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EXPLORE B: A prospective, long-term natural history study of patients with acute hepatic porphyria with chronic symptoms

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Abstract

One-year data from EXPLORE Part A showed high disease burden and impaired quality of life (QOL) in patients with acute hepatic porphyria (AHP) with recurrent attacks. We report baseline data of patients who enrolled in EXPLORE Part B for up to an additional 3 years of follow-up. EXPLORE B is a long-term, prospective study evaluating disease activity, pain intensity, and QOL in patients with AHP with ≥1 attack in the 12 months before enrollment or receiving hemin or gonadotropin-releasing hormone prophylaxis. Data were evaluated in patients with more (≥3 attacks or on prophylaxis treatment) or fewer (<3 attacks and no prophylaxis treatment) attacks. Patients in the total population ($N = 136$), and more ($n = 110$) and fewer ($n = 26$) attack subgroups, reported a median (range) of 3 (0–52), 4 (0–52), and 1 (0–2) acute attacks, respectively, in the 12 months prior to the baseline visit. Pain, mood/sleep, digestive/bladder, and nervous system symptoms were each experienced by ≥80% of patients; most received hemin during attacks. Almost

three-quarters of patients reported chronic symptoms between attacks, including 85% of patients with fewer attacks. Pain intensity was comparable among both attack subgroups; most patients required pain medication. All groups had diminished QOL on the EuroQol visual analog scale and the European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 versus population norms. Patients with AHP with recurrent attacks, even those having fewer attacks, experience a high disease burden, as evidenced by chronic symptoms between attacks and impaired QOL.

KEYWORDS

chronic symptoms, disease burden, hepatic complications, porphyria attack, porphyrias, prospective studies

1 | INTRODUCTION

Acute hepatic porphyria (AHP) comprises a group of rare genetic diseases characterized by potentially life-threatening acute attacks and, in some cases, chronic manifestations that impair daily functioning and quality of life (QOL).[1–4] The four AHP types include acute intermittent porphyria (AIP, most common), variegate porphyria (VP), hereditary coproporphyria (HCP), and delta-aminolevulinic acid (ALA) dehydratase-deficiency porphyria (ADP).[2,5] AHP results from hepatic heme biosynthesis defects,[6,7] leading to induction of ALA synthase 1 (ALAS1), the initial and rate-controlling enzyme in heme biosynthesis[7–9] and accumulation of the heme intermediates ALA and porphobilinogen (PBG), which likely are responsible for disease manifestations.[9–11]

Common attack symptoms include severe abdominal pain, nausea, vomiting, constipation, tachycardia, hypertension, mental status changes, muscle weakness, hyponatremia, and urine color change.[1,3,4,12] Attacks often require hospitalization and, without prompt treatment, may result in paralysis, respiratory failure, and, rarely, death.[4,13,14] Some patients experience debilitating chronic symptoms (e.g., pain, neuropathy, fatigue, nausea, insomnia, anxiety, depression) between attacks.[3–5,15,16] Long-term AHP-related (particularly AIP-related) complications and comorbidities include chronic kidney disease, systemic arterial hypertension, chronic neuropathy, and liver disease.[3–5,17–22] Progressive physical and mental deterioration in patients with recurrent attacks can impair daily living activities and ability to work, and significantly reduce QOL.[4,15,23] Patients with recurrent attacks often experience difficulties adjusting to the limitations of AHP, negatively impacting relationships.[23]

Givosiran (Givlaari; Alnylam Pharmaceuticals, Cambridge, MA), a once-monthly subcutaneous injection, is an ALAS1-directed small interfering RNA approved for AHP treatment in adults in the United States and adults and adolescents age ≥ 12 years in the European Union.[24,25] Givosiran treatment can lead to nausea, fatigue, injection-site reactions, serum aminotransferase elevations, decreased estimated glomerular filtration rate, increased blood homocysteine, or anaphylactic reactions in some patients.[24,26] Other management strategies include trigger avoidance, acute attack treatment with intravenous hemin, and hemin prophylaxis.[26,27] Hemin use carries acute (e.g., headache, phlebitis) and chronic risks (e.g., iron overload, venous thrombosis/obliteration, central venous catheter complications).[10,27–29] For women with attacks associated with the menstrual cycle's luteal phase, gonadotropin-releasing hormone (GnRH) analogs have been used prophylactically.[30,31] Their use, which can be complicated, is effective in some cases.[31]

The EXPLORE study (NCT02240784) is a prospective natural history study of AHP patients who experienced recurrent attacks (≥3 attacks within the 12 months before baseline visit or on prophylactic treatment).[4] EXPLORE Part A followed patients for up to 1 year using telephone and clinic visits. The study population had a high disease burden and impaired QOL, with attacks that frequently required hemin or treatment at a healthcare facility, and chronic symptoms that impaired daily functioning.[4] EXPLORE Part B (EXPLORE B) included optional long-term evaluation of pain intensity and disease activity changes in Part A eligible patients and newly enrolled patients, for up to 3 additional years (Part A, potentially on study for up to 4 total years; newly enrolled patients, 3 total years). We report disease activity, pain, and chronic symptom impact on QOL and work in EXPLORE B patients at baseline, including patients who experienced relatively few attacks (<3 attacks without prophylaxis within the past 12 months).

