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Patient experience with acute hepatic porphyria before and after long-term givosiran treatment in a qualitative interview study

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ABSTRACT

Background: Acute hepatic porphyria (AHP) is characterized by debilitating and potentially life-threatening neurovisceral attacks, possible chronic symptoms, and long-term complications. In a phase 1/2 open-label extension (OLE) study and the phase 3 ENVISION study, givosiran led to sustained improvement in annualized attack rate and quality of life (QOL) measures. To capture the patient experience of symptoms and impacts of AHP, and any changes experienced during treatment with givosiran, qualitative interviews were conducted with study participants.

Methods: Participants who continued givosiran treatment after completing the phase 1/2 OLE study and the phase 3 ENVISION study participated in semi-structured interviews (i.e., loosely structured interviews on a predetermined topic without strict adherence to wording or order of questions) in 2022 that were developed and executed by RTI Health Solutions. Transcripts were assessed using thematic analysis methods. Authors/investigators categorized symptoms as likely acute attack-related or chronic based on the participants' descriptions. Select clinical trial results (baseline characteristics and QOL scores from the phase 1/2 and ENVISION studies) from interview participants were compiled.

Results: Duration of givosiran treatment in the 21 participants at the time of interview was approximately 4–5 years (mean [SD], 51.8 [7.9] months; median [range], 49.7 [41.4, 69.1] months). Participants reported experiencing AHP symptoms prior to the phase 1/2 OLE or phase 3 studies, including abdominal pain ($n = 20/21$ [95 %]) and fatigue ($n = 20/21$ [95 %]), with impacts including work/school ($n = 21/21$ [100 %]) and family and intimate relationships ($n = 20/21$ [95 %]). Post-treatment, participants reported improvements in symptoms including abdominal pain ($n = 20/20$ [100 %] participants), fatigue ($n = 20/20$ [100 %]), and nausea ($n = 19/19$ [100 %]), and in impacts, including family and intimate relationships ($n = 20/20$ [100 %]) and work/school ($n = 19/21$ [90 %]). Most participants ($n = 19/21$ [90 %]) used opioids prior to the trials, and many reported stopping opioids ($n = 10/17$ [59 %]) or using a lower dose ($n = 4/17$ [24 %]). Participants reported complete relief of certain symptoms, including vomiting ($n = 8/11$ [73 %]), nausea ($n = 10/15$ [67 %]), and abdominal pain ($n = 8/19$ [42 %]). Participants with complete relief of pain or cessation of opioid use tended to be younger and more recently diagnosed, with higher baseline EuroQOL visual analog scale scores during the clinical trials. Participants with prior hemin prophylaxis at entry into the clinical trials were more likely to have experienced abdominal pain, neuropathic pain/paresthesia, and gastrointestinal symptoms before the study, and were generally more or as likely to have complete relief of these symptoms (e.g., $n = 6/8$ [75 %] participants with prior hemin prophylaxis reported complete relief of abdominal pain vs $n = 2/11$ [18 %] participants without prior hemin prophylaxis). All participants reported being "very satisfied" with givosiran.

Abbreviations: AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, aminolevulinic acid; *ALAS1*, ALA synthase 1; EQ-VAS, EuroQoL visual analog scale; MCS, mental component summary; OLE, open-label extension; PBG, porphobilinogen; PCS, physical component summary; QOL, quality of life; SF-12, Short Form Health Survey..

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Conclusions: Participants reported meaningful improvements in AHP symptoms, increased QOL, and reduced opioid use with long-term monthly givosiran treatment.

1. Introduction

Acute hepatic porphyria (AHP) is a family of rare genetic disorders caused by dysregulation of heme biosynthesis, resulting in the accumulation of neurotoxic heme intermediates delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) [1,2]. AHP is characterized by debilitating and potentially life-threatening acute neurovisceral attacks, long-term complications, and chronic symptoms [1–4]. Acute attacks are associated with severe abdominal pain, as well as other symptoms that may include vomiting, nausea, diarrhea, constipation, muscle weakness/paresis, tachycardia, hypertension, hyponatremia, psychiatric issues (e.g., anxiety, depression), mental status changes, and seizures [1–3]. Some patients, generally women, develop ≥4 attacks per year [1,5,6]. Chronic manifestations can include pain (e.g., abdominal, arm, back), fatigue, neuropathy, and nausea between attacks [1,7,8]. Potential long-term complications include primary liver cancer, chronic kidney disease, hypertension, and chronic neuropathy [1,9,10]. Opioids may be used to manage chronic pain, but this approach has a risk of opioid dependence [11].

AHP is associated with a significant burden on patients, families, and caregivers. Patients describe negative impacts in domains including physical, mental, emotional, social, and ability to work or go to school [3,4,7,12,13]. The financial aspect can be burdensome, as debilitating attacks, chronic symptoms, and repeat hospitalizations may preclude employment and be associated with significant medical expenses and debt [7,12,13]. Families and caregivers describe financial, social, and psychological impacts in their own lives related to caring for patients who struggle to perform self-care or fulfill other responsibilities [13]. These negative impacts on functioning are often accompanied by reduced quality of life (QOL) [3,4,14].

Management includes identification and avoidance of triggers (i.e., lifestyle modifications) and use of intravenous hemin or glucose if hemin is unavailable, as is the case in certain regions, for acute attacks. Prophylactic hemin infusions are sometimes used for recurrent attacks [11,15]. Management with prophylactic hemin is highly individualized, with infusions given as often as once weekly in some patients [11]. Potential adverse effects associated with hemin infusions include phlebitis, thrombocytopenia, and venous damage [1,11]. Long-term use can result in hepatic iron overload and tachyphylaxis [1]. Liver transplantation is often used as a last option in some patients with severe, treatment-resistant attacks due to its association with morbidity and mortality [11,15].

Givosiran, an RNA interference therapeutic [16], was approved in the United States in 2019 for the treatment of adults with AHP [17] and in the European Union in 2020 for the treatment of AHP in adults and adolescents aged ≥12 years [18]. Givosiran targets messenger RNA encoding ALA synthase 1 (*ALAS1*), the rate-controlling enzyme of the hepatic heme biosynthetic pathway [1], preventing accumulation of ALA and PBG [16–18]. In randomized controlled trials, givosiran reduced annualized attack rate, use of hemin for attacks, and ALA and PBG levels when administered by subcutaneous injection at a recommended dose of 2.5 mg/kg once monthly [19–22]. Givosiran also was effective at reducing some chronic symptoms and improving patient-reported QOL assessments [21,22]. The most frequent adverse reactions associated with givosiran treatment include injection site reactions, nausea, and fatigue [22].

