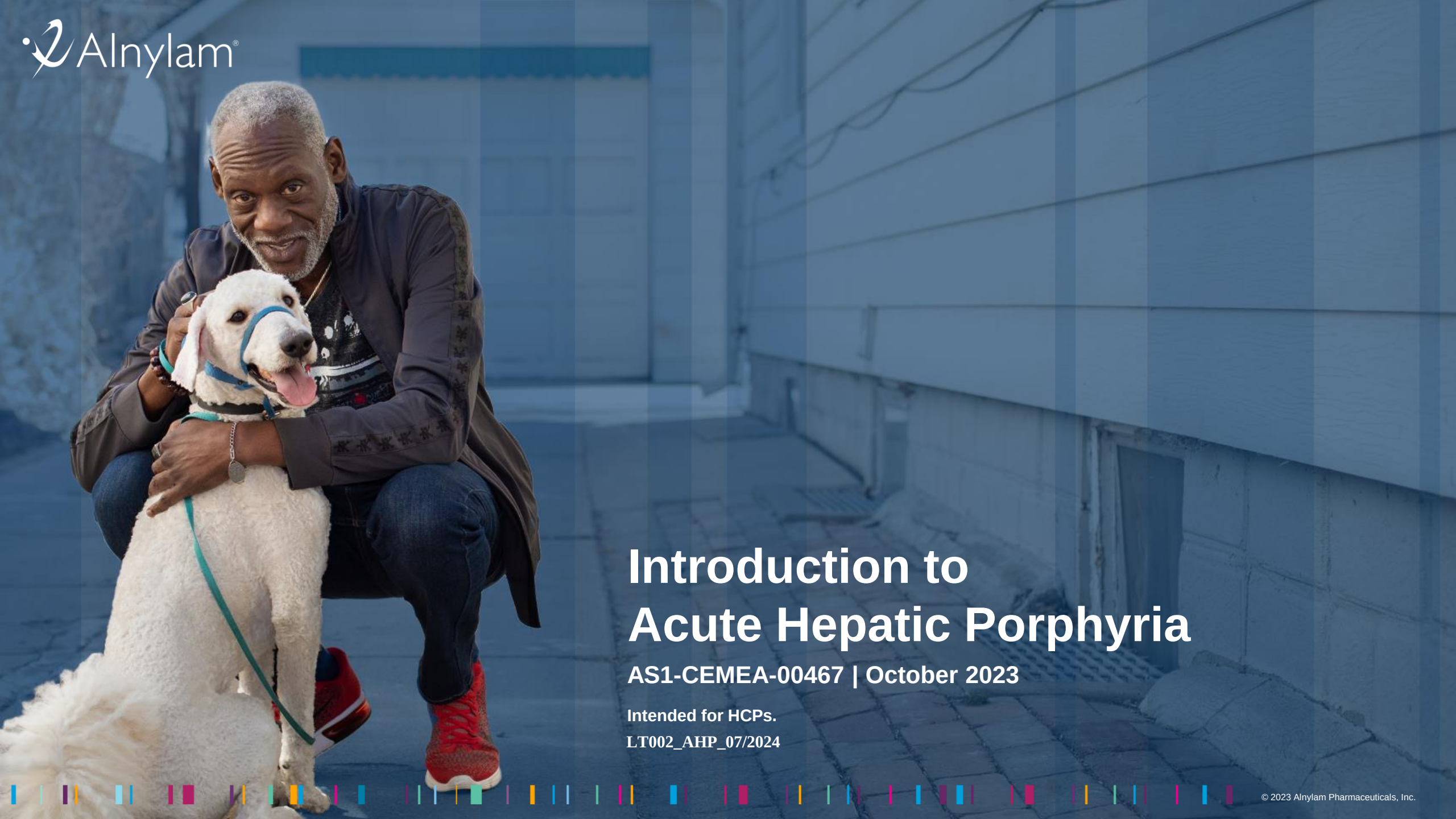


Introduction to Acute Hepatic Porphyria

AS1-CEMEA-00467 | October 2023

Intended for HCPs.

LT002_AHP_07/2024

Contents

Alnylam®

Acute Hepatic Porphyria: Disease Overview

Alnylam®

Porphyria

- Porphyria is a group of rare metabolic disorders resulting from abnormalities in heme biosynthesis
- Porphyria is classified according to clinical symptoms and enzymatic defects at different stages of heme biosynthesis

Hepatic or Erythropoietic

Heme precursors accumulate in either the liver or bone marrow, which are the tissues most active in heme biosynthesis

Acute or Cutaneous

Major clinical manifestations are either neurologic, usually in the form of acute attacks, or cutaneous, resulting from phototoxicity

Ramanujam VMS & Anderson KE. *Curr Protoc Hum Genet* 2015;86:1–26.

