Reduction in Pain during and between Attacks in Patients with Acute Hepatic Porphyria Treated with Givosiran: A Post-Hoc Analysis of the Phase 3 ENVISION Study

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Disclosure Slide

Dr. Susana Monroy reports receiving Advisory Board fees from Alnylam Pharmaceuticals and Speakers Bureau fees from Recordati Rare Diseases

Dr. Raili Kauppinen reports receiving personal compensation for serving as a Consultant for Alnylam, stock or an ownership interest from Orion pharmaceuticals, and publishing royalties from a publication relating to health care

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Acute Hepatic Porphyria (AHP) and Givosiran

Disease Overview and Pathophysiology

- Family of rare, genetic diseases resulting from deficiency in one of the enzymes responsible for heme biosynthesis in the liver, leading to accumulation of neurotoxic intermediates ALA/PBG[1,2]
- Characterized by acute neurovisceral attacks with common symptoms of severe abdominal pain and muscle weakness[3,4]
  - Without proper treatment, attacks can progress to paralysis, respiratory failure, and death
- Patients also experience chronic debilitating symptoms, most commonly severe pain[3–5]
- Acute attacks often require hospitalization with supportive care, opioid analgesics, and hemin[4]

Givosiran

- RNAi therapeutic targets ALAS1, decreasing ALA/PBG that are causal for disease manifestations[6,7]
- Approved in the US for the treatment of adults with AHP and in the EU for treatment of AHP in adults and adolescents aged ≥12 years[8,9]
  - In patients with AIP (most common AHP type), givosiran significantly reduced the annualized rate of porphyria attacks, urinary ALA and PBG, days of hemin use, and improved multiple other disease manifestations compared with placebo, with an acceptable and monitorable safety profile
  - Daily worst pain[a] (p=0.0530 [pre-specified ANCOVA]; p=0.0455 [post-hoc Wilcoxon]) and analgesic use were reduced compared with placebo

[a]Pain data not normally distributed; ANCOVA method not valid. Post-hoc analysis using non-parametric stratified Wilcoxon method

AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; ANCOVA, analysis of covariance; EU, European Union; PBG, porphobilinogen; RNAi, RNA interference

1. Puy et al. *Am J Hum Genet* 1997;60:1373–83; 2. Balwani & Desnick. *Blood* 2012;120:4496–504; 3. Gouya et al. *Hepatology* 2019;DOI:10.1002/hep.30936; 4. Pischik & Kauppinen. *Appl Clin Genet* 2015;8:201–14; 5. Simon et al. *Patient* 2018;11:527–37; 6. Bissell et al. The Liver Meeting (AASLD) 2019. Presentation; 7. Sardh et al. *N Engl J Med* 2019;380:549–58; 8. GIVLAARI US Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/0212194s000lbl.pdf (accessed March 8, 2021); 9. GIVLAARI EU Summary of Product Characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf (accessed March 8, 2021)

ENVISION Phase 3 Study Design

Randomized, Double-Blind, Placebo-Controlled Study in Patients with AHP[1]

94 patients enrolled at 36 sites in 18 countries

Patient Population (N=94)

- Age ≥12 years
- Diagnosis of AHP
- ≥2 attacks within prior 6 months
- Willing to discontinue and/or not initiate hemin prophylaxis

1:1 RANDOMIZATION

6-Month, Double-Blind Period

- **Givosiran** SC qM 2.5 mg/kg
- or
- **Placebo** SC qM

Primary Endpoint

- Composite annualized attacks (attacks requiring hospitalization, urgent health care, or IV hemin administration at home) in AIP at 6 months[a]

Secondary Endpoints[b]

- ALA and PBG
- Hemin doses
- Composite annualized attacks in AHP over 6 months[a]
- **Pain**
- Fatigue
- Nausea
- PCS of **SF-12**

30-Month Open-Label Extension Period

Open-Label Extension

Daily eDiary captured:
- **Daily Worst Pain** (numeric rating scale: 0=none at all; 10=as bad as you can imagine)[c]
- **Analgesic use**

SF-12 subscale of **Overall Bodily Pain** (recall period of 4 weeks)

Aim of current post-hoc analysis of ENVISION

- Assess reduction in pain and analgesic use during and between attacks over 6 months

[a]Attacks requiring hospitalization, urgent health care, or IV hemin administration at home; composite annualized attack rate calculated for each patient by dividing the total number of porphyria attacks by the total number of days in the treatment period before multiplying by 365.25. [b]Endpoints evaluated in genetically confirmed AIP patients, unless otherwise noted. [c]A score ≥7 was defined as severe pain[2]