Little is known about the long-term use of AHP treatments and impact on QOL. In the phase 3 ENVISION study of givosiran, patient-reported physical and mental health, assessed using the 12-item Short Form Health Survey (SF-12) [23], and patients' perception of overall health, assessed using the EuroQoL visual analog scale (EQ-VAS) [24], improved with givosiran compared with placebo, and those benefits were maintained long-term with continuing givosiran treatment for up to 36 months [20–22].

Both objective measures and subjective reports of the patient experience are necessary for a more complete understanding of AHP and treatment effects. To this end, in a standalone study conducted after completion of a givosiran phase 1/2 OLE study or the phase 3 ENVISION study, qualitative interviews were conducted with study participants. These interviews sought to capture, in their own words, the symptoms and impacts of AHP and any changes the participants experienced during treatment with givosiran, including the perceived meaningfulness of these changes.

2. Methods

Clinical trials of givosiran for AHP include a phase 1 study (NCT02452372) [19], the phase 1/2 OLE study (NCT02949830) [25], and a phase 3 study (ENVISION; NCT03338816) [20–22]. In the phase 1/2 OLE study, participants received givosiran for up to 48 months. ENVISION comprised a double-blind period and an OLE; participants received placebo or givosiran for 6 months during the double-blind period [20] and givosiran for up to an additional 30 months in the OLE [21,22].

Participants in this standalone interview study were a subset of participants in the phase 1/2 OLE study, which was separate from and followed the phase 1 study, or the ENVISION study, which comprised the double-blind stage and an OLE. Eligible participants were aged ≥18 years, completed either the phase 1/2 OLE study or the double-blind and OLE stages of ENVISION, were currently receiving givosiran through an expanded access program or commercial drug use, and were willing to provide verbal consent for and participate in the interview study. Participants had experienced repeated porphyria attacks at entry into the phase 1/2 study and ENVISION [19,20]. The interview study was conducted with participants from the US, Spain, and the UK. Relevant institutional review board and ethics approvals were obtained. The interviews were conducted by a central group, RTI Health Solutions or Global Perspectives Healthcare Research and Insight. Eligible patients in these 3 countries were informed of the study by a patient advocacy group (in the US only by the United Porphyrias Association) and/or the clinical trial sites (i.e., US, Spain, and the UK). Interested patients were provided information to either directly contact or be contacted by the central group to learn more about and potentially schedule the interview. Verbal informed consent was obtained from participants prior to the interview.

One-hour telephone interviews were conducted in-language by in-country native language–speaking moderators. Interviews were completed using a semi-structured interview guide developed by RTI Health Solutions and the study sponsor (**Appendix A**). Interviews were audio-recorded and transcribed, and thematic analysis methods were used to analyze transcripts [26]. Important concepts and dominant trends were identified in each interview and compared across interviews [27] to allow for assessment of patterns in participants' responses. Interview data were analyzed using standardized qualitative research methods for 2 periods: prestudy (i.e., before study enrollment) and post-treatment (i.e., after the participant started receiving givosiran during the clinical trial).

The coding and data analysis processes were facilitated using qualitative analysis software (ATLAS-ti 7.5 or higher; ATLAS.ti Scientific Software Development GmbH, Berlin, Germany). Approximately 10 %

of the interview transcripts were coded by 2 different people. The initial coding framework was adapted, and new codes were added to the codebook as new concepts were identified during review of interview transcripts. To ensure consistency across the interview, all coding and analyses were conducted in accordance with the final codebook and the final qualitative analysis plan for the study.

Formal hypotheses were not tested as this was a qualitative study. Descriptive statistics of select themes were tabulated. Data were analyzed and summarized in aggregate for the full sample, or, where applicable, for the subset of participants who responded, and for select tabulated data by subgroups (i.e., participants with complete vs partial relief of select symptoms, and participants with vs without a history of hemin prophylaxis). Deidentified, patient-level baseline characteristics data and scores on QOL measures (i.e., SF-12 [23] and EQ-VAS [24]) from the clinical trials were obtained for interview participants for subgroup analyses. On the SF-12, which was assessed in ENVISION only, higher physical component summary (PCS) and mental component summary (MCS) scores (range: 0–100) indicate improved self-reported functioning in physical and mental domains, respectively. On the EQ-VAS, which was assessed in both studies, higher scores (range: 0–100) indicate better self-reported health state.

Prespecified analyses were performed to address the study's primary research questions, which included the following: what improvements were noticed after initiating givosiran, including the experience and severity of acute attacks, specific symptoms, and impacts of AHP; whether givosiran changed the participants' lives; whether, and if so, how givosiran addressed the participants' previously most bothersome or important symptoms and impacts; approximately when each symptom improvement was first experienced (i.e., after how many treatments) and the general course and speed of that improvement; the impact of givosiran on use of opioids; and whether participants' were satisfied with givosiran treatment, and if so, how it compared to previous treatments. The semi-structured interview guide did not explicitly differentiate between acute attack-related and chronic symptoms of AHP. Therefore, the authors/investigators categorized symptoms as likely acute or chronic based on the participants' descriptions.

Each participant received a monetary honorarium in compensation for time spent participating in the telephone interview.

3. Results

3.1. Participants

Interviews were conducted from January through August 2022. Twenty-one participants from the US, UK, and Spain were interviewed; most ($n = 18$ [86 %]) were female and the mean (SD) age was 39.3 (9.0) years (Table 1). All participants had acute intermittent porphyria with mutations in the hydroxymethylbilane synthase gene. Eight (38 %) participants had a history of hemin prophylaxis. Mean (SD) duration of givosiran treatment at the time of interview was 51.8 (7.9) months, or 4.3 (0.7) years; median (range) duration of givosiran treatment was 49.7 (41.4, 69.1) months.

Sex and age were similar among participants from the phase 1/2 OLE ($n = 7$) and ENVISION ($n = 14$) studies (**Table S1**). Duration of givosiran treatment at the time of interview was longer, on average, among participants from the phase 1/2 OLE study (mean [SD]: 61.3 [4.6] months, or 5.1 [0.4] years) compared with ENVISION (47.1 [3.6] months, or 3.9 [0.0] years).