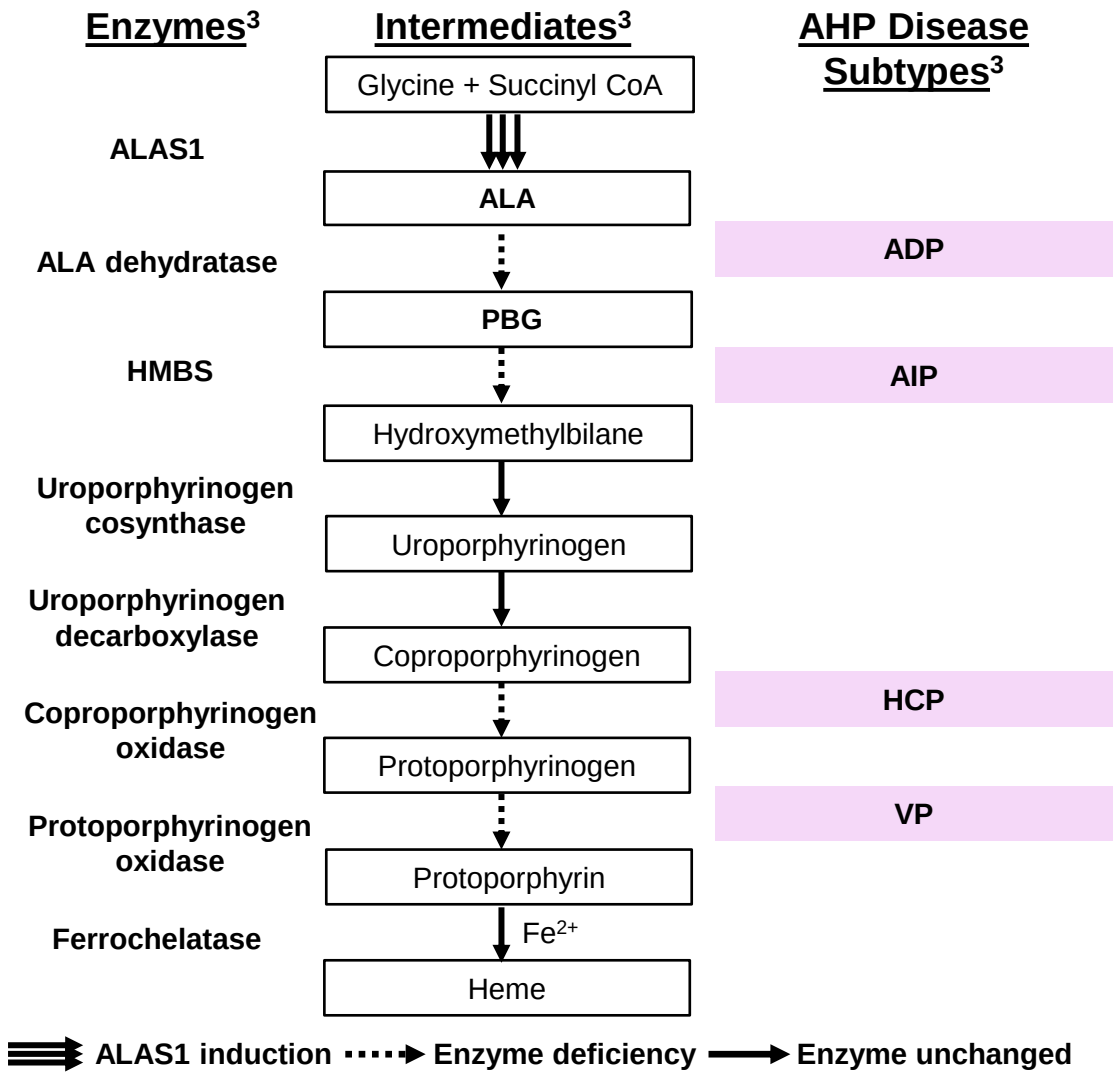
AHP Disease Overview and Pathophysiology

Disease Overview[1,2]

- Family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis in liver
- AIP most common, with mutation in hydroxymethylbilane synthase
- Predominantly affects women
- Age of onset varies
  - Onset between the second and fourth decades of life is most common

Disease Pathophysiology[4]

- Induction of *ALAS1* leads to accumulation of neurotoxic heme intermediates ALA and PBG
- ALA and PBG are factors associated with attacks or other disease manifestations of AHP



ADP, ALA dehydratase-deficient porphyria; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, 5-aminolevulinic acid; ALAS1, ALA synthase 1; CoA, coenzyme A; HCP, hereditary coproporphyria; HMBS, hydroxymethylbilane synthase; PBG, porphobilinogen; VP, variegate porphyria.

