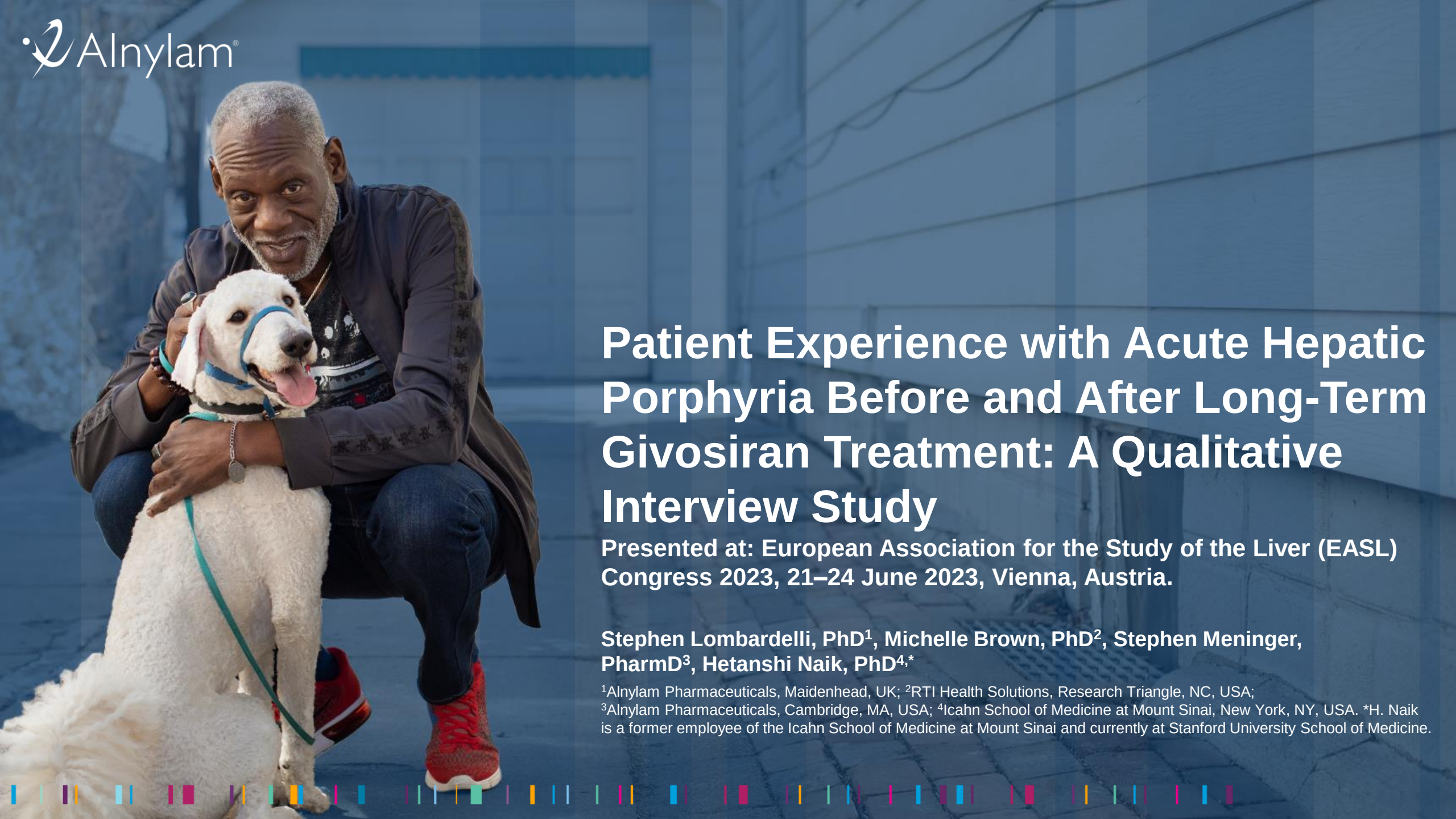

Patient Experience with Acute Hepatic Porphyria Before and After Long-Term Givosiran Treatment: A Qualitative Interview Study