Of the 21 participants, 3 participants experienced intermittent symptoms in the years prior to their first attack (i.e., prestudy, before givosiran treatment; for 3, 6, and 18 years, respectively) such as abdominal pain, fatigue, and nausea before experiencing their first attack, 15 participants did not experience intermittent symptoms prior to their first attack, and data for 3 participants were not obtained. Mean (SD) time from first attack to AHP diagnosis was 0.8 (8.2) years; 10 participants were diagnosed the same year as their first attack, and 7 were diagnosed 1–24 years later. Two participants were diagnosed before their first attack due to a family history of the disease. Regarding the period between their first attack and initiation of givosiran treatment, 17 (81 %) participants described their attacks as becoming increasingly frequent and/or having more severe or chronic symptoms.

Table 1
Participant characteristics at baseline of the clinical trials.

Characteristic	Total $N = 21$
Clinical trial, *n* (%)	
Phase 1/2 OLE	7 (33)
ENVISION	14 (67)
Sex, *n* (%)	
Male	3 (14)
Female	18 (86)
AIP with mutation in *HMBS* gene, *n* (%)[a]	21 (100)
Age at trial enrollment, years	
Mean (SD)	34.6 (9.2)
Years since diagnosis[a]	
Mean (SD)	7.2 (5.6)
Median (range)	6.1 (0.9, 19.2)
Historical AAR[a]	
Mean (SD)	18.7 (14.1)
Median (range)	14.0 (4.0, 46.0)
Number of attacks in past 12 months[b]	
Mean (SD)	11.4 (11.4)
Median (range)	10 (3, 36)
Previous hemin prophylaxis, *n* (%)	8 (38)
Chronic symptoms at baseline, *n* (%)	10 (48)
Givosiran treatment duration, months[c,d]	
Mean (SD)	51.8 (7.9)
Median (range)	49.7 (41.4, 69.1)

AAR, annualized attack rate; AIP, acute intermittent porphyria; *HMBS*, hydroxymethylbilane synthase; SD, standard deviation.
[a] Available for participants in ENVISION only ($n = 14$).
[b] Available for participants in the phase 1/2 OLE study only ($n = 7$).
[c] First dose of givosiran to interview.
[d] All participants were continuing to receive givosiran at the time of the interview.

3.2. Symptom relief

When describing their prestudy experience, participants reported AHP symptoms in multiple domains, particularly abdominal pain ($n = 20/21$ [95 %]), fatigue ($n = 20/21$ [95 %]), nausea ($n = 19/21$ [90 %]), and neuropathic pain and paresthesia, including neuropathy, burning, or tingling ($n = 16/21$ [76 %]) (Table 2). Based on the participants' descriptions, abdominal pain and nausea were judged by authors/investigators to be likely attack related, whereas fatigue and neuropathic pain and paresthesia were judged by authors/investigators to be likely chronic. Abdominal pain ($n = 14/21$ [67 %]), other types of pain ($n = 8/21$ [38 %]), and muscle weakness, paralysis, and numbness ($n = 4/21$ [19 %]) were most often reported as the "most bothersome" prestudy symptom. Sixteen participants spontaneously reported they experienced symptoms between attacks, including abdominal pain ($n = 13/16$ [81 %]), fatigue ($n = 13/16$ [81 %]), and nausea ($n = 11/16$ [69 %]). Most participants ($n = 19/21$ [90 %]) reported having used opioids prestudy; relief of acute and/or chronic pain was described as somewhat effective ($n = 16/19$ [84 %]), not effective or mildly effective ($n = 5/19$ [26 %]), and/or effective only in the hospital (intravenous; $n = 4/19$ [21 %]).

All participants ($n = 21/21$ [100 %]) reported improvements in multiple symptoms after starting givosiran. Among participants who experienced the following symptoms prestudy, 100 % reported post-treatment improvement: abdominal pain ($n = 20/20$), limb pain ($n = 13/13$), back pain ($n = 11/11$), body pain ($n = 7/7$), nausea ($n = 19/19$), vomiting ($n = 15/15$), fatigue ($n = 20/20$), sleep disturbance ($n = 15/15$), cognition ($n = 9/9$), muscle weakness and paralysis ($n = 5/5$), and/or anger/agitation/aggression ($n = 8/8$) (Table 2). All participants ($n =$

Table 2
Symptoms of AHP, prestudy and post-treatment.

Symptom[a]	Experienced Symptom Prestudy, *n*(%)	Post-treatment Improvement[b]		Participant Description of Symptom	
		n[c]	Yes, *n* (%)	Prestudy[a]	Post-treatment[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."*
				Likely attack related[e]	*Likely attack related*[e]
Neuropathic pain/ paresthesia[f]	16 (76)	14	13 (93)[g]	*"It's not widespread neuropathy, but my hands and feet will tingle, or I'll still have some pains in my back and the back of my legs; but once the nerve is damaged, it's pretty damaged, so they said that it may or may not continue to improve."*	*"The feeling in my hands, like at 1 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."*
				Likely chronic[e]	*Likely chronic* [e]
Other pain				*"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."*	*"On the very odd occasion I do have some discomfort, [but] it's not anywhere near going towards an attack."*
Limb pain	13 (62)	13	13 (100)		
Back pain	11 (52)	11	11 (100)		*Likely attack related*[e]
Headache	7 (33)	6	5 (83)[g]	*Likely attack related*[e]	
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)[g]	*Likely attack related*[e]	*Likely attack related*[e]
				"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."*
Fatigue	20 (95)	20	20 (100)	*Likely chronic*[e]	*Likely chronic*[e]
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."*
				Likely chronic[e]	*Likely chronic*[e]
Cognition (e.g., 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."*
				Likely chronic[e]	*Likely chronic*[e]
				"[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."*
Muscle weakness and paralysis	11 (52)	5	5 (100)	*Likely chronic*[e]	*Likely chronic*[e]
Mood					
Anxiety, fear, and worry	16 (76)	14	13 (93)[g]	*"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)[g]		
Anger, agitation, and aggression	9 (43)	8	8 (100)	*Likely chronic*[e]	*Likely chronic*[e]

AHP, acute hepatic porphyria.
[a] Prior to phase 1/2 OLE 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 does not suggest the presence or absence of symptom improvement.
[c] Based on those reporting prestudy symptoms and not including missing data.
[d] Prestudy and post-treatment symptom descriptions are not necessarily from the same participant.
[e] The semi-structured interview guide did not explicitly differentiate between acute attack-related and chronic symptoms of AHP. Authors/investigators subjectively assessed symptoms as acute or chronic based on the patients' descriptions.
[f] Neuropathic pain/paresthesia was coded for any mention of neuropathy, burning, or tingling.
[g] 1 participant each reported no change in their neuropathic pain/paresthesia, anxiety/fear/worry, depression/sadness, and constipation. 1 patient reported the worsening of headaches.