2 | PATIENTS AND METHODS

Patients were included in EXPLORE B if they had AHP (diagnosis of AIP, VP, HCP, or ADP made by a porphyria specialist based on history of clinical manifestations of AHP, biochemical evidence of an AHP attack, and molecular confirmation of a pathogenic genetic variant or decreased hydroxymethylbilane synthase activity) and met one of the following criteria: (1) experienced ≥1 attack (requiring increased pain medication, antiemetic, or carbohydrate intake, hemin administration, or hospitalization for symptoms and signs of acute porphyria, such as abdominal pain, vomiting, and constipation, tachycardia, and hypertension, or hyponatremia) in the prior 12 months; (2) were receiving hemin prophylaxis at an average of ≥1 time per month over the 12 months prior to baseline; or (3) were receiving GnRH prophylaxis. Patients were excluded if they were participating in a clinical trial with an investigational product or if they were not considered by the study investigator to be appropriate candidates for the study.

2.1 | Outcome measures

Pain intensity and impact were measured using the Brief Pain Inventory short form (BPI-SF), which obtains information about current pain and pain in the past 24 h, using a scale of 0–10, where higher scores denote worse pain. The BPI-SF also measured pain relief, based on a scale where 0% denotes no relief and 100% denotes complete relief, provided by pain treatments or medications in the past 24 h. Changes in disease activity were captured on survey questionnaires, with changes in porphyria symptoms, potential precipitants of porphyria attacks, medical history, and medications recorded. QOL was evaluated using the EuroQol Five Dimensions Questionnaire 5-Level Scale (EQ-5D-5L) and the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30). The EQ-5D-5L enables patients to self-report their health status across five domains (mobility; self-care; usual activities; pain/discomfort; anxiety/depression) and by using the EuroQol visual analog scale (EQ-VAS).[32] The EQ-VAS is a standard vertical 20-cm visual analog scale, which ranges from 0 ("the worst imaginable health state") to 100 ("the best imaginable health state"), and is used to record an individual's rating of their overall current health-related QOL. The EORTC QLQ-C30 captures QOL information pertaining to activities of daily living on a scale of 0–100 for total scores and subscale scores.[33] On the functioning and global health scales of the EORTC QLQ-C30, higher scores denote better functioning, whereas on the symptom scales, higher scores denote higher levels of symptoms (i.e., a worse state for the patient). EXPLORE B assessments were conducted by mail and confirmed by telephone without required clinic visits. BPI-SF was assessed every 3 months until Month 12, then every 6 months through Month 36; EORTC QLQ-C30 and EQ-5D-5L were assessed every 6 months. The Screening Porphyria Questionnaire, which captured healthcare experience and activities of daily living, was completed at baseline by all patients who did not participate in Part A and in patients whose last completed assessment in Part A was >6 months prior to beginning EXPLORE B.

2.2 | Statistical analysis

Data were analyzed for all patients who were enrolled in EXPLORE B and by subgroups, which included those who had ≥3 attacks or were receiving prophylaxis and those having <3 attacks without prophylaxis in the 12 months before enrollment. As EXPLORE B was an observational study, no formal hypothesis testing was conducted, and the sample size was not based on statistical considerations. Results were analyzed using descriptive statistics.

3 | RESULTS

3.1 | Study population

A total of 136 patients were enrolled from 18 countries: 43 patients (32%) provided consent from Part A, and 93 were new patients (68%). One hundred fifteen patients (85%) withdrew before completing the 36-month study period, primarily because of termination of the study by the sponsor (40%), patients leaving to enroll in another study (ENVISION) (15%), or patients leaving to receive givosiran outside of a clinical study (12%) (Figure 1). Of the 136 enrolled patients, 83 (61%), 37 (27%), and 21 (15%) completed 12, 24, and 36 months of the study period, respectively. Patients spent a median (range) duration of 14.6 (2.0–41.5) months in the study. Mean (SD) age of patients at enrollment was 41.0 (12.6) years. Most patients were female (90%), and most were white (85%) (Table 1). Most patients had AIP (90%), followed by VP (8%) and HCP (1%).

3.2 | Attack frequency and hemin use at baseline

In the 12 months before the study, patients reported a median (range) of 3 (0–52) investigator-confirmed acute attacks; 46% of patients received hemin or GnRH