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Background and Aims

- AHP is a group of rare, chronic, multisystem disorders with acute attacks, progressive elements, and long-term complications requiring proactive management and treatment[1-3]
  - The life-threatening acute neurovisceral attacks are characterized by severe abdominal pain and other symptoms (eg, nausea, vomiting, tachycardia, hypertension, hyponatremia, mental status changes, and muscle weakness)[1,4]
  - Chronic manifestations, such as pain, fatigue, and nausea between attacks, may be present and may impact quality of life[2,5-7]
  - Acute and chronic pain may require opioid treatment, putting patients at risk of opioid dependence[8,9]
- Givosiran is a subcutaneously administered RNA interference therapeutic for the treatment of AHP in adults and adolescents age 12 years and older[10]
- In Phase 1/2 (NCT02949830) and Phase 3 (ENVISION; NCT03338816) studies, givosiran treatment led to sustained improvement in AAR and other outcome measures[11-14]
- Qualitative interviews were conducted with study participants to capture, in the patients' own words, the symptoms and impacts of AHP and any changes the patients experienced during treatment with givosiran, including the perceived meaningfulness of these changes

AAR, annualized relapse rate; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; RNA, ribonucleic acid.

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Methods

- Participants were individuals with AHP (located in the United States, Spain, or United Kingdom) who were continuing givosiran treatment after completing open-label extension periods of the Phase 1/2 or ENVISION studies
- Individuals participated in 1-hour semistructured telephone interviews about prestudy and posttreatment symptoms and impacts of AHP, and satisfaction with and perceived benefits of givosiran treatment
- Interviews were audio-recorded and transcribed, and thematic analysis methods were used[15,16]
- Formal hypotheses were not tested; descriptive statistics were tabulated

AHP, acute hepatic porphyria.

15. Braun V, Clarke V. *Qual Res Psychol*. 2006;3(2): 16. Boeije H. *Qual Quant.* 2002;36(4):391-409.

Results

Table 1. Participant characteristics

- There were 21 participants (Table 1)

Characteristic	Total (N=21)
Clinical trial, N (%)	
Phase 1/2	7 (33)
ENVISION	14 (67)
Female, N (%)	18 (86)
AIP with mutation in *HMBS* gene, N (%)	21 (100)
Age at trial enrollment, years, mean (SD)	34.6 (9.2)
Years since diagnosis[a], median (min, max)	6.1 (0.9, 19.2)
Historical AAR[a], median (min, max)	14.0 (4.0, 46.0)
Number of attacks in past 12 months[b], median (min, max)	10 (3, 36)
Previous hemin prophylaxis, N (%)	8 (38)
Chronic symptoms at baseline, N (%)	10 (48)
Givosiran treatment duration[c,d], months, median (min, max)	49.7 (41.4, 69.1)

AAR, annualized relapse rate; AIP, acute intermittent porphyria; HMBS, hydroxymethylbilane synthase.
[a]Available for participants in ENVISION only (N=14).
[b]Available for participants in the Phase 1/2 study only (N=7).
[c]Interval between first dose of givosiran and interview.
[d]All participants were continuing to receive givosiran at the time of the interview.

Results

- Participants reported prestudy AHP symptoms in multiple domains, and improvements after starting givosiran (Table 2)
- All participants (100%) reported posttreatment improvements in AHP attacks; attacks were gone (62%), less severe (33%), or less severe but not less frequent (5%)
- Improvements considered "most important" included pain alleviation (43%), less fatigue (10%), fewer attacks (10%), improved mood/well-being, and less fear (10%)
  - Most interviewees (90%) had used opioids prestudy; relief of acute and/or chronic pain was somewhat effective (84%), not effective or mildly effective (26%), and/or effective only in the hospital (intravenous; 21%)

AHP, acute hepatic porphyria.