21/21 [100 %]) reported improvements in AHP attacks post-treatment compared with prestudy, including 13/21 (62 %) participants who reported that attacks were gone, 7/21 (33 %) participants who reported that attacks were less frequent and less severe, and 1/21 (5 %) participant who reported that attacks were less severe but not less frequent.

Most participants reported post-treatment improvements among symptoms that they considered "most bothersome," including

abdominal pain (100 % of participants) and other types of pain (83 %–100 % of participants), and muscle weakness/paralysis (100 % of participants). Pain alleviation was mentioned most frequently as the "most important improvement" (n = 9/21 [43 %]); others were less fatigue (n = 2/21, 10 %), fewer attacks (n = 2/21, 10 %), and improved mood/well-being and less fear (n = 2/21, 10 %). Among 17 participants who used opioids prestudy and responded to interview questions related to post-treatment opioid use, 10/17 (59 %) participants stopped using opioids entirely (Fig. 1).

While all participants reported meaningful post-treatment improvements in their AHP symptoms and attacks, some participants did not achieve complete relief of symptoms (Table 3). Among participants who reported experiencing a symptom prestudy, symptoms that were most often described as being completely relieved included vomiting (n = 8/11 [73 %]), nausea (n = 10/15 [67 %]), and abdominal pain (n = 8/19 [42 %]). Symptoms that were still present, but less severe, included back pain (n = 7/7 [100 %]), muscle weakness and paralysis (n = 4/5 [80 %]), fatigue (n = 14/18 [78 %]), and neuropathic pain and paresthesia (n = 6/9 [67 %]).

For some participants, symptoms improved quickly, after 1 or 2 monthly givosiran treatments, but complete or partial relief of symptoms typically occurred after 3 or more treatments (Table 3). The symptoms that participants most often described as being slow to improve were back pain (n = 6/7 [86 %]), fatigue (n = 11/18 [61 %]), limb pain (n = 6/11 [55 %]), and abdominal pain (n = 8/19 [42 %]). No specific timeline was ascertained.

Participants reporting complete relief of symptoms tended to be younger than those reporting partial relief of symptoms (Table 4). Mean age of participants with complete versus partial relief of individual symptoms was 30.4 versus 38.6 years for abdominal pain, 28.7 versus 38.7 years for neuropathic pain, 30.8 versus 37.4 years for other pain, and 30.9 versus 40.9 years for opioid use. Participants with complete relief of symptoms also tended to have been diagnosed with AHP more recently than participants with partial relief of symptoms. Mean time since diagnosis for participants with complete versus partial relief of individual symptoms was 7.3 versus 8.2 years for abdominal pain, 3.9 versus 8.5 years for neuropathic pain, 8.4 versus 8.6 years for other pain, and 6.9 versus 8.5 years for opioid use. Finally, participants reporting complete relief of symptoms tended to have higher baseline EQ-VAS scores, indicating better patient-perceived general health, than those reporting partial relief of symptoms. Mean baseline EQ-VAS score for participants with complete versus partial relief of individual symptoms was 72.3 versus 60.5 for abdominal pain, 65.0 versus 61.2 for neuropathic pain, 67.0 versus 65.0 for other pain, and 72.1 versus 58.9 for opioid use.

3.3. Changes/improvement in QOL

Prestudy, the impacts of AHP were wide-ranging, affecting work/school (n = 21/21 [100 %]), family and intimate relationships (n = 20/21 [95 %]), daily and physical activities (n = 18/21 [86 %]), social activities (n = 17/21 [81 %]), hospitalizations (n = 14/21 [67 %]), and financial impacts (n = 4/21 [19 %]) (Table 5). Most daily routines and activities were affected, including ability to care for or spend time with children and attend to home responsibilities. Participants described loss of intimate relationships (e.g., "It destroyed my marriage"), friendships (e.g., "I lost a lot of friends because I was unreliable for years, you know, I couldn't be there for them"), and jobs (e.g., "I had a really good career—then, lost my job"). Repeat hospitalizations were disruptive to daily life (e.g., "I think that I managed to survive school because I had accommodations with the Office of Disability and so all my professors knew that I was certainly going to be hospitalized at least a few times a semester").

Participants who reported an impact in a specific area prestudy generally reported post-treatment improvement in that area. The areas included work/school (n = 19/ 21 [90 %]), family and intimate relationships (n = 20/20 [100 %]), daily and physical activities (n = 17/18 [94 %]), social activities (n = 15/17 [88 %]), hospitalizations (n = 14/14 [100 %]), and financial impacts (n = 4/4 [100 %]) (Table 5). Participants described a return to normality, including increased ability to care for children and other family members (e.g., "I am doing the same as what the other parents do in terms of juggling work and life"), work, and attend school, as well as resumption of social activities (e.g., "My social life was back to normal") and physical activities (e.g., "I can swim and do all of the things that I did pre-porphyria") that had become difficult or impossible to perform.