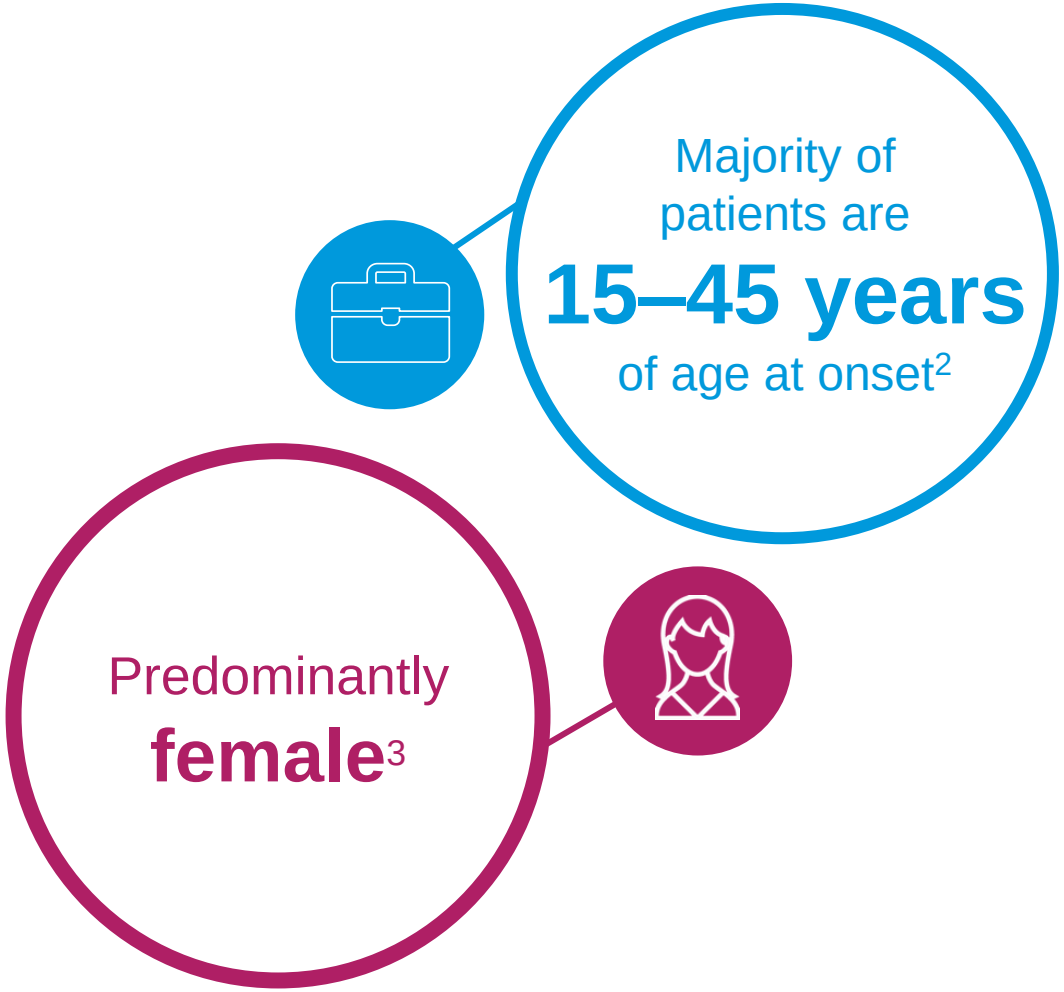
1. Bonkovsky HL et al. *Am J Med* 2014;127:1233–1241; 2. Elder G et al. *J Inherit Metab Dis* 2013;36:849–857; 3. Balwani M et al. *Hepatology* 2017;66:1314–1322; 4. Bonkovsky HL et al. *Mol Genet Metab* 2019;128:213–218.

AHP Patient Population

- Rare disease disproportionately impacting female patients of working and childbearing age[1,2]

PREVALENCE

~~9 per 1,000,000~~
diagnosed with symptomatic AHP in Europe[1]



AHP, acute hepatic porphyria.

1. Elder G et al. *J Inherit Metab Dis* 2013;36:849–857; 2. Bissell DM & Wang B. *J Clin Transl Hepatol* 2015;3:17–26; 3. Bissell DM et al. *N Engl J Med* 2017;377:862–872.

Alnylam®

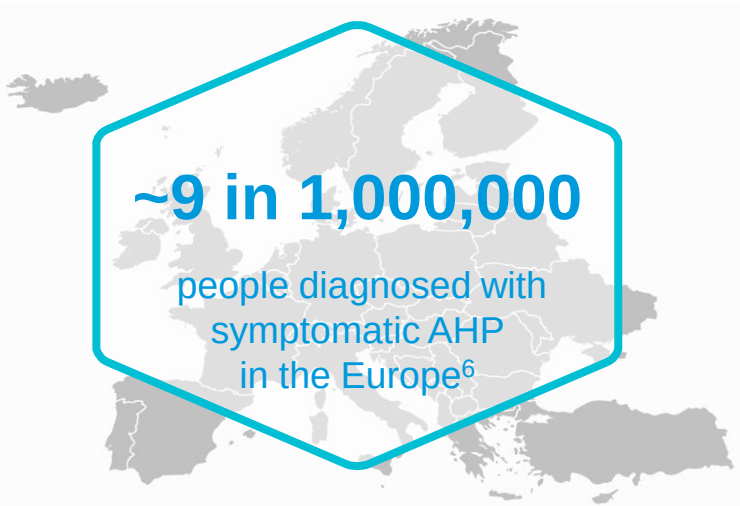
AHP Types[1]