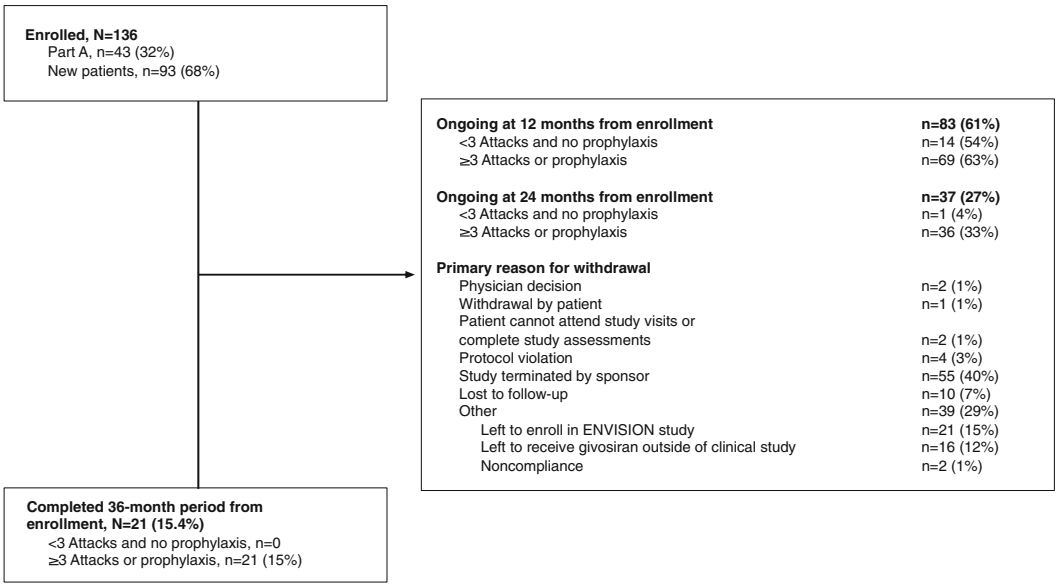

FIGURE 1 Patient disposition

prophylaxis (Table 2). The subgroup of 110 patients with more attacks, defined as those who had ≥3 attacks or were receiving prophylaxis, reported a median (range) of 4 (0–52) investigator-confirmed acute attacks in the 12 months prior to baseline visit; 56% received hemin or GnRH prophylaxis (Table 2). Pain, mood/sleep, digestive/bladder, and nervous system symptoms associated with attacks were reported by greater than 80% of patients. Most patients in the more-attacks subgroup required hemin (80%) and pain medication (88%), including opioids (53%) (Table 3), and most of these patients (72%) experienced chronic symptoms in the 12 months prior to baseline visit. The subgroup of 26 patients with fewer attacks, defined as those having <3 attacks without prophylaxis, had a median (range) of 1 (0–2) acute attack reported in the past 12 months, with pain being the most common symptom in 100% of the attacks (Table 2). The next most common symptom was mood/sleep symptoms (96%), followed by digestive/bladder and nervous system symptoms, both of which were reported by >84% of patients. In this subgroup with fewer attacks, most patients received hemin (69%) and pain medication (96%), including opioids (62%), during attacks (Table 3), and the majority of patients (85%) reported chronic symptoms between attacks in the past 12 months.

3.3 | Patient-reported outcomes

At baseline, mean (SD) worst pain and average pain in the past 24 h, assessed using the BPI-SF, were 4.3 (3.1) and 3.6 (2.4), respectively, in the total population (Figure 2). In the total population, 29% (39/136) patients and 8% (11/136) patients reported severe pain (≥7 pain score) for worst and average pain, respectively. Among those with available data ($n = 112$), patients reported their treatments provided, on average, 46% pain relief in the past 24 h. In the subgroup of patients with ≥3 attacks or prophylaxis with available data ($n = 107$), mean (SD) worst pain and average pain scores on the BPI-SF were 4.5 (3.1) and 3.7 (2.4), respectively, at baseline (Figure 2). In the subgroup of patients with ≥3 attacks or prophylaxis, 32% (35/110) patients and 8% (9/110) patients reported severe pain for worst and average pain, respectively. Treatments provided on average 47% pain relief in the past 24 hours in those taking pain medications ($n = 94$) in the subgroup of patients with ≥3 attacks or prophylaxis. In those with <3 attacks and no prophylaxis ($n = 26$), mean (SD) worst pain and average pain scores captured on the BPI-SF were 3.5 (3.1) and 3.3 (2.5), respectively, at baseline (Figure 2). Severe pain was reported by 15% (4/26) patients and 8% (2/26) patients for worst and average pain, respectively. In this subgroup of patients with <3 attacks and no prophylaxis, pain medications provided on average 44% pain relief in the past 24 h in the 18 patients using these medications.

3.4 | Quality of life

Overall, patients with AHP had impaired QOL at baseline, including those patients in the subgroup with fewer

TABLE 1 Baseline demographic and disease characteristics[a]

Characteristic	<3 attacks and no prophylaxis (*N* = 26)	≥3 attacks or prophylaxis (*N* = 110)	Total population (*N* = 136)
Age at time of consent, years			
Mean (SD)	36 (11)	42 (13)	41 (13)
Median (range)	34 (17–57)	42 (22–83)	40 (17–83)
Female sex, *n* (%)	24 (92)	99 (90)	123 (90)
Race, *n* (%)			
White	19 (73)	96 (87)	115 (85)
Asian	3 (12)	6 (5)	9 (7)
Black/African American	3 (12)	3 (3)	6 (4)
Other	1 (4)	4 (4)	5 (4)
Not stated	0	1 (1)	1 (1)
Geographic region, *n* (%)			
Europe	16 (62)	54 (49)	70 (51)
North America	5 (19)	51 (46)	56 (41)
Other (Africa, Asia, Australia)	5 (19)	5 (5)	10 (7)
Years since AHP diagnosis			
n	26	108	134
Mean (SD)	7.2 (9.3)	12.3 (12.0)	11.3 (11.7)
Median (range)	3.5 (0.1–35.9)	8.5 (0.0–45.7)	6.3 (0.0–45.7)
AHP etiology, *n* (%)			
AIP	22 (85)	101 (92)	123 (90)
VP	3 (12)	8 (7)	11 (8)
HCP	1 (4)	1 (1)	2 (1)
ADP	0	0	0
Months on study			
n	26	110	136
Mean (SD)	13.4 (5.8)	18.7 (11.7)	17.7 (11.0)
Median (range)	12.6 (5.5–25.8)	15.4 (2.0–41.5)	14.6 (2.0–41.5)

Abbreviations: ADP, delta-aminolevulinic acid dehydratase-deficiency porphyria; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; GnRH, gonadotropin-releasing hormone; HCP, hereditary coproporphyria; VP, variegate porphyria.