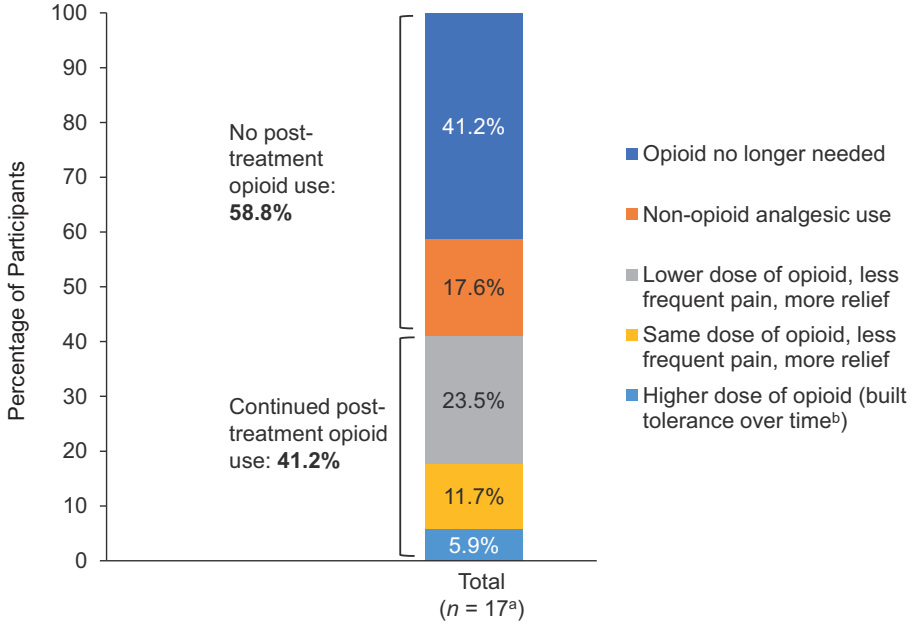

Fig. 1. Post-treatment opioid use.
[a]Participants who used opioids prestudy and responded to questions related to post-treatment opioid use during the interview.
[b]Built tolerance over time based on participant report.

Table 3
Post-treatment symptom improvement timeline.

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 (Participant-Perceived)	Slow (Participant-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 (i.e., number of weeks or months) for each symptom was not specifically probed; instead, participants were asked which symptoms they experienced 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/paresthesia was coded for any mention of neuropathy, burning, or tingling.

Table 4
Characteristics of participants with complete versus partial relief of symptoms at baseline of the clinical trials.

Baseline Characteristic	Abdominal Pain		Neuropathic Pain		Other Pain		Opioid Use	
	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 at trial enrollment, 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
Mean (SD)	7.3 (4.7)	8.2 (6.8)	3.9 (1.6)	8.5 (1.8)	8.4 (5.3)	8.6 (8.7)	6.9 (6.0)	8.5 (4.0)
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[a] at baseline								
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)

EQ-VAS, EuroQOL visual analog scale; MCS, mental component summary; PCS, physical component summary; SD, standard deviation; SF-12, 12-item Short Form Health Survey.
[a] ENVISION only.

Several participants described specific post-treatment improvements as the "most important" improvement they experienced. These included caring for children and spending time with family (5/21 [24 %]), fewer hospitalizations (4/21 [19 %]), improved social life (e.g., planning events, traveling; *n* = 3 [14 %]), and work/school (e.g., going back to work or school, changing jobs; *n* = 1 [5 %]). Seven participants (33 %) reported overall improvement (e.g., "everything," "live life," "be normal," "freedom") as the "most important."

Consistent with these reported improvements, scores on the SF-12 and EQ-VAS increased during the studies for these participants (**Table S2**). Mean (SD) change in SF-12 PCS and MCS scores (*n* = 6) from baseline to Month 36 were 7.8 (9.5) and 9.2 (4.6), respectively, and mean (SD) change in EQ-VAS score (*n* = 10) from baseline to Month 36 was 15.9 (14.1).

3.4. History of hemin prophylaxis

All participants (*n* = 21/21 [100 %]) reported using hemin for treatment of acute attacks before enrolling in a givosiran clinical trial, and 8 (38 %) participants had received hemin prophylactically. Baseline characteristics by history of hemin prophylaxis are presented in **Table S3**. On average, at entry into the clinical trials, participants with prior hemin prophylaxis had been diagnosed with AHP more recently, compared with participants with no prior hemin prophylaxis.

Table 5
Impacts of AHP, prestudy and post-treatment.

Impact	Characterization of Impact	Experienced Impact Prestudy[a,b]	Post-treatment Improvement		Participant Description of Impact	
		n (%)[c]	*n*[d]	Yes, *n* (%)[e]	Prestudy[a]	Post-treatment[f]
Work/school	Not being able to attend class; needing to quit a job; needing modifications to work or school routines and schedules	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-h shifts…"*
Family and intimate relationships	Not being able to spend time with children, parents, or partner; strain on these 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	Not being able to walk, clean, cook, or care for children	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 h 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	Not being able to spend time with friends, make friends, date, or plan any activities, such as events or vacations	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	Frequent 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	Inability to provide for family, travel, or feel financially stable	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 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 OLE study or ENVISION.
[b] Interviewers used general probes to elicit comments from participants about the prestudy and post-treatment impacts of AHP on their lives (i.e., not specific questions necessitating a yes/no response). Hence, participants who did not mention a prestudy impact or post-treatment 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 post-treatment impact descriptions are not necessarily from the same participant.

Based on interview feedback, participants with prior hemin prophylaxis ($n = 8$) were more likely to have experienced some symptoms prestudy than participants without prior hemin prophylaxis ($n = 13$). These symptoms included abdominal pain ($n = 8/8$ [100 %] participants with prior hemin prophylaxis and $n = 11/13$ [85 %] participants without prior hemin prophylaxis, respectively), neuropathic pain and paresthesia ($n = 5/8$ [63 %] and $n = 4/13$ [31 %], respectively), nausea ($n = 6/8$ [75 %] and $n = 9/13$ [69 %], respectively), and vomiting [$n = 5/8$ [63 %] and $n = 6/13$ [46 %], respectively) (Table 6). Participants with prior hemin prophylaxis were also more likely to have complete relief of certain symptoms than participants without prior hemin prophylaxis. These symptoms included abdominal pain ($n = 6/8$ [75 %] participants with prior hemin prophylaxis and $n = 2/11$ [18 %] participants without prior hemin prophylaxis, respectively), neuropathic

pain and paresthesia ($n = 2/5$ [40 %] and $n = 1/4$ [25 %], respectively), limb pain ($n = 1/2$ [50 %] and $n = 3/9$ [33 %], respectively), body pain ($n = 3/3$ [100 %] and $n = 1/4$ [25 %], respectively), nausea ($n = 5/6$ [83 %] and $n = 5/9$ [56 %], respectively), fatigue ($n = 2/7$ [29 %] and $n = 2/11$ [18 %], respectively), and cognitive symptoms ($n = 1/1$ [100 %] and $n = 1/4$ [25 %], respectively). Participants with prior hemin prophylaxis were less likely to have experienced certain symptoms prestudy than participants without prior hemin prophylaxis. These symptoms included limb pain ($n = 2/8$ [25 %] participants with prior hemin prophylaxis and $n = 9/13$ [69 %] participants without prior hemin prophylaxis, respectively), back pain ($n = 2/8$ [25 %] and $n = 5/13$ [38 %], respectively), headache ($n = 1/8$ [13 %] and $n = 3/13$ [23 %], respectively), cognitive symptoms ($n = 1/8$ [13 %] and $n = 4/13$ [31 %], respectively), and muscle weakness and paralysis ($n = 1/8$ [13 %] and $n = 4/13$ [31 %], respectively) (Table 6).