AHP Type[1]	Sex[1]	Age of Onset	Typical Presenting Symptoms[1]		Estimated % of AHP
			Acute Attacks	Cutaneous	
AIP	Symptomatic patients are predominantly female[1–3]	15–45 years[4]	✓		Most prevalent AHP type (~80%)[5]
VP			✓	✓	Less prevalent[6]
HCP			✓	✓	Less prevalent[6]
ADP	All recorded symptomatic patients have been male[1]	Variable[1]	✓		Least prevalent <10 cases ever reported worldwide[1]

Increasing prevalence

Mutation* Prevalence[7,8]
~1 in 1600–1700

Disease penetrance[7,8]
~1%



*Only referring to a mutation in the *HMBS* gene.[6]

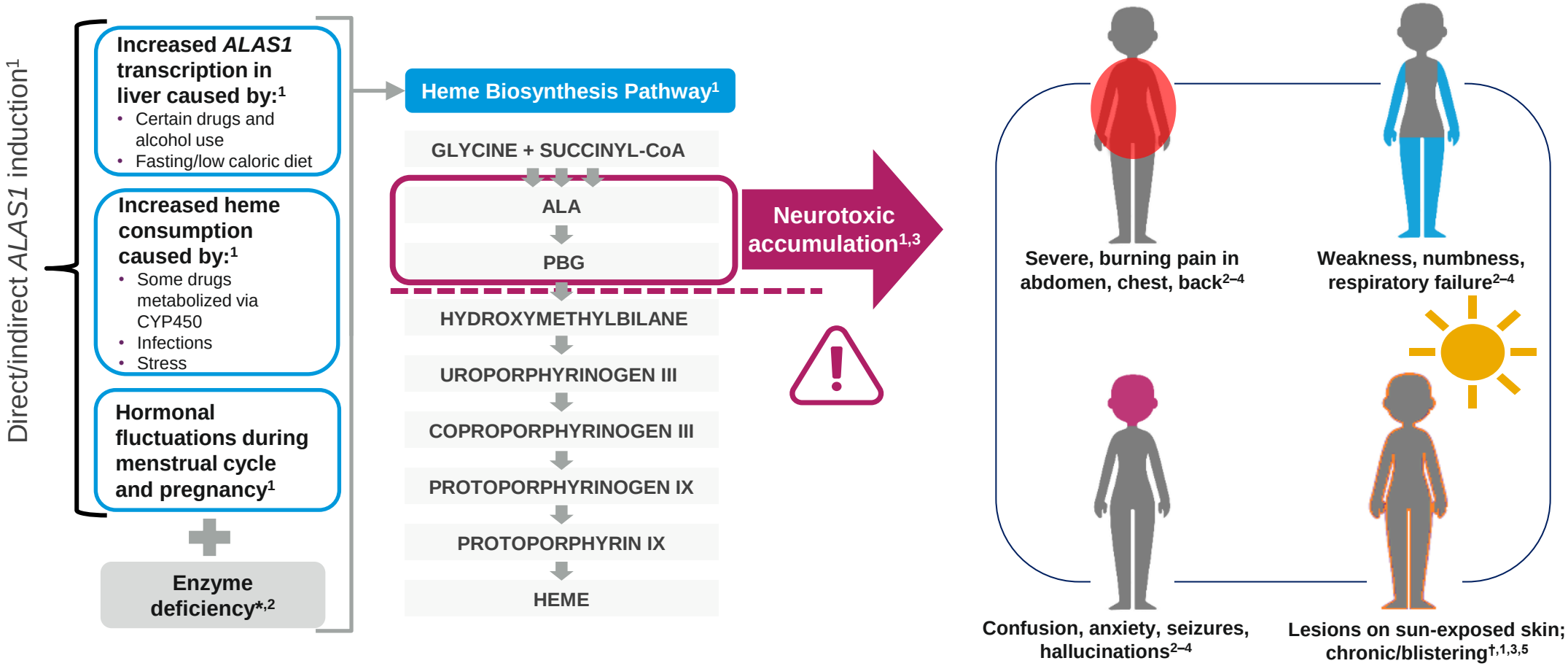
ADP, ALA dehydratase-deficient porphyria; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, 5-aminolevulinic acid; HCP, hereditary coproporphyria; HMBS, hydroxymethylbilane synthase; VP, variegate porphyria.

1. Ramanujam VMS & Anderson KE. *Curr Protoc Hum Genet* 2015;86:1–26; 2. NORD. Varigate porphyria – Affected Populations. Available at: https://rarediseases.org/rare-diseases/variegate-porphyria/#affected (accessed October 2023); 3. Sam SS et al. *J Hematol* 2016;5:67–69; 4. Bissell DM & Wang B. *J Clin Transl Hepatol* 2015;3:17–26; 5. Simon A et al. *Patient* 2018;11:527–537; 6. Elder G et al. *J Inherit Metab Dis* 2013;36:849–857; 7. Nordmann Y et al. *J Intern Med* 1997;242:213–217; 8. Chen B et al. *Hum Mutat* 2016;37:1215–1222.