[a]<3 attacks and no prophylaxis = patients who had <3 attacks and were not receiving hemin or GnRH prophylaxis in the 12 months before enrollment; ≥3 attacks or prophylaxis = patients who had ≥3 attacks or were receiving hemin or GnRH prophylaxis in the 12 months before enrollment.

attacks. At baseline, mean (SD) EQ-VAS scores were 64.6 (20.2), 62.9 (20.8), and 71.8 (15.9) in the total population, in patients with ≥3 attacks or prophylaxis, and in patients with <3 attacks and no prophylaxis, respectively (Figure 3A). Mean (SD) EORTC overall health/QOL scores were 56.5 (23.9), 53.8 (24.6), and 68.0 (17.1) in the total population, in patients with ≥3 attacks or prophylaxis, and in patients with <3 attacks and no prophylaxis, respectively (Figure 3B). Impairment, including significant fatigue, was reported in all the individual domains across all three groups. At baseline, the three dimensions most affected by AHP across all three subgroups were pain and discomfort, anxiety and depression, and ability to perform usual activities (Figure 4).

3.5 | Healthcare utilization, economic impact, and disability impact

Patients with AHP reported a high level of healthcare utilization during EXPLORE B, including in patients experiencing fewer attacks. At baseline (during past 12 months), patients in the total population reported means (SDs) of 4.1 (4.2) emergency department visits and

TABLE 2 History of attacks, prophylaxis, and chronic symptoms before enrollment[a]

Characteristic	<3 attacks and no prophylaxis ($N = 26$)	≥3 attacks or prophylaxis ($N = 110$)	Total population ($N = 136$)
Number of attacks[b]			
n	26	81	107
Median (range)	1.0 (0–2)	4.0 (0–52)	3.0 (0–52)
Hemin or GnRH prophylaxis, *n* (%)	0	62 (56)	62 (46)
Hemin prophylaxis	0	56 (51)[c]	56 (41)[c]
GnRH prophylaxis	0	17 (15)	17 (13)
Symptoms usually associated with attacks, *n* (%)			
Pain	26 (100)	97 (88)	123 (90)
Mood/sleep	25 (96)	92 (84)	117 (86)
Digestive/bladder	23 (88)	95 (86)	118 (87)
Nervous system	22 (85)	89 (81)	111 (82)
Other	19 (73)	87 (79)	106 (78)
Patients reporting chronic symptoms when not having an attack, *n* (%)	22 (85)	79 (72)[c]	101 (74)[c]

Abbreviation: GnRH, gonadotropin-releasing hormone.

[a]<3 attacks and no prophylaxis = patients who had <3 attacks in the 12 months before enrollment and were not receiving hemin or GnRH prophylaxis; ≥3 attacks or prophylaxis = patients who had ≥3 attacks in the 12 months before enrollment or were receiving hemin or GnRH prophylaxis.

[b]Investigator-confirmed attacks using inclusion criteria for attack (requiring increased pain medication, antiemetic, or carbohydrate intake, hemin administration, or hospitalization for symptoms and signs of acute porphyria, such as abdominal pain, vomiting, and constipation, tachycardia, and hypertension, or hyponatremia).

[c]Data were missing for seven patients.

4.2 (6.9) overnight stays in a hospital (Table 4). Patients with ≥3 attacks or prophylaxis reported means (SDs) of 4.2 (4.5) and 4.5 (6.7) emergency department visits and overnight stays in a hospital, respectively, in the past 12 months, and those with <3 attacks and no prophylaxis reported means (SDs) of 3.4 (3.1) emergency department visits and 3.5 (7.8) overnight stays in a hospital during the same period.

AHP also had a significant economic impact on patients across all three groups. Overall, 33% of the total population, 31% of patients with ≥3 attacks or prophylaxis, and 42% of patients with <3 attacks and no prophylaxis were employed full-time at baseline (Table 4). Of those employed part-time or full-time, 36%, 35%, and 42% of the total group, patients with ≥3 attacks or prophylaxis, and patients with <3 attacks and no prophylaxis, respectively, missed workdays in the past 12 months due to an attack, with means (SDs) of 33.9 (61.6), 36.6 (69.5), and 25.2 (20.9) days missed, respectively (Table 4). In addition, 32%, 34%, and 27% of the total group, patients with ≥3 attacks or prophylaxis, and patients with <3 attacks and no prophylaxis, respectively, required a caregiver during the past 12 months. Of the caregivers who held a paying job, 60% (21/35), 62% (18/29), and 50% (3/6), respectively, reported lost workdays during the 12 months prior to enrollment. Overall, 77% of the total population, 76% of patients with ≥3 attacks or prophylaxis, and 81% of patients with <3 attacks and no prophylaxis did not receive compensation from the government in the past 12 months.