Regardless of history of hemin prophylaxis, symptoms most often required 3 or more givosiran treatments to achieve complete resolution or were described as being slow to improve (Table 6). Symptoms that were experienced by 5 or more participants and required 3 or more treatments to achieve complete resolution included, but were not limited to, nausea ($n = 9/15$ [60 %]), body pain ($n = 4/7$ [57 %]), and vomiting ($n = 5/11$ [45 %]).

3.5. Treatment satisfaction

When asked how satisfied they were with givosiran treatment, all participants ($n = 21/21$ [100 %]) said that they were "very satisfied." Participants described an overall positive impact (e.g., "It's been great for my life"). For some, the benefits exceeded expectations (e.g., "I had expected it to just… my hope was that it would significantly decrease my symptoms to the point that I would be able to function a little bit more. I had never expected to be able to get off of disability"). Compared with previous treatment, several advantages of givosiran were reported (Fig. 2), including efficacy, disease-modifying characteristics, and convenience (e.g., shorter duration of infusions, less frequent infusions, port not required).

Six of 21 (29 %) participants said they were unable to comment on anything they wished to improve further. Among participants with partial relief of symptoms, the symptom most frequently reported as needing additional improvement was fatigue ($n = 5/21$ [24 %]), which was judged by authors/investigators to be likely chronic, followed by problems with cognition ($n = 2/21$ [10 %]); others that were mentioned by 1 out of 21 (5 %) participants each were body aches and pains, nerve damage, vomiting, kidney function (high creatinine levels [$n = 1$] and kidney impacts from AHP [$n = 1$]), high blood pressure, and paralysis. Impacts reported as needing additional improvement were worsening in the work impact of AHP ($n = 1/21$ [5 %]), issues with insurance

Table 6
Post-treatment symptom improvement timeline, by history of hemin prophylaxis.

Symptom[a]	Participants Reporting, *n*[b]	Complete Relief, *n*(%)			Improved but Still Present (Participant-Perceived), *n* (%)		
		After 1 or 2 Treatments	After 3+ Treatments	Total	Quick	Slow	Total
Prior hemin prophylaxis ($n = 8$)							
Abdominal pain	8 (100)	1 (13)	5 (63)	6 (75)	1 (13)	1 (13)	2 (25)
Neuropathic pain/paresthesia[c]	5 (63)	1 (20)	1 (20)	2 (40)	0 (0)	3 (60)	3 (60)
Other pain							
Limb pain	2 (25)	0 (0)	1 (50)	1 (50)	0 (0)	1 (50)	1 (50)
Back pain	2 (25)	0 (0)	0 (0)	0 (0)	1 (50)	1 (50)	2 (100)
Headache	1 (13)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)
Body pain	3 (38)	0 (0)	3 (100)	3 (100)	0 (0)	0 (0)	0 (0)
Gastrointestinal							
Nausea	6 (75)	1 (17)	4 (67)	5 (83)	0 (0)	1 (17)	1 (17)
Vomiting	5 (63)	1 (20)	2 (40)	3 (60)	0 (0)	2 (40)	2 (40)
Fatigue	7 (88)	0 (0)	2 (29)	2 (29)	2 (29)	3 (43)	5 (71)
Other							
Sleep	1 (13)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Cognition	1 (13)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Muscle weakness and paralysis	1 (13)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)
No prior hemin prophylaxis ($n = 13$)							
Abdominal pain	11 (85)	1 (9)	1 (9)	2 (18)	2 (18)	7 (64)	9 (82)
Neuropathic pain/paresthesia[c]	4 (31)	0 (0)	1 (25)	1 (25)	2 (50)	1 (25)	3 (75)
Other pain							
Limb pain	9 (69)	0 (0)	3 (33)	3 (33)	1 (11)	5 (56)	6 (67)
Back pain	5 (38)	0 (0)	0 (0)	0 (0)	0 (0)	5 (100)	5 (100)
Headache	3 (23)	2 (67)	0 (0)	2 (67)	0 (0)	1 (33)	1 (33)
Body pain	4 (31)	0 (0)	1 (25)	1 (25)	0 (0)	3 (75)	3 (75)
Gastrointestinal							
Nausea	9 (69)	0 (0)	5 (56)	5 (56)	2 (22)	2 (22)	4 (44)
Vomiting	6 (46)	2 (33)	3 (50)	5 (83)	0 (0)	1 (17)	1 (17)
Fatigue	11 (85)	0 (0)	2 (18)	2 (18)	1 (9)	8 (73)	9 (82)
Other							
Sleep	1 (8)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Cognition	4 (31)	0 (0)	1 (25)	1 (25)	1 (25)	2 (50)	3 (75)
Muscle weakness and paralysis	4 (31)	1 (25)	0 (25)	1 (25)	0 (0)	3 (75)	3 (75)

[a] Symptom change timeline data were not obtained for symptoms of constipation; diarrhea; anxiety, fear, and worry; depression and sadness; and anger, agitation, and aggression.

[b] Based on participants reporting symptoms prestudy, and not including missing data for symptom improvement timelines. Improvement timeline (i.e., number of weeks or months) for each symptom was not specifically probed; instead, participants were asked which symptoms were completely relieved and which symptoms improved slowest and fastest.

[c] Neuropathic pain/paresthesia was coded for any mention of neuropathy, burning, or tingling.