Alnylam®

AHP Pathophysiology

- Triggers induce heme synthesis through direct/indirect *ALAS1* activation[1]
- Resulting accumulation of toxic heme metabolites, leading to symptoms in several organ systems[1]



*Enzyme deficiency in the heme synthesis pathway;[2] †Occurs primarily in VP and HCP[3]

ALA, δ-aminolevulinic acid; ALAS1, ALA synthase 1; CoA, coenzyme A; CYP450, cytochrome P450; HCP, hereditary coproporphyria; PBG, porphobilinogen; VP, variegate porphyria

1. Pischik & Kauppinen. *Appl Clin Genet* 2015;8:201–14; 2. Besur et al. *Metabolites* 2014;4:977–1006;
3. Anderson et al. *Am J Med Sci* 2021;362:113–121; 4. Ventura et al. *Eur J Intern Med* 2014;25:497–505; 5. Gouya et al. *Hepatology* 2020;71:1546–58.

Symptoms and Complications Experienced by Patients with AHP

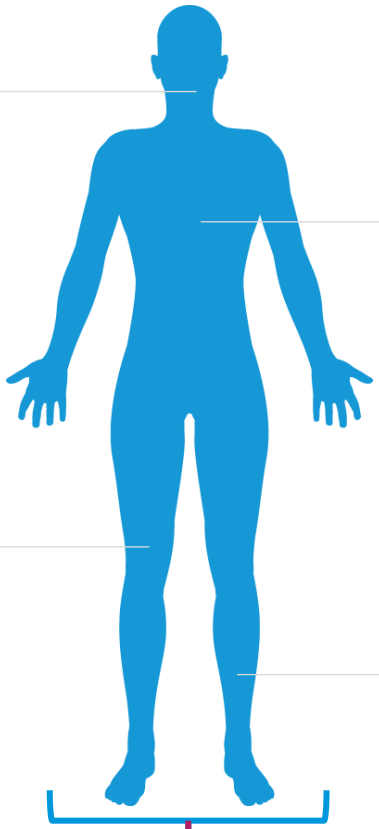
Diverse Clinical Characteristics and Associated Conditions Potentially Experienced

CNS Manifestations[1–4]

- Confusion
- Anxiety
- Memory loss
- Depression
- Insomnia
- Hallucinations*
- Seizures*

PNS Manifestations[1–4]

- Neuropathic pain
- Sensory loss
- Muscle weakness
- Paralysis*
- Respiratory failure*



ANS Manifestations[1–5]

- Severe pain in the abdomen, chest, or back
- Hypertension
- Tachycardia
- Nausea and vomiting
- Constipation
- Hyponatremia

Cutaneous Manifestation†[1,3]

- Lesions on sun-exposed skin

Long-term Complications[1,3]

- Hepatocellular carcinoma
- Chronic kidney disease
- Neuronal damage
- Hypertension

Chronic Complications[6]

- Anxiety and depression
- Trouble sleeping/fatigue
- Pain
- Nausea

The symptoms presented are not all of the possible symptoms of AHP

AHP is a multisystem disease characterized by attacks, chronic symptoms, and long-term complications[6]

*Only occurs in severe cases;[4] †Primarily occurs in VP and HCP.[1]
ANS, autonomic nervous system; CNS, central nervous system; HCP, hereditary coproporphyria; PNS, peripheral nervous system; VP, variegate porphyria.

1. Anderson KE. *Mol Genet Metab* 2019;128:219–227; 2. Gouya L et al. Presented at the International Liver Congress, April 11–15, 2018, Paris, France. Presentation; 3. Pischik E & Kauppinen R. *Appl Clin Genet* 2015;8:201–214; 4. Simon A et al. *Patient* 2018;11:527–537; 5. Anderson KE et al. *Am J Med Sci* 2022;363:1–10; 6. Wheeden K et al. *Adv Ther* 2022;39:4330–4345.

Alnylam®

Diagnosing AHP

- Average duration from presentation to accurate diagnosis can be up to 15 years or more[1,2]
  - Diagnostic testing in patients with suspected AHP will reduce diagnostic delay[2]
- Accuracy and speed are vital in diagnosing patients as delaying treatment of an AHP attack can result in greater morbidity and even mortality[2]
- Diagnosis is based on clinical judgement of diagnosing physician

Biochemical Testing[1,3,4]

- Random (spot) urine tests for ALA, PBG, and porphyrins can help to diagnose AHP
  - Urine porphyrins is a non-specific test and should not be used in isolation for diagnosing AHP
  - Ideal time to test is during or shortly after an attack; however, testing can be performed anytime if there is suspicion of AHP*
- Additional biochemical tests including plasma or fecal porphyrins and plasma fluorescence scanning can be performed to help diagnose or confirm a diagnosis or AHP type but are not specific for AHP when tested alone

Genetic Testing[1,3,4]

- Genetic testing can be performed to help confirm AHP type
  - Can rule out AHP if patient does not have mutation
  - Important for carrier/family testing
  - Can provide important information for patients being evaluated outside of an attack - where ALA/PBG may be normal

*Results should be normalized to urine creatinine.[2]

ALA, 5-aminolevulinic acid; AHP, acute hepatic porphyria; PBG, porphobilinogen.