Results

Table 2. Improvement in AHP Symptoms, Prestudy[a] to Posttreatment

Symptom[a]	Experienced Symptom Prestudy, N (%)	Posttreatment Improvement[b]		Participant Description of Symptom	
		N[c]	Yes, N (%)	Prestudy[a]	Posttreatment[d]
Abdominal pain	20 (95)	20	20 (100)	*It would usually start with severe stomach pain, intractable vomiting; it would expand to a full body, horrible, searing, and indescribable level of pain.*	*The stabbing pain that I used to get in the upper right quadrant is completely gone. Now if it hurts, it's more of an ache. I never have that searing knife-like, sharp pain anymore.*
Neuropathic pain/paresthesia	16 (76)	14	13 (93)[e,f]	*I had this spine pain, which was at the base of my neck; it would hurt so bad; I would be at work like laying on tennis balls to relieve the pressure and I just knew that I'd be hospitalized.*	*The feeling in my hands, like at one point in time, I was having a hard time just gripping things; that like regenerated on its own after receiving the medicine for, you know, so many months. I definitely noticed reversals in a lot of symptoms, including neuropathy.*
Other pain					
Limb pain	13 (62)	13	13 (100)		
Back pain	11 (52)	11	11 (100)		
Headache	7 (33)	6	5 (83)[f]		
Body pain	7 (33)	7	7 (100)		
Gastrointestinal					
Nausea	19 (91)	19	19 (100)	*[O]nce I started throwing up, I couldn't stop throwing up. Then having thrown up for 3 days and then I'd have to go to the hospital.*	*I don't really vomit anymore though; that has been a big change.*
Vomiting	15 (71)	15	15 (100)		
Constipation	4 (19)	3	2 (67)[f]		
Fatigue	20 (95)	20	20 (100)	*I could barely go up the stairs anymore… when I would get home from work, I felt like I couldn't get up the stairs in my house so I would just stay on the couch the whole night and just keep stuff downstairs.*	*The fatigue is definitely better, and I actually started trying to get my [work] license back. I've started the process to get that back, so it's definitely improved, and it doesn't affect me on a daily basis.*
Other					
Sleep (excessive or minimal)	15 (71)	15	15 (100)	*I couldn't sleep at all; I would be up sitting there just staring at the ceiling.*	*I get a better quality of sleep.*
Cognition (eg, concentration, confusion)	10 (48)	9	9 (100)	*You can tell me something so simple, and I'll forget.*	*I was able to think much clearer.*
Muscle weakness and paralysis	11 (52)	5	5 (100)	*[I]t feels like you're wearing a lead suit so it's just this heaviness… I couldn't stand up from a seated position.*	*Yeah, so just physically able to do more. Slightly stronger muscle tone, able to walk slightly further. I don't fall over anymore. I just have the residual paralysis that I have, but physically I'm definitely stronger than I was.*
Mood					
Anxiety, fear, and worry	16 (76)	14	13 (93)[f]	*To be honest, I didn't do anything. I didn't want to go outside; I didn't want to speak to anybody; I was angry at life, at the world.*	*The depression has significantly improved. I kind of feel like I'm getting back to my old self.*
Depression and sadness	13 (62)	12	11 (92)[f]		
Anger, agitation, and aggression	9 (43)	8	8 (100)		

AHP, acute hepatic porphyria.[a]Prior to Phase 1/2 study or ENVISION; [b]Only abdominal pain, fatigue, and nausea were probed specifically for improvement (among those reporting these symptoms prestudy). Other prestudy symptoms were not systematically or consistently probed on improvement. Missing data do not suggest the presence or absence of symptom improvement; [c]Based on those reporting prestudy symptoms and not including missing data; [d]Prestudy and posttreatment symptom descriptions are not necessarily from the same interviewee; [e]Neuropathic pain and paresthesia were coded for any mention of neuropathy, burning, or tingling; [f]One patient each reported no change in their neuropathic pain/paresthesia, constipation, anxiety/fear/worry, and depression/sadness. One patient reported worsening of headaches.