4 | DISCUSSION

EXPLORE B was a long-term, prospective, multinational, observational study that evaluated disease activity, pain intensity, and QOL in patients with AHP who experienced recurrent attacks or were receiving treatment to prevent attacks. Data compiled from this study are important for understanding the disease manifestations and burden of AHP and for assessing the need for potential new therapies. The study population had a history of attacks (defined as ≥1 attack in the 12 months before enrollment) or were receiving hemin/GnRH prophylaxis, with defined subgroups to allow for evaluation of disease activity/burden in patients with a history of more (≥3 attacks or receiving prophylaxis treatment) or fewer attacks (<3 attacks and not receiving prophylaxis treatment) in a given time period.

The results show that patients with AHP experience a variety of symptoms during attacks. Pain, digestive/bladder symptoms, and nervous system symptoms were

TABLE 3 Treatment for prior attacks and current medications at screening[a]

Characteristic	<3 attacks and no prophylaxis ($N = 26$)	≥3 attacks or prophylaxis ($N = 110$)	Total population ($N = 136$)
Median (range) number of attacks[b] in past 12 months[c] requiring:			
Overnight stay at hospital	1 (0–3)	1 (0–180)	1 (0–180)
Treatment in emergency department	0 (0–3)	0 (0–25)	0 (0–25)
Treatment at clinic or infusion center	0 (0–1)	0 (0–52)	0 (0–52)
Treatment at home	0 (0–7)	0 (0–200)	0 (0–200)
Patients who ever received hemin treatment during an attack, *n* (%)	18 (69)	88 (80)[d]	106 (78)[d]
Patients who received pain medication during an attack, *n* (%)	25 (96)	97 (88)[d]	122 (90)[d]
Opioid	16 (64)	58 (60)	74 (61)
Non-opioid	1 (4)	13 (13)	14 (12)
Both	8 (32)	23 (24)	31 (25)
Missing	0	3 (3)	3 (2)
Currently taking hemin to prevent attacks at baseline, *n* (%)	0	56 (51)	56 (41)
Biweekly dosing	0	7 (6)	7 (5)
Weekly dosing	0	23 (21)	23 (17)
Monthly dosing	0	13 (12)	13 (10)
Other	0	13 (12)	13 (10)
Currently taking pain medication when not having an attack, *n* (%)	10 (38)	52 (47)[e]	62 (46)[e]

Abbreviation: GnRH, gonadotropin-releasing hormone.

[a]<3 attacks and no prophylaxis = patients who had <3 attacks in the 12 months before enrollment and were not receiving hemin or GnRH; ≥3 attacks or prophylaxis = patients who had ≥3 attacks in the 12 months before enrollment or were receiving hemin or GnRH prophylaxis.

[b]Self-reported attacks.

[c]Refers to 12 months prior to baseline visit.

[d]Data were missing for three patients.

[e]Data were missing for seven patients.

the most commonly reported manifestations associated with attacks, which is consistent with the literature.[3,15,34] Mood and sleep disorders were also common in this study. Notably, acute symptoms were highly prevalent in the subgroup with fewer attacks (<3 attacks and no prophylaxis), particularly pain; mood/sleep, digestive/bladder, and nervous system symptoms were also common.

A substantial number of patients (almost three-quarters) reported chronic symptoms between attacks, including in patients with fewer attacks, 85% of whom reported chronic symptoms. The proportion of patients reporting chronic symptoms in the current study was higher than that in observational studies, in which chronic symptoms were noted in 18%– 22% of patients.[3,35] This may be because questionnaires were self-completed by patients in the current study.

Patients with fewer attacks (<3 attacks and no prophylaxis) reported a comparable mean level of pain intensity as those who had more attacks (≥3) or were receiving prophylaxis, as assessed by BPI-SF worst pain and average pain. The majority of patients (90%) were using pain medications, and >50% were using opioids during an attack. Nonetheless, these medications had provided <50% pain relief over the past 24 h. Of relevance to patients, pain can have a substantial impact on daily life and can be isolating for some people.[23]

Patients in the current study, particularly those in the subgroup with ≥3 attacks or prophylaxis, reported diminished QOL on the EORTC and EQ-VAS compared with population norms.[36,37] Mean EORTC overall health/QOL scores were diminished when compared with mean scores of patients with malignancies.[38] Mean EQ-VAS scores were comparable to those reported in patients with chronic obstructive pulmonary disease.[39–42] In particular, impairment was seen in all groups, as reflected by the symptom