1. Bonkovsky HL et al. *Am J Med* 2014;127:1233–1241; 2. Anderson KE et al. *Am J Med Sci* 2021;362:113–121; 3. Whatley SD & Badminton MN. In: Adam MP et al. eds. *Acute Intermittent Porphyria*. GeneReviews. Seattle, WA: University of Washington; 2013;1993–2021; 4. Anderson KE et al. *Ann Intern Med* 2005;142:439–450.

Alnylam®

Acute Hepatic Porphyria: Disease Burden

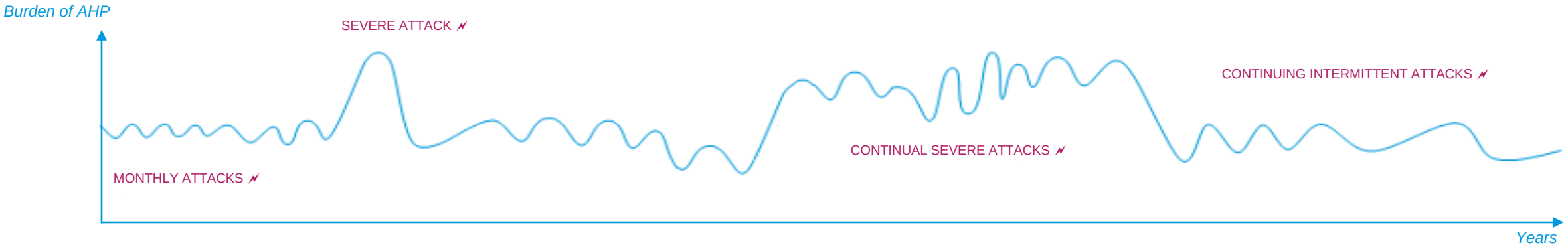
Alnylam®

Acute Hepatic Porphyria

Unpredictable Nature of AHP Places Burden on Patients

- Patients are frequently misdiagnosed (e.g., nonspecific abdominal pain, fibromyalgia, depression, endometriosis) and undergo potentially unnecessary surgeries (e.g., cholecystectomy, appendectomy, hysterectomy)[1–3]
- Frequent healthcare utilization, reduced quality of life, and reduced employment can all contribute to disease burden[4,5] and the unpredictable nature of attacks can be a source of fear and anxiety for some patients[6]

Illustrative Patient Experience with AHP



"I think the unpredictability [of] porphyria is frustrating. It's difficult to make plans far out because of porphyria. I've missed friends' weddings. I've had to cancel trips. Even appointments that day." – Patient with AHP[6]

"I think one of the biggest ways that porphyria impacts your life is that it's completely unpredictable. There's no way I could be a reliable employee to somebody because I could not guarantee that I will be there tomorrow for work."– Patient with AHP[6]

AHP, acute hepatic porphyria.

1. Bissell DM et al. *N Engl J Med* 2017;377:862–872; 2. Ko JJ et al. Presented at the American College of Gastroenterology Scientific Meeting, October 5–10, 2018, Philadelphia, PA, USA; 3. Anderson KE et al. *Am J Med Sci* 2021;362:113–121; 4. Bylesjö I et al. *Scand J Clin Lab Invest* 2009;69:612–618; 5. Gouya L et al. *Hepatology* 2020;71:1546–1558; 6. Simon A et al. *Patient* 2018;11:527–537.

Alnylam®

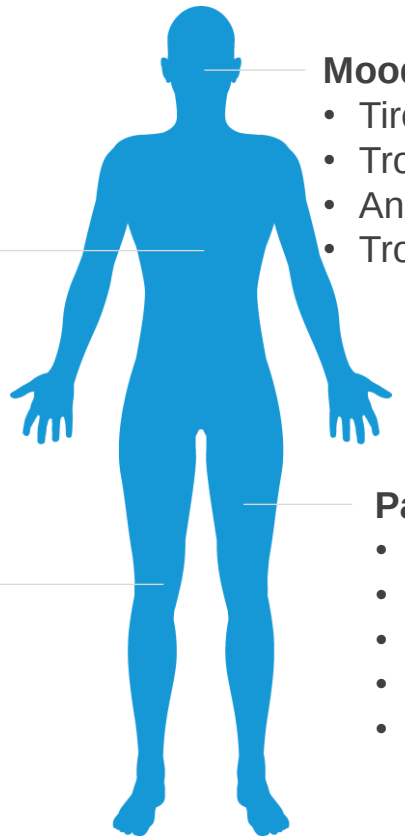
Patients with AHP Experience Unpredictable Attacks

Attack Symptomatology in Patients with AHP

- During an acute attack, multiple symptoms are experienced simultaneously, caused by dysfunction across the autonomic, central, and peripheral nervous system[1–3]
- In **EXPLORE A**, an observational, multinational, prospective natural history study, **pain was the most prominent symptom** experienced during attacks, with abdominal pain being the most frequently reported (92%)[1]
- Other common attack symptoms reported by patients in **EXPLORE** and other studies included tiredness, nausea, constipation, change in urine color, and weakness[1,4,5]

Patients with AHP describe attacks as "completely unbearable" and pain symptoms as "agonizing" and "stabbing, knife-like."[6]

Frequently Reported Symptoms (≥50%) by Patients During an Attack at Baseline in EXPLORE A (n=112)[1]



Mood or sleep symptoms
- Tiredness
- Trouble sleeping
- Anxiety
- Trouble concentrating

GI symptoms
- Nausea
- Constipation
- Loss of appetite
- Vomiting

Pain symptoms
- Abdominal pain
- Arm/leg pain
- Back pain
- Muscle pain
- Headache

Other symptoms
- Changes in urine color
- Weakness
- Fast heartbeat
- Sweating

AHP, acute hepatic porphyria; GI, gastrointestinal.