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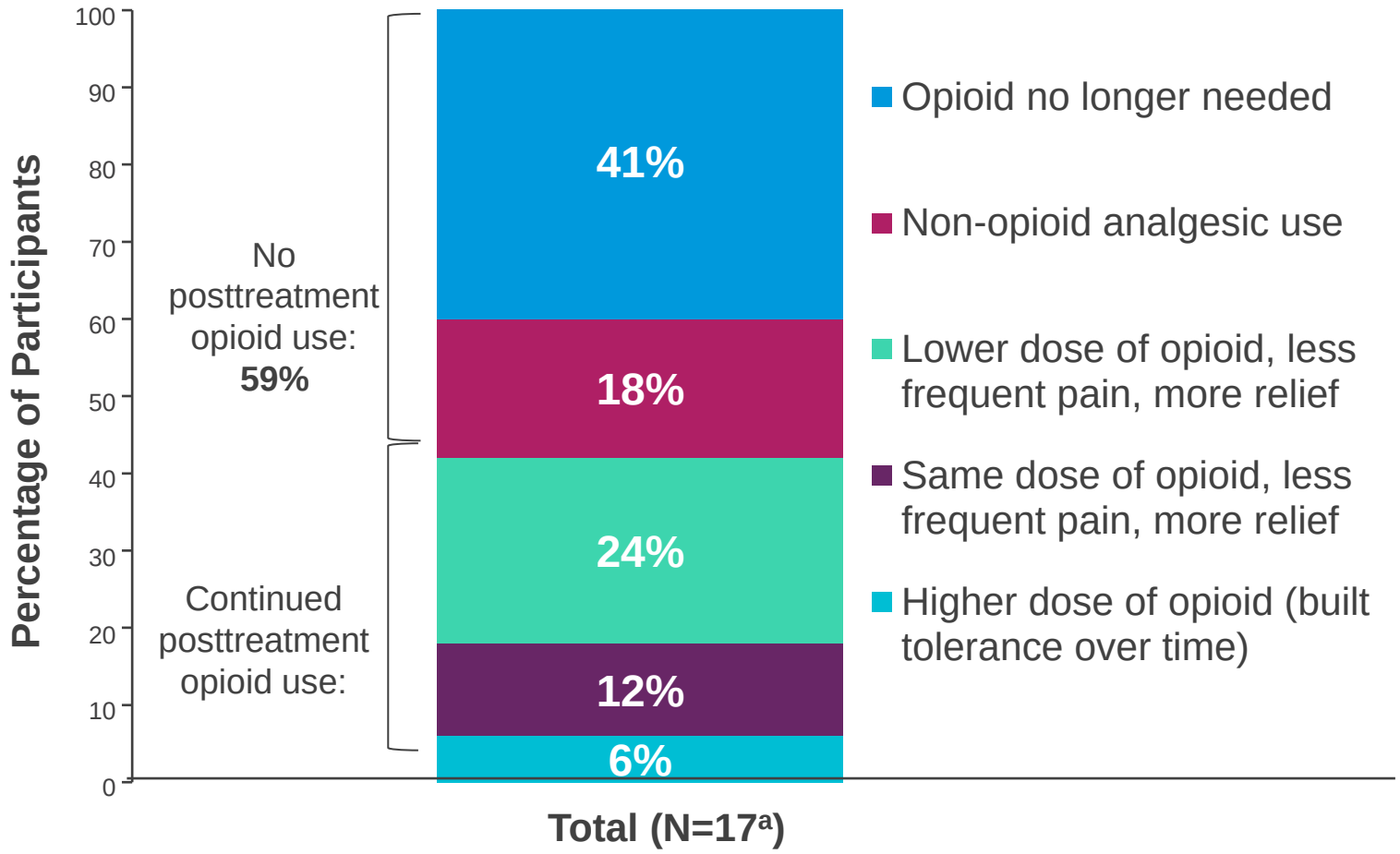
Results

Figure 1. Posttreatment Opioid Use

- Some participants who used opioids prestudy stopped using opioids entirely (Figure 1)



[a]Participants who used opioids prestudy and responded to questions related to posttreatment opioid use during the interview.

Results

Table 3. AHP Impacts, Prestudy and Posttreatment

- The impacts of AHP symptoms were wide-ranging (Table 3)
- Several participants mentioned improvements involving quality of life impacts as the “most important improvement”, including caring for children and spending time with family (24%) and fewer hospitalizations (19%)

AHP, acute hepatic porphyria.

