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

Kauppinen R[1], *Kuo H-C[2], Oh J[3], Hother-Nielson O[4], Petrides PE[5], Kuter D[6], Monroy S[7], Fanelli M-J[8], Hua Z[8], He Q[8], Ko JJ[8], Simon A[8], Rees D[9]*

[1]Helsinki University Central Hospital, Helsinki, Finland; [2]Chang Gung Medical Foundation – Linkou Chang Gung Memorial Hospital, Taoyuan City, Taiwan; [3]Konkuk University Hospital, Chungju, South Korea; [4]Odense University Hospital, Odense, Denmark; [5]Hematology Oncology Center, University of Munich Medical School, Munich, Germany; [6]Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA; [7]Instituto Nacional de Pediatría, Mexico City, Mexico; [8]Alnylam Pharmaceuticals, Cambridge, Massachusetts, USA; [9]King's College Hospital, London, UK

23–26 May 2020 | European Academy of Neurology (EAN) Congress | Paris, France (held virtually)

Disclosure Slide

- Dr. Kauppinen reports receiving advisory board fees from Alnylam Pharmaceuticals, advisory fees from Recordati Rare Diseases, travel support from Sanofi, and ownership of stock in the Orion Corporation

Acute Hepatic Porphyria (AHP)

- Family of rare, genetic diseases resulting from deficiency in one of the enzymes responsible for heme biosynthesis in the liver[1,2]
  - Induction of ALAS1 leads to accumulation of neurotoxic heme intermediates ALA/PBG
- Characterized by acute neurovisceral attacks with dysfunction across the peripheral, autonomic, and central nervous systems[3,4]
  - Patients commonly have severe abdominal pain and muscle weakness, which without proper treatment can progress to paralysis, respiratory failure, and death
- Patients also experience chronic debilitating symptoms, most commonly severe pain[3–5]
  - Chronic abdominal pain, neuropathic pain, or incomplete recovery of motor function can result from nerve injury sustained during a severe attack or from multiple attacks[6,7]
- Acute attacks often require hospitalization with supportive care, opioid analgesics, and hemin[4]

AHP, acute hepatic porphyria; ALA, delta-aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; PBG, porphobilinogen

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 and Kauppinen. *Appl Clin Genet* 2015;8:201–14; 5. Simon et al. *Patient* 2018;11:527–37; 6. Puy et al. *Lancet* 2010;375:924–37; 7. Jaramillo-Calle & Aguirre Acevedo. *JIMD Reports* 2018;44:65–72

Givosiran

- RNAi therapeutic targets ALAS1, decreasing ALA/PBG that are causal for disease manifestations[1,2]
- 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 and older[3,4]
  - Givosiran significantly reduced the annualized rate of porphyria attacks and improved multiple other disease manifestations in patients with AIP (most common AHP type) experiencing ongoing attacks, compared with placebo and demonstrated an acceptable and monitorable safety profile
  - In patients with AIP, givosiran led to reductions in urinary ALA and PBG, days of hemin use (all P<0.001)
  - Daily worst pain* (P=0.0530 [pre-specified ANCOVA]; P=0.0455 [post-hoc Wilcoxin]) and analgesic use were reduced compared with placebo

*Pain data not normally distributed; ANCOVA method not valid. Post-hoc analysis using non-parametric stratified Wilcoxon method
AHP, acute hepatic porphyria; ALA, delta-aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; EU, European Union; mRNA, messenger RNA; PBG, porphobilinogen; RNAi, RNA interference
1. Bissell et al. The Liver Meeting (AASLD) 2019. Presentation; 2. Sardh et al. N Engl J Med 2019;380:549–58; 3. GIVLAARI US Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/0212194s000lbl.pdf (accessed March 19, 2020); 4. GIVLAARI EU Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf (accessed March 19, 2020)

ENVISION Phase 3 Study Design

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

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

6-Month Double-Blind Period

1:1 RANDOMIZATION

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

Primary Endpoint

- Composite annualized attacks (attacks requiring hospitalization, urgent health care, or intravenous hemin administration at home) in Acute Intermittent Porphyria (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
- Physical Component Summary (PCS) of Short Form (12-item) Health Survey (SF-12)