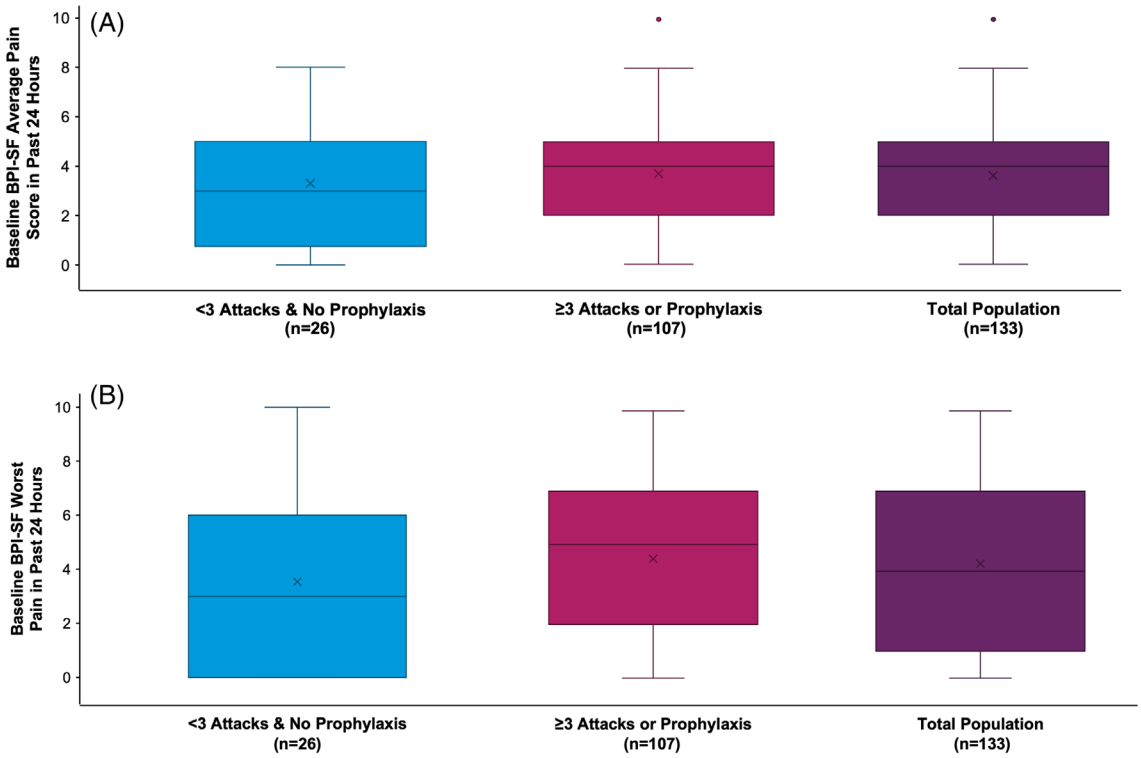

FIGURE 2 Pain intensity at baseline as assessed by BPI-SF scores for (A) average pain score and (B) worst pain score in the past 24 h, in the total population and for subsets of patients with <3 attacks and no prophylaxis or ≥3 attacks or prophylaxis. BPI-SF, Brief Pain Inventory short form. The BPI-SF uses a scale of 0–10, where higher scores denote worse pain. Horizontal line within box indicates median. Bottom and top edge of box indicates quartiles 1 and 3, respectively. X indicates mean. Vertical lines indicate range of observed values

subscale scores for fatigue and nausea/vomiting, which are commonly experienced attack symptoms of AHP.[3,15] These results are also consistent with other studies that showed diminished QOL in patients with AHP compared with controls.[43–46] Within the EQ-5D-5L across all subgroups, the three dimensions most affected by AHP were pain and discomfort, anxiety and depression, and ability to perform usual activities. These most affected domain results for the subgroup with ≥3 attacks or prophylaxis are consistent with a previous study in the same population.[4] Another previous study of patients with <4 attacks per year reported mobility (30%), pain and discomfort (30%), and anxiety and depression (19%) as the most affected domains.[44] In the current study, the subgroup with <3 attacks and no prophylaxis had a higher proportion of patients affected by pain and discomfort (58%), anxiety and depression (46%), and ability to perform usual activities (42%).

Our results also suggest that a significant economic burden is associated with AHP. Patients in EXPLORE B, including those with fewer attacks, exhibited high healthcare utilization and a median of 2–3 weeks of workdays lost due to attacks over the year prior to enrollment. Less than 45% of those with fewer attacks and no prophylaxis and less than 35% of those with more attacks or using prophylaxis were in full-time employment. This observation is consistent with previously reported data from qualitative interviews of patients with AHP, in which more than 50% of respondents reported that they had to stop working due to their disease.[23]

There are several potential limitations to interpretation of results from our study. In EXPLORE B, 85% of patients withdrew before completing the 36-month study period. In addition, data on attacks and chronic symptoms were patient-reported and did not require confirmation by a clinician, nor were they corroborated by documentation of ALA and PBG levels. Nonetheless, this method of attack ascertainment is typically used in clinical practice once a patient has been diagnosed with AHP. In real-world settings, patients are not always seen by a porphyria specialist for every attack, and ALA and PBG measurements are usually not obtained or available in real time at patient presentation. Another potential confounding factor is that patients may have overestimated attacks, given that they could have experienced symptoms similar to those of AHP attacks that were not actually due to AHP.

In conclusion, these data show that, for patients with AHP and recurrent attacks, including those with relatively few attacks, the burden of disease is high, as reflected by patients' reports of chronic symptoms between attacks and QOL assessments.