Results

Table 3. AHP Impacts, Prestudy and Posttreatment

Impact	Experienced Impact Prestudy[a,b], N[c] (%)	Posttreatment Improvement[b]		Participant Description of Impact	
		N[d]	Yes, N (%[e])	Prestudy[a]	Posttreatment[f]
Work/school	21 (100)	21	19 (90)	*It impacted everything from my work. I had a really good career—then, lost my job.*	*Yeah, even after 6 months it became less and less…I went from… you know, when I started the trial, I was pretty much bedridden. I went from that to after… I started going to school in the fall of 2019, I graduated, I ended up changing my degree, got a degree in respiratory therapy and I'm now back to working full time, 12-hour shifts…*
Family and intimate relationships	20 (95)	20	20 (100)	*It was severely upsetting because I couldn't do anything and I felt like I couldn't be with my family and I wasn't able to take care of my child in the way that I wanted to, so it was awful.*	*I'm present with my children. I don't even think that they realize I'm sick, which is wonderful.*
Daily and physical activities	18 (86)	18	17 (94)	*So, everything that is physical activity, I couldn't do it. As I also lost strength, I couldn't do many activities that required strength. Um, even moving a table to do some cleaning, I couldn't do it, I couldn't open jars either.*	*I can go do stuff. So, before I was saying I'm in bed all day, 1 hour maybe I'm up and bags lined up next for me to puke in, none of that anymore, okay, so not at all. I go out and do stuff every day. Like for example today I've already, I took my kids to school this morning at like 7 AM. Oh yeah, I walk my dogs. I have 2 dogs. I walk my dogs 3 times a day.*
Social activities	17 (81)	17	15 (88)	*I felt really left out not being able to go to school like all the other children, and all the kids, they used to play on the weekends and after school go out, go bike riding together, or just go to the cinema or do bowling. I could never be a part of any of that.*	*But I got back in contact with my friends, this has allowed me to plan activities, trips, or meet friends, which I couldn't do before, and it has also allowed me to do activities that I could not do before, due to a lack of strength or mobility, like for example, what I said earlier, going shopping and spending all day walking, or going hiking in the mountains, or, or doing sport.*
Hospitalizations	14 (67)	14	14 (100)	*During those attacks it wasn't just going and getting the infusion when it grew to vomiting and bad pain, I had to go and stay in the hospital for 4 to 5 days. I used to get admitted there and then I was under observation getting my hematin for 3 to 4 or 4 to 5 days in a line. I used to stay for those many days in hospital.*	*Well, I guess, I mean the biggest one is I don't, that I don't spend any time in the hospital anymore and I don't spend weeks at a time in bed so that's a huge improvement.*
Financial	4 (19)	4	4 (100)	*There's lot of things I wanted to do. I couldn't really provide financially for my family, which isn't a good feeling, but at the time, like I'm lucky enough to have a supportive family.*	*So… I suppose the main thing for me is being able to work more which means I'm a reliable worker. I've been able to get a loftier job, which has led to more financial security and has led to me being able to buy my own home. So, that's a massive step forward for me. One I thought that would never be possible. So, financial security has a big impact obviously. I've lost a lot of years.*

AHP, acute hepatic porphyria.
[a]Prior to Phase 1/2 study or ENVISION. [b]Interviewers used general probes to elicit comments from participants about the prestudy and posttreatment impacts of AHP on their lives (ie, not specific questions necessitating a yes/no response). Hence, participants who did not mention a prestudy impact or posttreatment improvement in a specific domain may still have experienced an impact or improvement in that domain. Moreover, a direct relationship between prestudy impacts and poststudy improvements cannot be inferred. [c]N=21. [d]Number of participants who experienced an impact in the domain prestudy. [e]Based on number of participants who experienced an impact in the domain prestudy. [f]Prestudy and posttreatment impact descriptions are not necessarily from the same interviewee.

Results

Table 4. Posttreatment Symptom Improvement Timeline

- All participants (100%) reported complete relief or meaningful improvements in symptoms (Table 4)
- Symptom relief typically occurred after 3 or more treatments (Table 4)

Symptom[a,b]	Participants Reporting, N[c]	Complete Relief, N (%)			Improved but Still Present, N (%)		
		After 1 or 2 Treatments	After 3+ Treatments	Total	Quick (Patient-Perceived)	Slow (Patient-Perceived)	Total
Abdominal pain	19	2 (11)	6 (32)	8 (42)	3 (16)	8 (42)	11 (58)
Neuropathic pain/paresthesia[d]	9	1 (11)	2 (22)	3 (33)	2 (22)	4 (44)	6 (67)
Other pain							
Limb pain	11	0 (0)	4 (36)	4 (36)	1 (9)	6 (55)	7 (64)
Back pain	7	0 (0)	0 (0)	0 (0)	1 (14)	6 (86)	7 (100)
Headache	4	2 (50)	0 (0)	2 (50)	1 (25)	1 (25)	2 (50)
Body pain	7	0 (0)	4 (57)	4 (57)	0 (0)	3 (43)	3 (43)
Gastrointestinal							
Nausea	15	1 (7)	9 (60)	10 (67)	2 (13)	3 (20)	5 (33)
Vomiting	11	3 (27)	5 (45)	8 (73)	0 (0)	3 (27)	3 (27)
Fatigue	18	0 (0)	4 (22)	4 (22)	3 (17)	11 (61)	14 (78)
Other							
Sleep	2	0 (0)	2 (100)	2 (100)	0 (0)	0 (0)	0 (0)
Cognition	5	0 (0)	2 (40)	2 (40)	1 (20)	2 (40)	3 (60)
Muscle weakness and paralysis	5	1 (20)	0 (0)	1 (20)	1 (20)	3 (60)	4 (80)