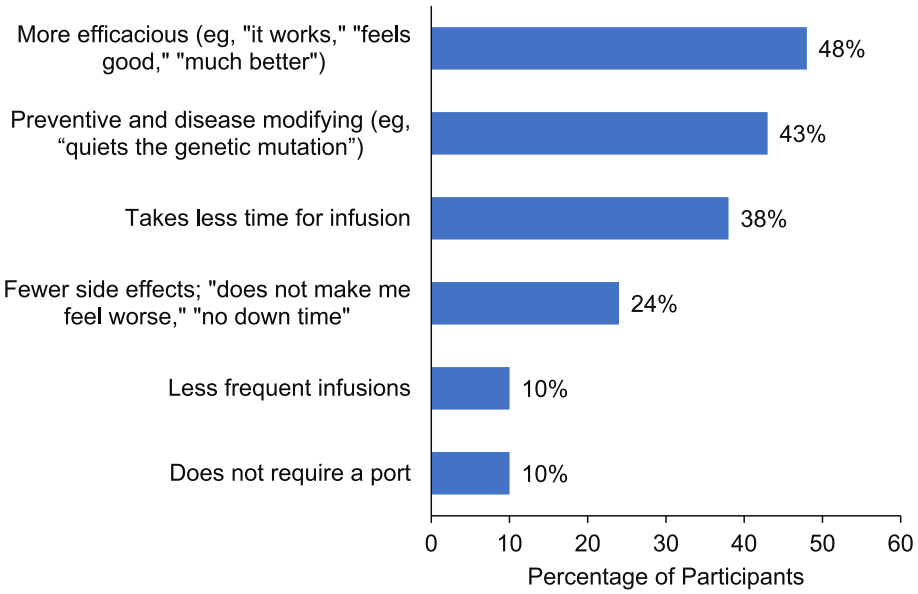

Fig. 2. Participant perspectives on givosiran versus previous treatments[a].
[a]All participants reported prior use of hemin (Panhematin, haem arginate).

coverage ($n = 1/21$ [5 %]), and access issues (i.e., having to drive 3 h for givosiran treatment; $n = 1/21$ [5 %]).

4. Discussion

AHP is a debilitating condition characterized by severe acute attacks and chronic symptoms in multiple domains, worsened QOL, and a heavy burden on patients, families, and caregivers [1,4,7,12,13]. The lived experience of patients with AHP is important to assess, as objective outcome measures utilized in clinical trials may overlook issues of importance to those with the disease [3,4,7,8,12,13]. Little is known about the patient perspective on givosiran, a novel treatment approved in 2019, particularly after a prolonged period of treatment (mean [SD] duration at interview, 4.3 [0.7] years). Results from this interview study help fill that gap, complementing previously published findings from the phase 1 [19], phase 1/2 OLE [25], and ENVISION [20–22] studies by adding participants' experiences in their own words. Overall, these findings support and expand upon previous literature, indicating that givosiran has a positive impact on many patients' lives as reflected by the participants' descriptions of treatment-related relief of symptoms of AHP, improvements in QOL, and a lower overall burden of disease.

All participants experienced AHP attacks prior to participation in the clinical studies. Symptoms reported included abdominal pain, other types of pain, gastrointestinal symptoms, fatigue, cognitive and psychiatric symptoms, sleep-related symptoms, and muscle weakness and paralysis (Table 2). The number and variability of the symptoms reported is consistent with the AHP literature [1,6]. All participants reported post-treatment improvement in attacks, consistent with objective findings of sustained reduction in attack frequency in the phase 1/2 OLE [25] and ENVISION [20–22] studies, and for each individual symptom, 67 % to 100 % of participants who experienced the symptom prestudy reported improvement following givosiran treatment (Table 2). Whereas prestudy symptoms were in some cases extremely severe (for example, a participant described a "horrible, searing, and indescribable level of pain"), participants reported post-treatment relief of pain or gastrointestinal problems, return of functioning that had been lost, and improvements in neuropsychological and cognitive issues.

All participants reported improvements in AHP attacks following treatment with givosiran, including 62 % who reported that attacks were gone. In comparison, in ENVISION, most participants were attack-free during the final 3 months of the OLE period (86 % in the continuous givosiran group and 92 % in the placebo crossover group) [22]. Potential reasons why the percentage was lower in the interview study compared with ENVISION include differences in the definition and measurement of attacks. First, in ENVISION, attacks were defined as requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home, whereas in the interview study, an explicit definition of attacks was not provided. Second, attacks were assessed prospectively in ENVISION and retrospectively during the interviews, introducing the possibility of recall bias.

Clinical study data suggest that givosiran reduces chronic pain in addition to acute pain associated with attacks. In a post hoc analysis of ENVISION, pain during attack-free periods (measured using a daily eDiary by a numeric rating scale [NRS; range, 0–10]) was assessed in participants with ≥1 attack. The proportion of attack-free days with pain that was worse than baseline was reduced in givosiran-treated participants compared with placebo (19 % vs 28 %). Givosiran-treated participants also reported nearly 50 % fewer days with severe pain, defined as NRS score ≥ 7, during attack-free periods (7 % vs 12 %) and were less likely to use opioids during attack-free periods (56 % vs 70 %), compared with participants who received placebo [28]. Some participants in the interview study spontaneously reported that certain symptoms were chronic, including pain, and that chronic symptoms were relieved with givosiran treatment. It is particularly notable that chronic symptoms related to neuropathy, including neuropathic pain and paresthesia (e.g., neuropathy, burning, tingling), improved in most (93 %) participants post-treatment. Neuropathy can be a long-lasting and burdensome condition in patients with AHP, but it is understudied [11]. Reports from study participants are in line with a recent case report of successful treatment of severe, chronic neuropathological symptoms with givosiran in a critically ill patient with AHP [29]. This case report remains the only literature on the use of disease-modifying treatment for neuropathy in AHP. Hence, participants' reports of improvement in neuropathy with long-term givosiran treatment are novel and important, requiring further research.

Some participants reported that improvement in symptoms of AHP was nearly immediate, but it was more typical for participants to report that 3 or more treatments were required (Table 3). Symptoms with partial improvement were generally described as "slow" to improve rather than "quick" based on the participants' perception. The time course of subjective symptom improvement stands in contrast to the rapid reduction in urinary ALA and PBG levels (within 1 month)

observed in clinical trials, including the phase 1 study [19] and ENVISION [20–22].