30-Month Open-Label Extension Period

Open-Label Extension

Aim of current post hoc analysis of ENVISION

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

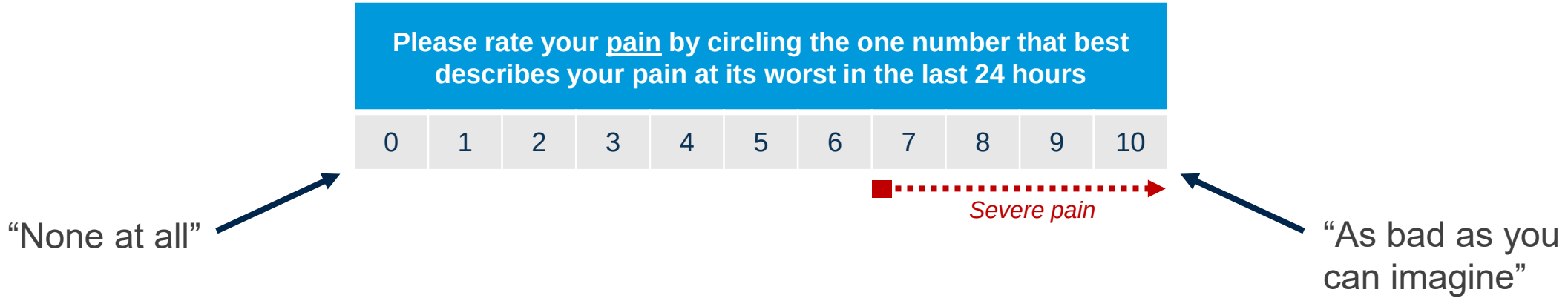
[a]Attacks requiring hospitalization, urgent health care, or intravenous hemin administration at home; composite annualized attack rate was calculated for each patient by dividing the total number of porphyria attacks by the total number of days in the treatment period before multiplying by 365.25'. [b]Endpoints evaluated in genetically confirmed AIP patients, unless otherwise noted
AIP, acute intermittent porphyria; PCS, Physical Component Summary; qM, every month; SC, subcutaneous; SF-12, Short-Form (12-item) Health Survey
Balwani et al. Presented at the *International Liver Congress*, April 2019

Daily Worst Pain Measurement (Secondary Endpoint)

Severity of Pain Captured Using a Daily eDiary by a Numeric Rating Scale (NRS)

Brief Pain Inventory Short Form, Question #3

- Patients chose the rating that described the worst level of pain experienced over the previous 24-hour period
- For daily worst pain, a score ≥7 was defined as severe pain[1]
- Opioid and non-opioid analgesic use was captured daily with the eDiary