IV, intravenous; PCS, Physical Component Summary; qM, every month; SC, subcutaneous; SF-12, Short-Form (12-item) Health Survey

1. Balwani et al. Presented at the *International Liver Congress*, April 2019; 2. Oldenmenger et al. *J Pain Symptom Manage* 2013;45:1083–93

Demographics and Baseline Characteristics of Patients with AHP

Baseline Characteristics Were Generally Balanced between Groups

Characteristic	Placebo[a] (n=46)	Givosiran (n=48)
Age at screening, years, median (range)	36 (20, 60)	42 (19, 65)
Female, n (%)	41 (89)	43 (90)
Years since diagnosis, median (range)	6.11 (0.1, 38.5)	6.98 (0.2, 43.3)
Prior hemin prophylaxis, n (%)	18 (39)	20 (42)
Historical AAR[b], median (range)	7.0 (0[a], 46)	8.0 (4, 34)
Chronic symptoms daily or most days between attacks, n (%)	26 (57)	23 (48)
Opioid use daily or most days between attacks, n (%)	13 (28)	14 (29)

[a]One patient in the placebo group did not meet inclusion criterion of ≥2 attacks requiring hospitalization, urgent healthcare visit, or IV hemin at home within 6 months prior to screening (patient had 2 attacks that were treated at home without IV hemin)

[b]Composite porphyria attacks are attacks requiring hospitalization, an urgent healthcare visit, or IV hemin treatment at home

AAR, annualized rate of composite porphyria attacks

Improvement in Number and Severity of Attacks in Givosiran-Treated Patients

Attacks[a]	Overall		With Prior Hemin Prophylaxis		Without Prior Hemin Prophylaxis	
	Placebo (n=46)	Givosiran (n=48)	Placebo (n=18)	Givosiran (n=20)	Placebo (n=28)	Givosiran (n=28)
Total number of attacks	297	90	186	48	111	42
Number of patients with ≥1 attack, n (%)	38 **(82.6)**	24 **(50.0)**	17 **(94.4)**	11 **(55.0)**	21 **(75.0)**	13 **(46.4)**
Total number of attacks with median pain scores ≥7, n (%)	95/297 **(32.0)**	19/90 **(21.1)**	66/186 **(35.5)**	9/48 **(18.8)**	29/111 **(26.1)**	10/42 **(23.8)**
Number of patients with ≥1 attack with median pain scores ≥7, n (%)	24/38 **(63.2)**	10/24 **(41.7)**	13/17 **(76.5)**	6/11 **(54.5)**	11/21 **(52.4)**	4/13 **(30.8)**

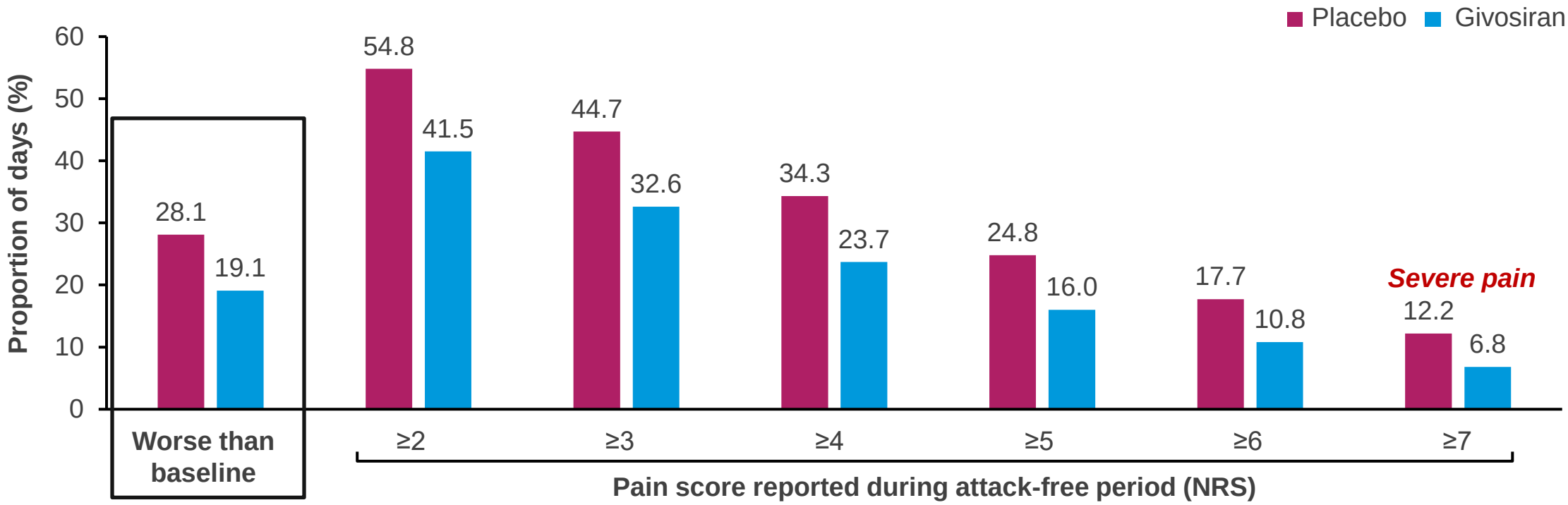
Regardless of prior hemin prophylaxis use:

- Givosiran led to reduction in total attack number compared with placebo
- Givosiran had a lower proportion of patients with ≥1 attack compared with placebo
- Givosiran treatment resulted in a lower proportion of patients with ≥1 attack with severe pain (median daily worst pain score ≥7) compared with placebo

[a]Attacks included are those requiring hospitalization, urgent care, or at-home hemin use. Median pain scores of these attacks were calculated based on scores collected during each attack

Reduced Daily Worst Pain Score during Attack-free Periods

- Fewer days with daily worst pain scores above baseline[a] for givosiran-treated vs placebo
- Patients receiving givosiran reported nearly 50% fewer days with severe pain compared with placebo (proportion of days with scores ≥7: 6.8% vs 12.2%, respectively)

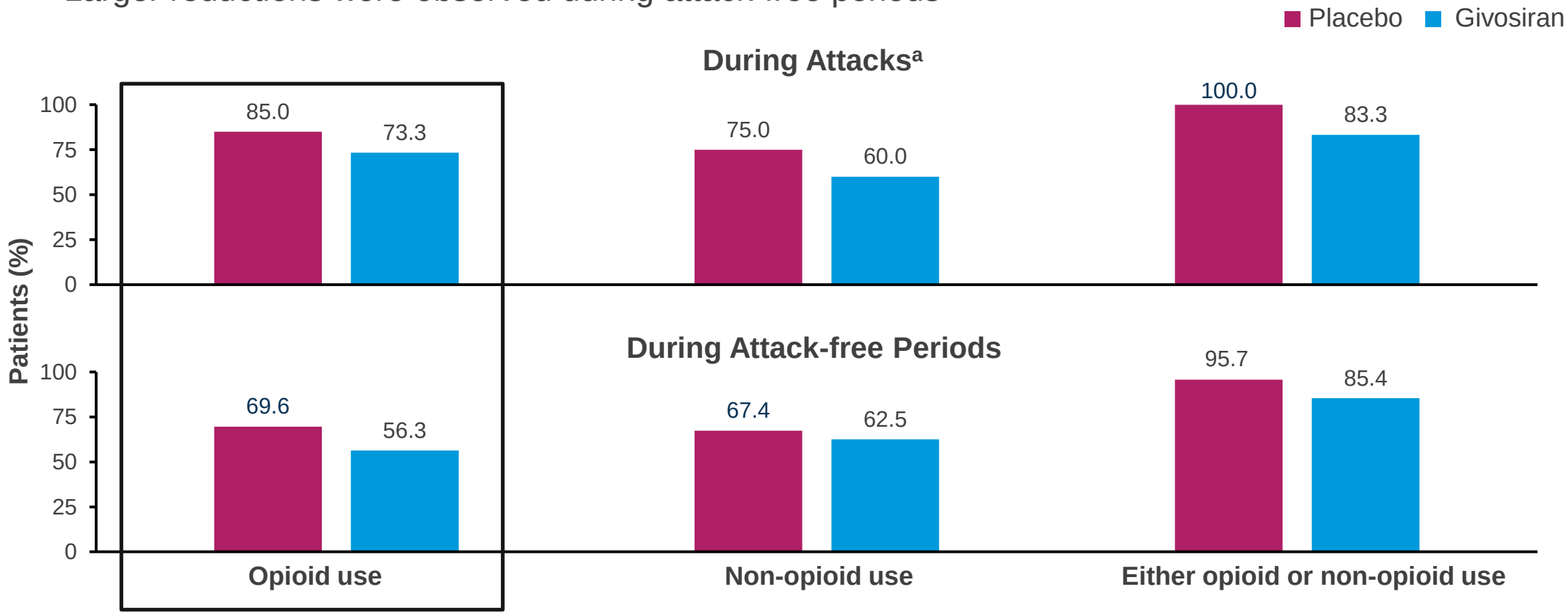


[a]Baseline pain score is the mean score from 4 to 7 days prior to first dose of study drug, when patient is not experiencing an attack

