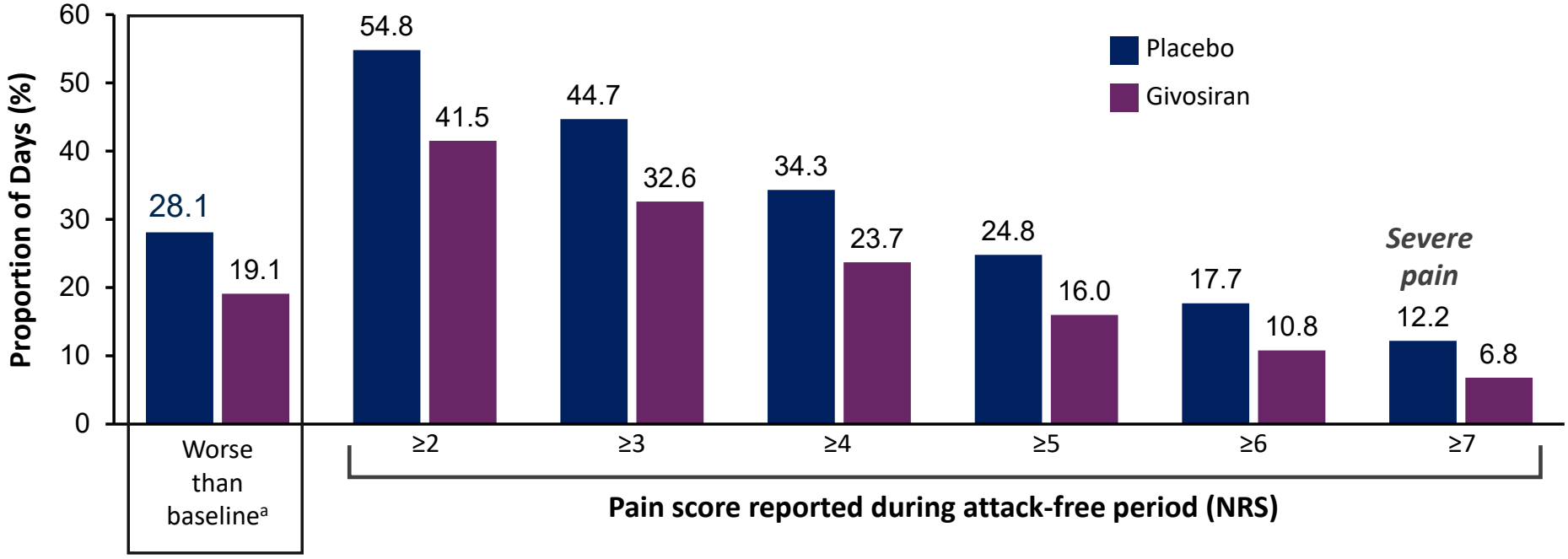


- Worsening of AHP likely occurs in the absence of effective disease-modifying treatment

AAR, annualized attack rate; AHP, acute hepatic porphyria

Givosiran Reduced Daily Worst Pain Scores during Attack-Free Periods

- Compared with placebo recipients, givosiran recipients had fewer days with daily worst pain scores above baseline and almost 50% fewer days with severe pain (respectively, 7% and 12% of days with scores ≥7)