Participants reporting complete symptom relief were generally younger, had a shorter time span between diagnosis of AHP and initiation of treatment with givosiran, and had higher self-ratings of physical and mental function and overall health, compared with participants reporting partial symptom relief (Table 4). The observed difference in the mean time since diagnosis of AHP for participants with complete versus partial relief of neuropathic pain (3.9 vs 8.5 years) was particularly notable, suggesting that both early diagnosis and early treatment with givosiran may be important in the management of neuropathy associated with AHP. In general, it is possible that participants with complete relief of symptoms may have experienced less severe symptoms prior to the start of the givosiran clinical trials, although the baseline severity of specific symptoms in these participants is unknown. However, participants with a history of hemin prophylaxis, who are likely to have had more severe baseline symptoms, were generally more likely to have complete relief of symptoms. Participants with a history of hemin prophylaxis also were more recently diagnosed with AHP, on average, than those without prior hemin prophylaxis, again suggesting that early treatment may be associated with improved long-term outcomes.

In the phase 1/2 OLE study [19] and ENVISION [20–22], baseline QOL and change in QOL following givosiran treatment were assessed with widely used, validated instruments, though not validated in AHP: the SF-12 (ENVISION only), which captures patient perspectives on QOL and health status [23], and the EQ-VAS (both studies) for patients to rate their health [24]. The SF-12, a brief version of the SF-36 Health Survey that has been used across populations and disease states, includes PCS and MCS scores, each with a mean (SD) norm-based scores of 50 (10) in the general US population [23]. Baseline PCS and MCS scores of interview participants demonstrated substantially reduced physical and mental functioning (mean: 37.9 and 39.7. respectively), consistent with participants' reports of negative impacts of AHP in basic functional domains, and in the range of scores observed in patients with other chronic diseases, such as cancer and coronary heart disease [30,31]. At Month 36 of ENVISION, mean PCS and MCS scores in interview participants increased significantly (by 7.8 and 9.2, respectively) exceeding the ≥2- to 5-point increase considered a clinically meaningful improvement for other chronic diseases [32,33]. Similarly, interview participants' mean scores on the EQ-VAS, for which the general US population norm is 80.0 (interquartile range, 73–91) [34], increased from 67.3 at baseline to 82.1 at Month 36, a change that exceeds the range estimated to represent a minimal clinically important difference, which is approximately 7–10 points [35,36]. Normalization of scores on these instruments following long-term givosiran treatment is aligned with participants' reports of substantial positive impacts of givosiran on functioning. These data further underscore the physical, emotional, and social burden of AHP, as well as the sustained beneficial effect of appropriate long-term treatment on chronic manifestations of the disease. The burden of chronic manifestations of AHP is often underappreciated because of a focus on acute attacks, which may be very intense and severe.

All participants reported they were "very satisfied" with givosiran treatment, and some participants identified specific advantages of givosiran over prior treatment. Among them were increased effectiveness and fewer side effects. Reported sources of dissatisfaction included difficulty with access to givosiran due to insurance coverage (1 participant) and needing to travel a long distance to receive the medication (1 participant).

This study has several strengths. Considering the rarity of AHP, the patient population was relatively large, having been drawn from 2 clinical studies, and included participants with variable symptoms, a wide range of ages and baseline disease severity, and history of hemin prophylaxis or lack thereof. The interview participants, who comprised 19 % of the populations of the clinical studies, were representative of the broader study populations in terms of demographics and disease characteristics. All interview participants had been treated with givosiran long-term, having elected to continue the treatment after completing 1 of the studies.

This study also has weaknesses. First, the possibility of selection bias should be considered, as participants had qualified for enrollment in the phase 1/2 OLE and ENVISION studies based on strict inclusion criteria. Second, interview participants were a subset of participants who completed the studies, opted to continue givosiran treatment thereafter, and agreed to participate in the interviews. Hence, interview participants may have had better outcomes and/or greater likelihood of being satisfied with givosiran treatment, compared with participants who did not complete the studies or did not agree to participate in the interviews. Recall bias is also possible, considering that this was a study that relied on memory. Third, the interview guide was not structured to explicitly differentiate between acute attack-related and chronic symptoms of AHP. Based on the participants' descriptions, symptoms were subjectively assessed by authors/investigators as acute or chronic, but an explicitly patient-guided classification of symptoms would be preferable. Fourth, the sample sizes for individual symptoms were relatively small, although trends may be suggested for symptoms experienced by 5 or more participants. Fifth, the number of treatments or time required to achieve complete or partial relief of symptoms was evaluated at a relatively high level (after 1–2 or 3+ treatments, or participant perception as "quick" or "slow"). Increased specificity on the time course of efficacy related to improvement in specific symptoms may be more helpful in guiding expectations of physicians and patients. Additionally, data were not obtained on the timeline of symptom changes for several symptoms: anxiety/fear/worry, depression/sadness, anger/agitation/aggression, constipation, and diarrhea. Finally, the interviews focused primarily on the effectiveness and benefits of givosiran treatment, with less opportunity to assess adverse events and treatment limitations.

In conclusion, overall, participants reported meaningful improvements in acute and chronic symptoms and impacts of AHP, increased QOL, and reduced opioid use with long-term monthly givosiran treatment. They were satisfied with givosiran treatment and felt that givosiran was superior to previous treatments in terms of efficacy, tolerability, and convenience. These findings further demonstrate the importance of early treatment.

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CRediT authorship contribution statement

Hetanshi Naik: Writing – review & editing, Writing – original draft, Visualization. **Michelle Brown:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Stephen Meninger:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Stephen Lombardelli:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

Hetanshi Naik is a consultant to Alnylam Pharmaceuticals, Recordati Rare Diseases, Disc Medicine, and Mitsubishi Tanabe and has received sponsorship fees for lectures on porphyria (Sarah Lawrence College, Keck Graduate Institute).

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.

Stephen Meninger and **Stephen Lombardelli** are employed by and own stock and stock options in Alnylam Pharmaceuticals.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2024.101174.

Data availability

Access to anonymized individual participant data that support these results is made available 12 months after study completion and not less than 12 months after the product and indication have been approved in the United States or the European Union. Data will be provided contingent upon the approval of a research proposal and the execution of a data sharing agreement. Requests for access to data can be submitted via the website www.vivli.org.

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