1. Gouya L et al. *Hepatology* 2020;71:1546–1558; 2. Bonkovsky HL et al. *Mol Genet Metab* 2019;128:213–218; 3. Anderson KE. *Mol Genet Metab* 2019;128:219–227; 4. Bonkovsky HL et al. *Am J Med* 2014;127:1233–1241; 5. Naik H et al. *Mol Genet Metab* 2016;119:278–283; 6. Simon A et al. *Patient* 2018;11:527–537.

Alnylam®

Patients with AHP Experience Chronic Symptoms

Chronic Symptoms in Patients with AHP

- Chronic symptoms* between attacks were reported by 65% of all patients with AHP (n=73)† in the **EXPLORE A study** (N=112), with 46% of patients (n=52) reporting **daily chronic symptoms**[1]
- A total of **38 unique chronic symptoms** were reported by participants in the **qualitative interview study** (N=14) including fatigue or tiredness (92.9% of patients), back pain, muscular body pain, nausea (57.1% of patients), abdominal pain and constipation (50.0% of patients)[2]

"I never feel well rested when I wake up, ever. **I can't remember the last time I felt rested**."– Patient with AHP[2]

"When it's chronic, it's something I'm constantly having to manage… **there will be pains where I feel like I'm getting stung by a swarm of bees** or something like that. But it doesn't get to the point where I'm having to go to the emergency room and vomiting." – Patient with AHP[3]

Most Common Chronic Symptoms Reported by Patients in EXPLORE A[1]

*Chronic symptoms are those that occur between attacks;[1,2] †Eligible patients had experienced ≥3 attacks in the prior 12 months or were receiving prophylactic treatment.[1]
AHP, acute hepatic porphyria.

1. Gouya L et al. *Hepatology* 2020;71:1546–1558; 2. Wheeden K et al. *Adv Ther* 2022;39:4330–4345; 3. Simon A et al. *Patient* 2018;11:527–537.

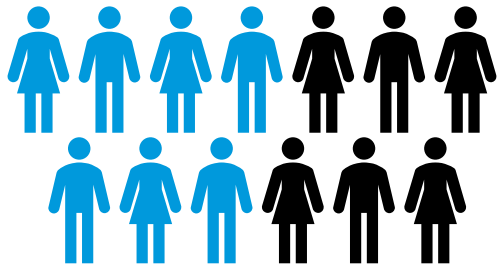
Alnylam®

Chronic Symptoms of AHP Can Vary in Intensity and Duration

Patients with AHP May Experience Symptomatic "Flare-up" or "Episodes"

- The **qualitative interview study** (N=14), consisting of semi-structured telephone interviews, captured what participants with AHP termed "flare-ups" or "episodes," when they experienced **increased severity, frequency, and/or duration** of one or more of their chronic signs/symptoms of AHP, but not to the extent that they considered the event to be an attack

In the qualitative interview study, flare-ups or episodes were reported by **53.8% (7/13) of participants**



Descriptions of Flare-up by Participants with AHP Varied and Some Individuals Described the Potential for an Episode to Turn Into an Attack:

"I have attacks. But then I also have what I refer to as a more, I guess, **mild but long-lasting flare-ups**. The flare-ups last anywhere from 7 to 14 days." – Patient with AHP

"I'd say, one episode that's wicked bad every, I'd say, 6 to 8 weeks, where I feel like complete shit for several days and barely get out of bed… That's on an irregular basis, **but it does not mean that I am getting an attack**." – Patient with AHP

"If I take it easy and—or take a day off work or do—you know, adjust what I'm eating or trying to get more sleep, it'll usually calm down. But it's when I try to do those things and the **pain continues to get worse** that it then turns more into an attack." – Patient with AHP

AHP, acute hepatic porphyria.
Wheeden K et al. *Adv Ther* 2022;39:4330–4345.