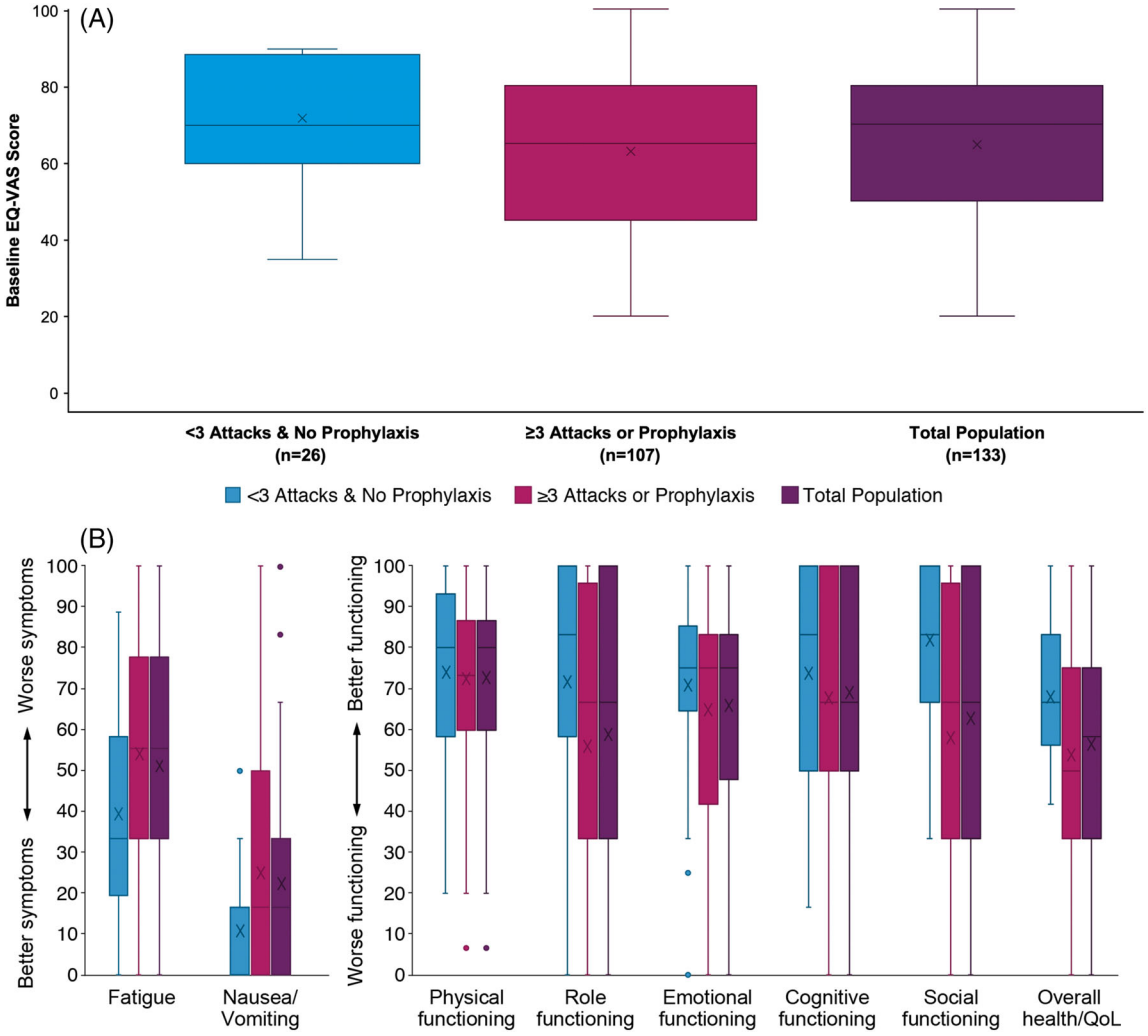

FIGURE 3 Quality of life at baseline as assessed by (A) EQ-VAS scores and (B) EORTC total and subscale scores for the total population and for subsets of patients with <3 attacks and no prophylaxis or ≥3 attacks or prophylaxis. EORTC, European Organisation for Research and Treatment of Cancer; EQ-VAS, EuroQol visual analog scale. The EQ-VAS, a standard vertical 20-cm visual analog scale used to record an individual's rating of their overall current health-related quality of life, ranges from 0 ("the worst imaginable health state") to 100 ("the best imaginable health state"). EORTC scale range is 0–100; for fatigue and nausea/vomiting symptoms subscales, higher scores denote worse symptoms; for functioning subscales, higher scores denote better functioning. Horizontal line within box indicates median. Bottom and top edge of box indicates quartiles 1 and 3, respectively. X indicates mean. Vertical lines indicate range of observed values