[a]Data were not obtained on the timeline of symptom changes for several symptoms: anxiety/fear/worry, depression/sadness, anger/agitation/aggression, constipation, and diarrhea.
[b]The improvement timeline for each symptom was not specifically probed; instead, patients were asked which symptoms achieved complete relief and which symptoms were the slowest and fastest to improve.
[c]Based on those reporting the symptoms prestudy and not including missing data for symptom improvement timelines.
[d]Neuropathic pain and paresthesia were coded for any mention of neuropathy, burning, or tingling.

Results

Table 5. Characteristics of Participants with Complete Versus Partial Relief of Symptoms

- Participants reporting complete relief of symptoms or cessation of opioid use tended to be younger and more recently diagnosed with AHP, and to have higher baseline EQ-VAS[17] scores (indicating better patient-perceived general health), compared with participants with partial relief of symptoms or continued opioid use (Table 5)

	Abdominal Pain		Neuropathic Pain		Other Pain		Opioid Use	
Baseline Characteristic	Complete Relief (N=8)	Partial Relief (N=11)	Complete Relief (N=3)	Partial Relief (N=6)	Complete Relief (N=6)	Partial Relief (N=9)	None (N=10)	Continued (N=7)
Age, years, mean (SD)	30.4 (5.7)	38.6 (10.3)	28.7 (11.0)	38.7 (3.8)	30.8 (9.0)	37.4 (10.3)	30.9 (7.2)	40.9 (8.6)
Years since diagnosis[a]								
N	7	6	3	3	4	4	7	4
Median (min, max)	6.5 (0.9, 15.3)	6.4 (2.1, 19.2)	3.1 (2.7, 5.7)	9.4 (6.5, 9.7)	7.6 (3.1, 15.3)	7.1 (1.0, 19.2)	5.7 (1.0, 19.2)	9.6 (2.7, 12.2)
Chronic symptoms at baseline, N (%)	3 (38)	5 (45)	2 (67)	3 (50)	3 (50)	4 (44)	5 (50)	4 (57)
Neuropathy at baseline, N (%)	3 (38)	7 (64)	2 (67)	3 (50)	2 (33)	6 (67)	5 (50)	4 (57)
Chronic opioid use at baseline, N (%)	2/7 (29)	3/6 (50)	2/3 (67)	1/3 (33)	1/4 (25)	1/4 (25)	3/7 (43)	2/4 (50)
SF-12 score at baseline[a]								
N	7	6	3	3	4	4	7	4
PCS, mean (SD)	37.5 (8.4)	38.3 (11.0)	41.3 (12.2)	39.7 (8.8)	43.9 (9.0)	33.5 (7.5)	37.1 (10.5)	36.8 (10.3)
MCS, mean (SD)	44.0 (9.2)	33.9 (11.5)	33.2 (17.3)	39.0 (9.8)	40.8 (14.5)	38.7 (9.4)	44.1 (7.8)	30.7 (11.6)
EQ-VAS score at baseline, mean (SD)	72.3 (13.7)	60.5 (16.0)	65.0 (21.8)	61.2 (7.1)	67.0 (11.8)	65.0 (20.3)	72.1 (11.8)	58.9 (22.8)

AHP, acute hepatic porphyria; EQ-VAS, EQ-5D-5L visual analogue scale; MCS, mental component summary; PCS, physical component summary; SD, standard deviation; SF-12, 12-item Short Form Health Survey.

[a]ENVISION only.