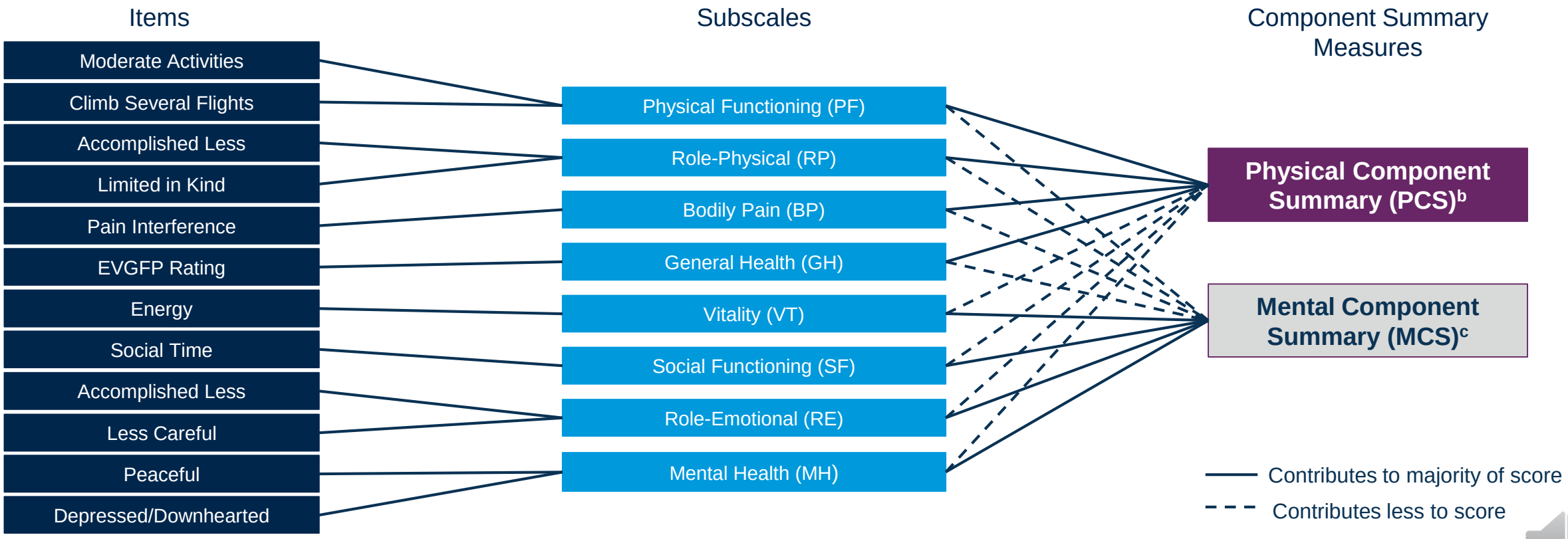
NRS, numeric rating scale

1. Oldenmenger et al. *J Pain Symptom Manage* 2013;45:1083–93

12-Item Short-Form Health Survey (SF-12)

SF-12[a] and 8 Subscales That Contribute to the Physical Component Summary (PCS)

- 12 items and 8 subscales feed into the PCS and Mental Component Summary (MCS); solid lines indicate the domains contributing most to PCS and MCS; dashed lines indicate those contributing less
- Question answers were scored into quantitative values from a pre-specified psychometrically validated algorithm



[a]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. [b]Secondary endpoint. [c]Exploratory endpoint
EVGFP, excellent, very good, good, fair, poor

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; IV, intravenous

Improvement in Number of Attacks in Givosiran-Treated Patients

	Overall		With Prior Hemin Prophylaxis		Without Prior Hemin Prophylaxis	
Attacks[a]	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)**

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

[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

Improvement in Attack Severity in Givosiran-Treated Patients

	Overall		With Prior Hemin Prophylaxis		Without Prior Hemin Prophylaxis	
Attacks[a]	Placebo (n=46)	Givosiran (n=48)	Placebo (n=18)	Givosiran (n=20)	Placebo (n=28)	Givosiran (n=28)
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)**

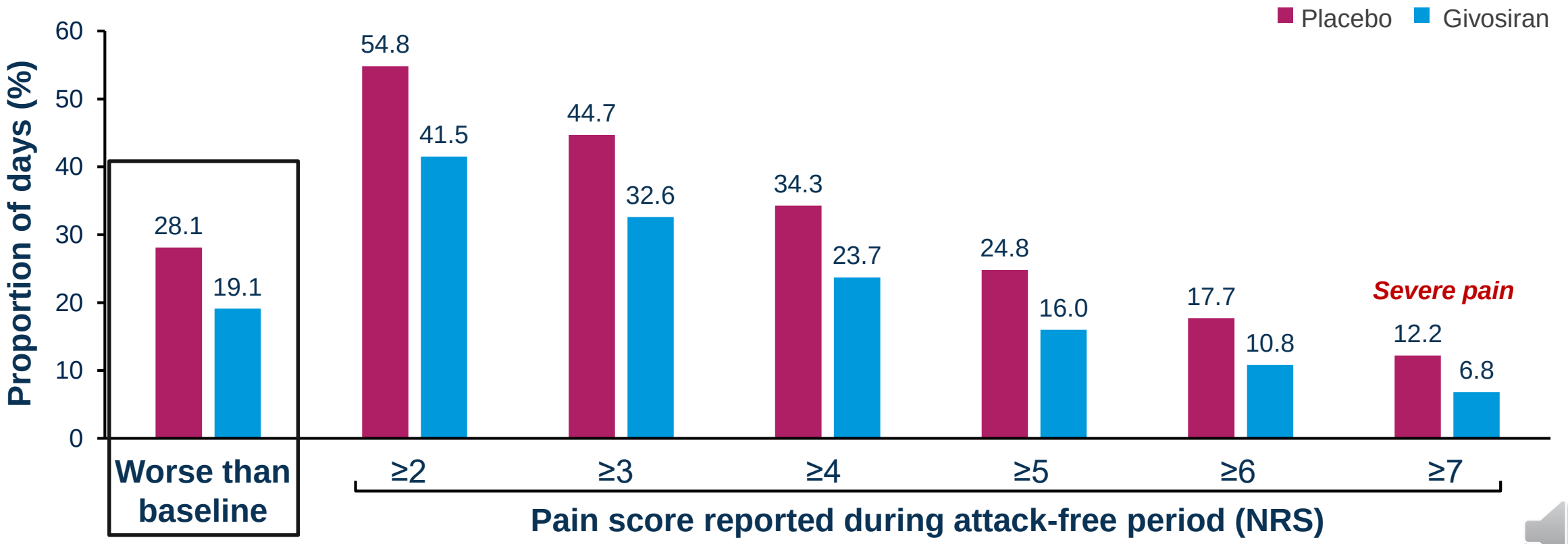
Regardless of prior hemin prophylaxis use:

- Givosiran 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

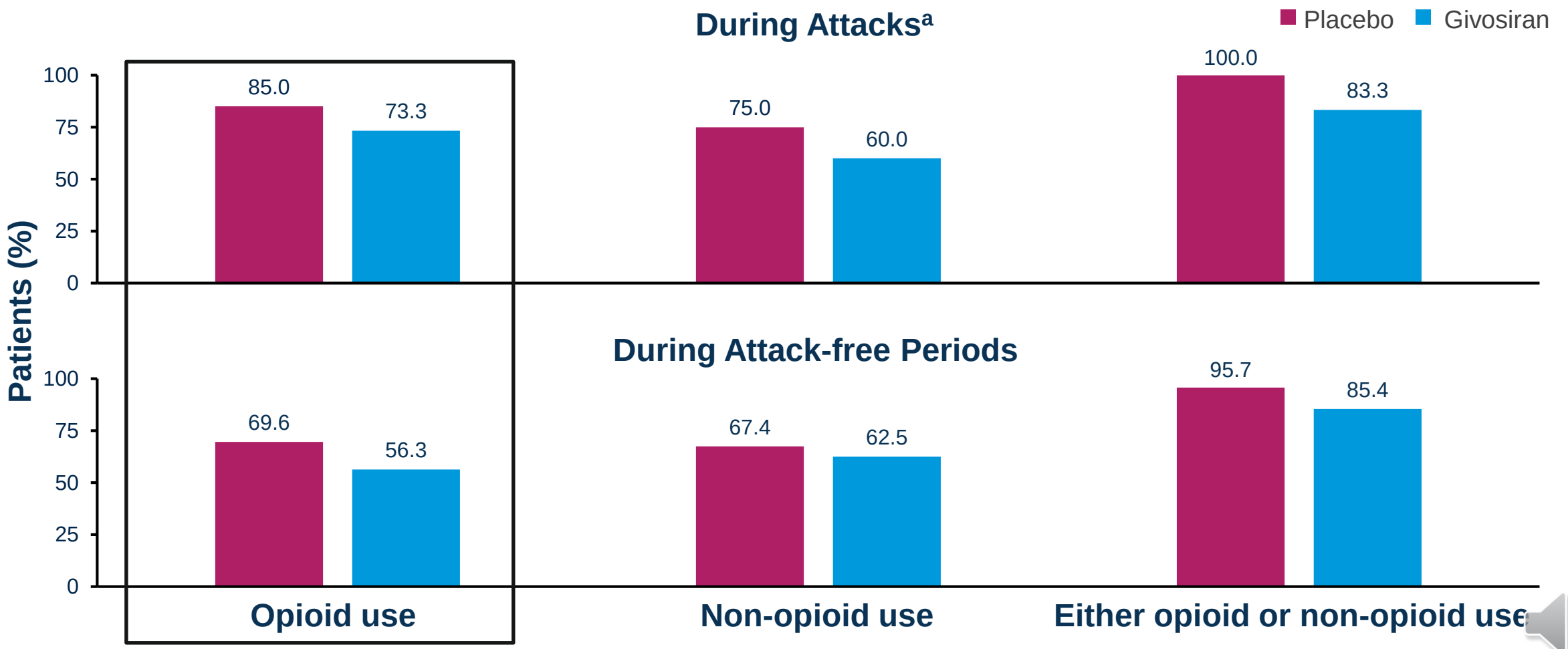
- Fewer days with daily worst pain scores above baseline[a] for givosiran-treated vs. placebo
- Patients receiving givosiran reported nearly 50% fewer days with severe pain compared with placebo (proportion of days with scores ≥7: 6.8% vs. 12.2%, respectively)