NRS, numeric rating scale

Reduced Analgesic Use in Patients Receiving Givosiran

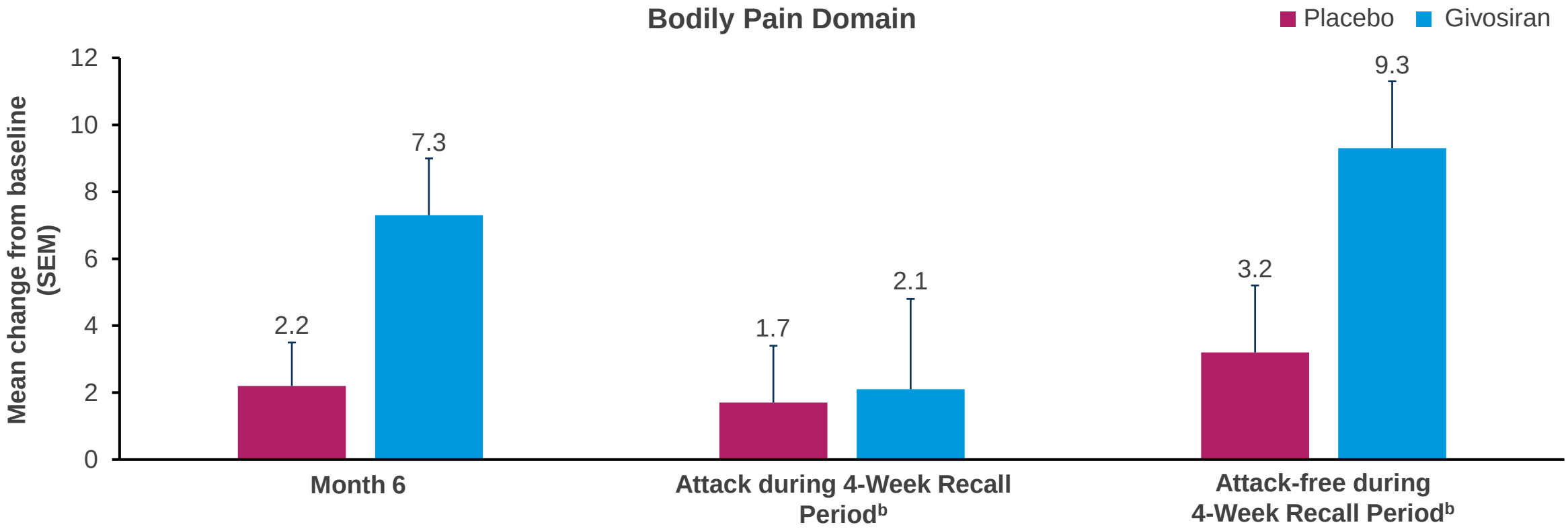
- Patients receiving givosiran had reductions in opioid use compared with placebo
  - Larger reductions were observed during attack-free periods



[a]All investigator-adjudicated attacks are included

Improvement in Overall Bodily Pain Domain in SF-12[a] Assessment

- Bodily pain domain had greater improvement (increase) with givosiran (7.3) vs placebo (2.2)
- Data suggest reduction in daily worst pain (along with decreased analgesic use) is clinically relevant as patients reported reduced interference with normal activities



[a]The SF-12 is scored on a scale of 0–100, where higher scores indicate improvement. All investigator-adjudicated attacks are included
[b]SF-12 (version 2) was assessed using a recall period (the time period patients are asked to consider in responding to a PRO item or question) of 4 weeks
SEM, standard error of the mean

Summary of ENVISION Post-Hoc Analysis

Givosiran Reduced Pain in Patients with AHP during and between Attacks

- Patients with AHP can experience chronic pain even during attack-free periods and require high levels of analgesics, including opioids, to manage pain during and between attacks
- Givosiran treatment reduced both the number and severity of attacks compared with placebo, regardless of prior hemin prophylaxis use
- Givosiran treatment reduced the level of pain patients report compared with placebo, both during attacks and between attacks
  - Treatment-related reductions in pain were not due to higher analgesic use; givosiran treatment was associated with reduced analgesic use compared with placebo
  - Givosiran-treated patients reported greater improvement in the SF-12 Bodily Pain domain, suggesting reduction in daily worst pain was clinically relevant

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