17. Herdman M, Gudex C, Lloyd A, et al. *Qual Life Res.* 2011;20(10):1727-36.

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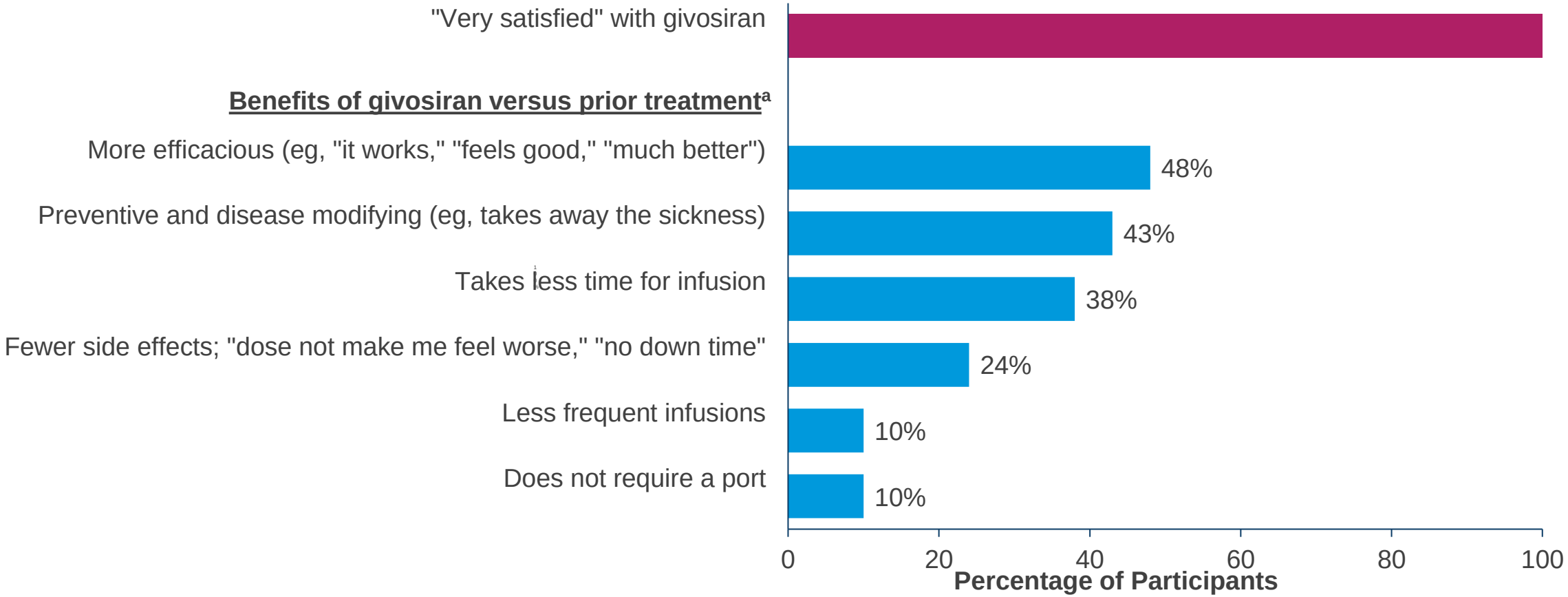
Results

Figure 2. Patient Perspectives on Givosiran

- Patient perspectives on givosiran are outlined in Figure 2



[a]All patients reported the use of hemin (Panhematin, haem arginate).

Study Limitations

- Interviewees were a subset of patients who continued givosiran treatment after completing the open-label extension periods of the Phase 1/2 and ENVISION studies, introducing the possibility of selection bias
- The interviews focused primarily on the effectiveness and benefits of givosiran treatment, with less opportunity to assess adverse events and treatment limitations

Conclusions

- Participants reported meaningful improvements in AHP symptoms and impacts, and reduction in opioid use, with continuing givosiran treatment
- All participants were “very satisfied” with givosiran treatment, with many noting that givosiran was superior to hemin in terms of efficacy, tolerability, and convenience

AHP, acute hepatic porphyria.

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Disclosures

- Stephen Lombardelli and Stephen Meninger are employed by and own stock and stock options in Alnylam Pharmaceuticals. Michelle Brown is employed by RTI Health Solutions, a not-for-profit research organization contracted with Alnylam Pharmaceuticals to partner with and conduct this study. Hetanshi Naik is a consultant to Alnylam Pharmaceuticals, Recordati Rare Diseases, Disc Medicine, and Mitsubishi Tanabe and has received sponsorship fees for lectures on the porphyrias (Sarah Lawrence College, Keck Graduate Institute).

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