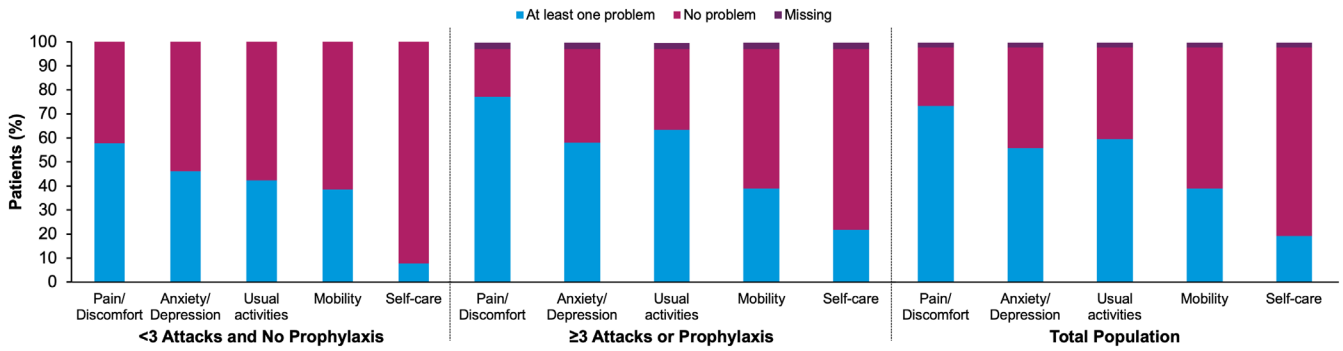

FIGURE 4 EQ-5D-5L dimension levels at baseline for the total population and for subsets of patients with <3 attacks and no prophylaxis or ≥3 attacks or prophylaxis. EQ-5D-5L, EuroQol Five Dimension Questionnaire 5-Level Scale. EQ-5D score was derived using the US reference value given for that particular set of responses in the five domains. US reference values were provided in the Crosswalk value dataset associated with this instrument

TABLE 4 Healthcare utilization and work impact at screening[a]

Characteristic	<3 attacks and no prophylaxis ($N = 26$)	≥3 attacks or prophylaxis ($N = 110$)	Total population ($N = 136$)
Number of healthcare utilizations in past 12 months, mean (SD)			
Overnight hospital stay	$n = 20$ 3.5 (7.8)	$n = 63$ 4.5 (6.7)	$n = 83$ 4.2 (6.9)
Emergency department visit	$n = 18$ 3.4 (3.1)	$n = 57$ 4.2 (4.5)	$n = 75$ 4.1 (4.2)
Specialist physician	$n = 20$ 3.5 (2.9)	$n = 96$ 10.2 (19.0)	$n = 116$ 9.1 (17.5)
Home visit	$n = 2$ 12.5 (16.3)	$n = 14$ 22.4 (27.4)	$n = 16$ 21.2 (26.0)
Other healthcare utilizations in past 12 months,[b] *n* (%)	7 (27)	45 (41)[c]	52 (38)[c]
Employment at baseline			
Full-time, *n* (%)	11 (42)	34 (31)	45 (33)
Part-time, *n* (%)	3 (12)	15 (14)	18 (13)
Missed workdays due to attacks in past 12 months, *n* (%)	11 (42)	38 (35)	49 (36)
Missing days of work, median (range)	$n = 11$ 14 (5–60)	$n = 36$ 16 (2–365)	$n = 47$ 15 (2–365)
Receiving compensation from government in past 12 months, *n* (%)	3 (12)[d]	15 (14)[e]	18 (13)[f]

Abbreviation: GnRH, gonadotropin-releasing hormone.

[a]<3 attacks and no prophylaxis = patients who had <3 attacks in the 12 months before enrollment and were not receiving hemin or GnRH prophylaxis; ≥3 attacks or prophylaxis = patients who had ≥3 attacks in the 12 months before enrollment or were receiving hemin or GnRH prophylaxis.

[b]Includes pain specialist, psychiatric therapist, and substance abuse support.

[c]Data were missing for seven patients.

[d]Data were missing for two patients.

[e]Data were missing for 11 patients.

[f]Data were missing for 13 patients.

AUTHOR CONTRIBUTIONS

Study design: Herbert L. Bonkovsky. **Study investigator**: David Cassiman, Raili Kauppinen, Herbert L. Bonkovsky, Manish Thapar, Encarna Guillén-Navarro, Anna-Elisabeth Minder, Aneta Ivanova. **Collection and assembly of data**: David Cassiman, Raili Kauppinen, Herbert L. Bonkovsky, Manish Thapar. **Data analysis**: David Cassiman, Cecilia Hale. **Data interpretation**: All authors. **Manuscript preparation**: Herbert L. Bonkovsky. **Manuscript review and revisions**: All authors. **Final approval of manuscript**: All authors.

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CONFLICT OF INTEREST

The authors declare the following competing interests: David Cassiman and the University of Leuven, University Hospital Leuven received research grants, travel and conference bursaries, speaker fees, and advisory board compensation from a.o. Sanofi-Genzyme, Takeda-Shire, Alexion, Alnylam, Biomarin, Actelion, Bayer, Roche, BMS, Schering-Plow, Synageva, and Chiesi. Raili Kauppinen was an Orion Pharmaceuticals stockholder and Alnylam expert consultant. Susana Monroy received advisory board fees

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DATA AVAILABILITY STATEMENT

De-identified individual participant data that support these results will be made available in a secure-access environment 12 months after study completion. Access will be provided contingent upon the approval of a research proposal and the execution of a data sharing agreement.

ETHICS APPROVAL

All patients provided written informed consent prior to participation. The study was approved by central and local institutional review boards or ethics committees according to the International Conference on Harmonization Guidelines for Good Clinical Practice and the World Health Organization Declaration of Helsinki.

PATIENT CONSENT

Not applicable.

USE OF LABORATORY ANIMALS

Not applicable.

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