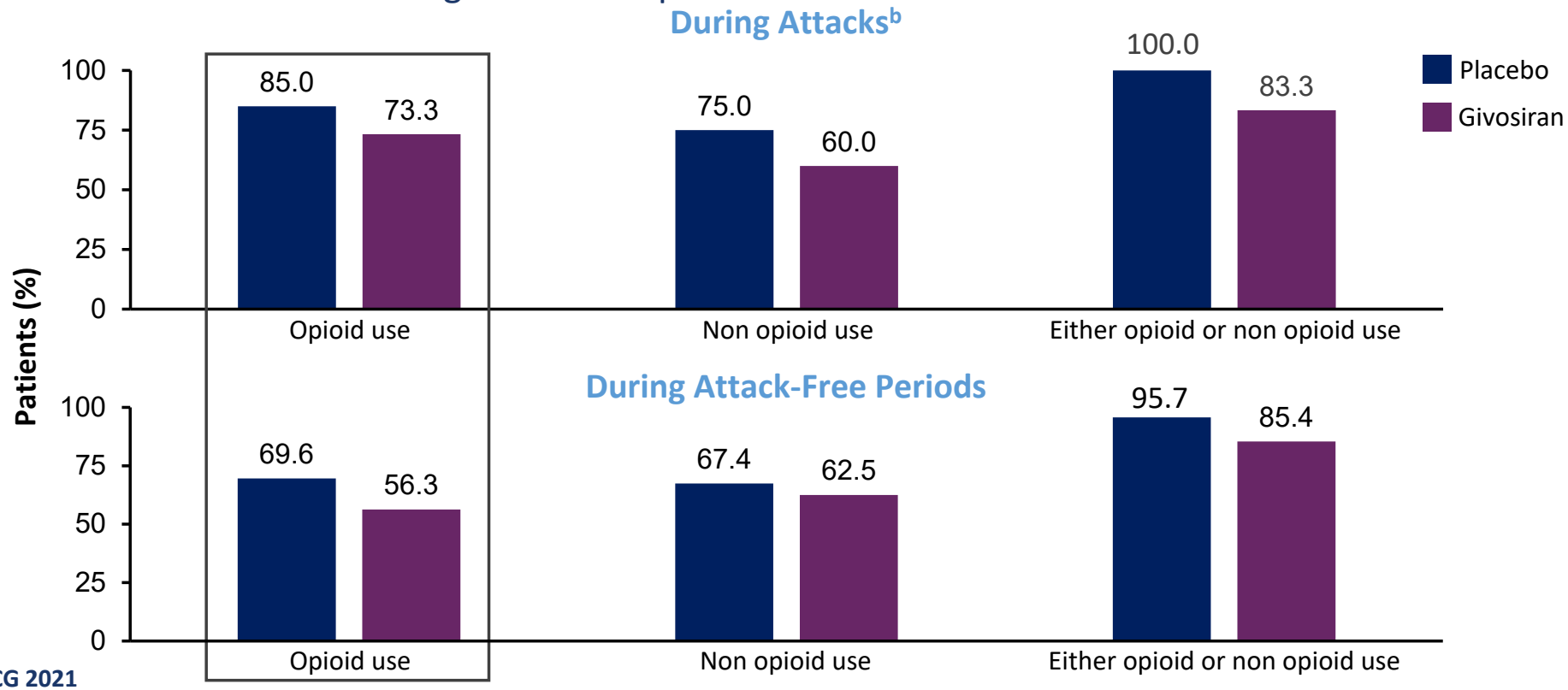


NRS, numeric rating scale

[a]Baseline pain score is mean score from 4 to 7 days before first dose of study drug when patient is not experiencing an attack

Givosiran Reduced Analgesic Use[a] during and between Attacks

- Opioid use was reduced in givosiran recipients compared with placebo recipients, with larger reductions observed during attack-free periods



[a]Analgesic use was an exploratory endpoint. An evaluation compared with baseline analgesic use cannot be conducted because the proportion of days with analgesic use was not captured at baseline.
[b]All investigator-adjudicated attacks are included

Conclusions

- These data from ENVISION are consistent with prior natural history reports[1,2] showing the severe disease burden of AHP
- At baseline, ENVISION patients had a high number of annual attacks, and a substantial proportion presented with chronic symptoms, comorbidities, and concomitant medication use, including opioid use daily or on most days between attacks in 29%
  of patients
- These baseline characteristics contributed to impaired physical and mental QOL
  and interference with normal functioning
- The relationship between time since diagnosis and AAR suggests patients may experience worsening disease and complications over time
- Givosiran reduced daily worst pain scores and analgesic use during and between attacks
- Earlier initiation of treatments such as givosiran—which prevent attacks and reduce chronic manifestations of AHP—may lead to improvement in patients' prognoses
- During the 6-month double-blind study, SAEs were reported in 21% of the givosiran group and 9% of the placebo group; 1 patient in the givosiran group discontinued treatment, and no deaths were reported[3]

AAR, annualized attack rate; AHP, acute hepatic porphyria; SAE, serious adverse event

1. Gouya L, et al. Hepatology. 2020;71(5):1546–1558; 2. Bonkovsky HL, et al. Am J Med. 2014;127(12):1233–1241; 3. Balwani M, et al. N Engl J Med. 2020;382;2289–2301