[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

Reduced Analgesic Use in Patients Receiving Givosiran

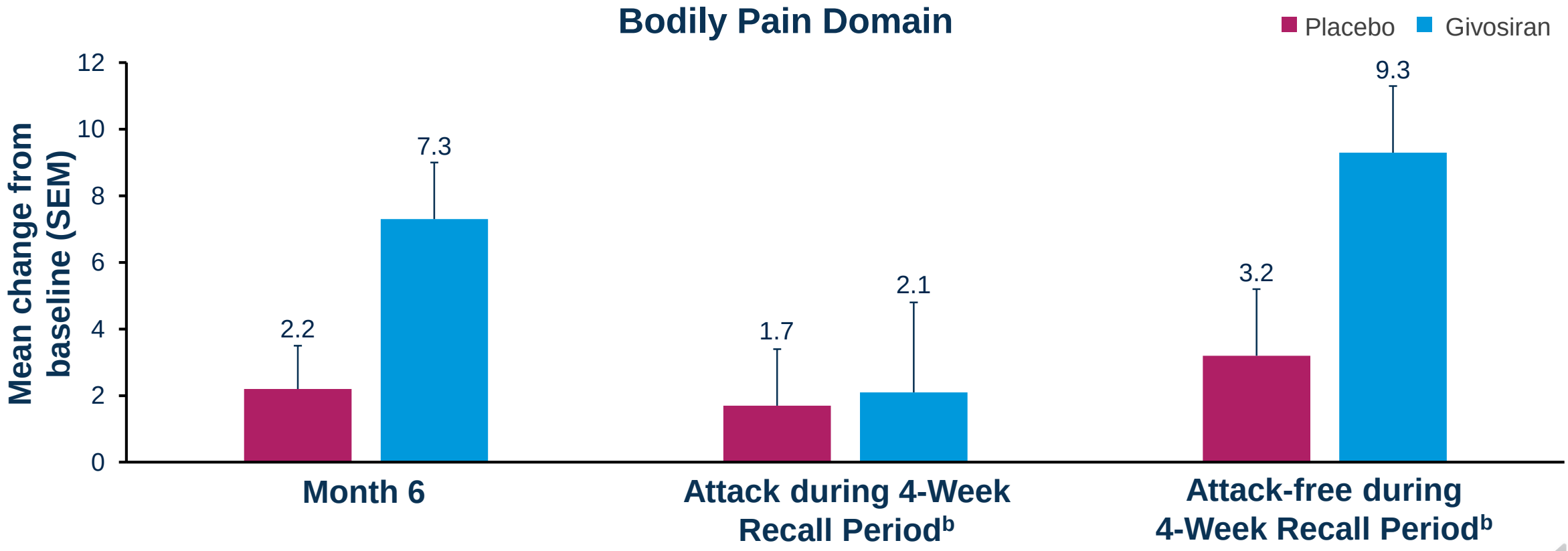
- Patients receiving givosiran had reductions in opioid use compared with placebo
  - Larger reductions were observed during attack-free periods



[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 AHP Patients 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 to placebo
  - Givosiran treated patients reported greater improvement in the SF-12 Bodily Pain domain, suggesting reduction in daily worst pain was clinically relevant

Acknowledgments

ENVISION Investigators

- Tomohide Adachi
- Paula Aguilera Peiro
- Karl Anderson
- Manisha Balwani
- Montgomery Bissell
- Herb Bonkovsky
- Maria Cappellini
- David Cassiman
- David Coman
- Delia D'Avola
- Yoshie Goto
- Laurent Gouya
- Encarna Guillén Navarro
- Pauline Harper
- Yutaka Horie
- Ole Hother-Nielsen
- Aneta Ivanova
- David Kuter
- Raili Kauppinen
- Sioban Keel
- Hung-Chou Kuo
- Janneke Langendonk
- Ming-Jen Lee
- Cynthia Levy
- Elisabeth Minder
- Susana Monroy
- Jeeyoung Oh
- Charles Parker
- Petro Petrides
- John Phillips
- David Rees
- Bruce Ritchie
- Gayle Ross
- Eliane Sardh
- Appalanaidu Sasapu
- Samuel Silver
- Penny Stein
- Peter Stewart
- Ulrich Stölzel
- Kei-ichiro Takase
- Manish Thapar
- Daphne Vassiliou
- Paolo Ventura
- Jiaan-Der Wang
- Bruce Wang
- Jerzy Windyga

We also wish to thank the study site staff, the patient organizations, and most importantly, the patients for participating