Alnylam®

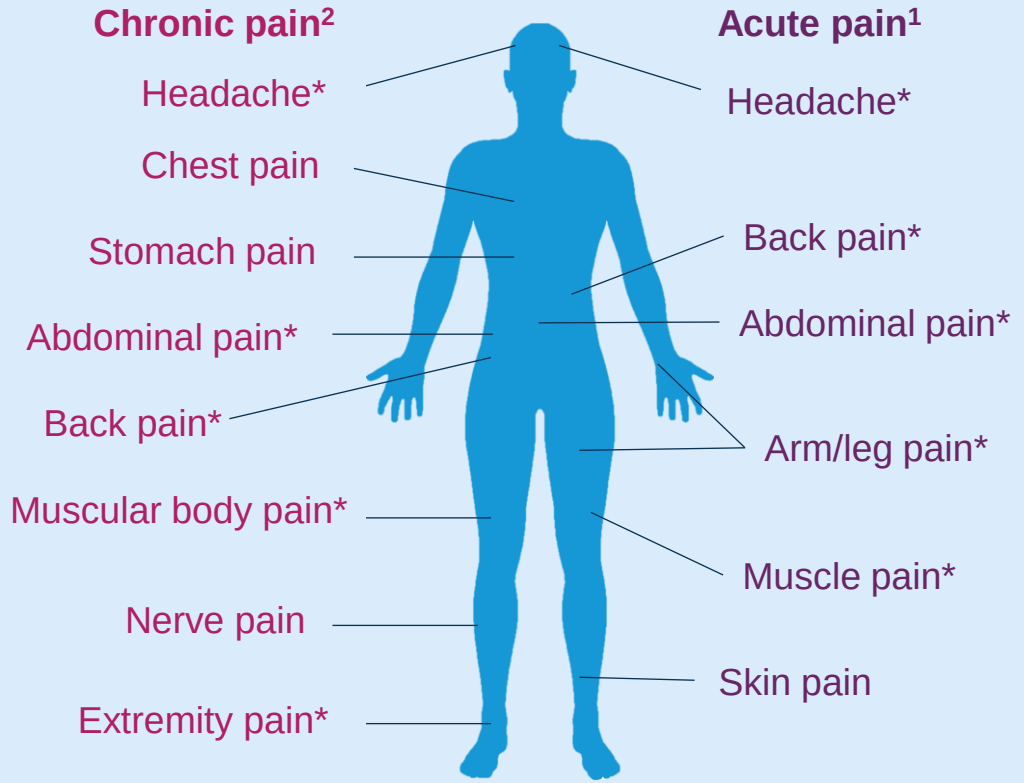
Pain is One of the Most Burdensome Symptoms of AHP[1–3] (1/3)

Patients with AHP Can Experience Both Acute and Chronic Pain

- Pain was reported by **99%** of patients with AHP during an acute attack in the **EXPLORE A study** (N=112)[4]
- Pain was not exclusive to attacks, with 92.8% of participants with AHP from the **qualitative interview study** (N=14) reporting **eight types of chronic pain[1]**
  - Participants reported taking medication to manage their chronic pain[1]

> "**I take a lot of drugs.** I know that sounds terrible, but I take [medication], so I've really gone the medication route to try and solve a lot of my problems." – Patient with AHP[1]

Patients with AHP May Experience Acute and/or Chronic Pain in a Variety of Areas[1,4]



*Frequently reported symptoms (≥50%).[1,2]
AHP, acute hepatic porphyria.

1. Wheeden K et al. *Adv Ther* 2022;39:4330–4345; 2. Dickey A et al. *JIMD Rep* 2022;64:104–113; 3. Cassiman D et al. *J Inherit Metab Dis* 2022;45:1163–1174; 4. Gouya L et al. *Hepatology* 2020;71:1546–1558; 2.

Alnylam®

Pain is One of the Most Burdensome Symptoms of AHP[1–3] (2/3)

Patients with AHP Can Experience Both Acute and Chronic Pain

Pain was reported as the most burdensome **acute and chronic symptom** experienced in the multinational **POWER study**[1]

- Patients with AHP in the POWER study (N=92) reported that:[1]
  - Pain limited the daily activities of 94.3% of patients
  - Over a third (37%) of patients in the study reported that their pain **no longer responds** well to therapy
- Pain reported in the POWER study was comparable with other, non-AHP chronic pain patients with conditions such as herniated disc or rheumatoid arthritis[1,4,*]

"During an attack, it [pain] would **bring me to my knees**. But just kind of every day, it's more of abdominal pain. It just kind of hurts as far as compared to debilitating during an attack."
– Patient with AHP[2]

"The pain in my legs has **increasingly gotten worse with time**, which is scary to me, like it started out a little bit, and then it became a little bit more, and now it's a little bit more often and it just feels like I just don't want to stand for long periods."
– Patient with AHP[2]

*The mean WHYMPI scores (scale, 0–6, lowest to highest impact) on subscales of interference, support, pain severity, self-control, and affective distress were: 3.6, 4.5, 3.4, 3.3 and 3.7, respectively, in patients with AHP reported in the POWER study and 3.74, 4.31, 3.55, 3.63, and 3.23, respectively, from a study of 120 non-AHP chronic pain patients.
AHP, acute hepatic porphyria.

1. Dickey A et al. *JIMD Rep* 2022;64:104–113; 2. Wheeden K et al. *Adv Ther* 2022;39:4330–4345; 3. Cassiman D et al. *J Inherit Metab Dis* 2022;45:1163–1174; 4. Kerns RD et al. *Pain* 1985;23:345–356.

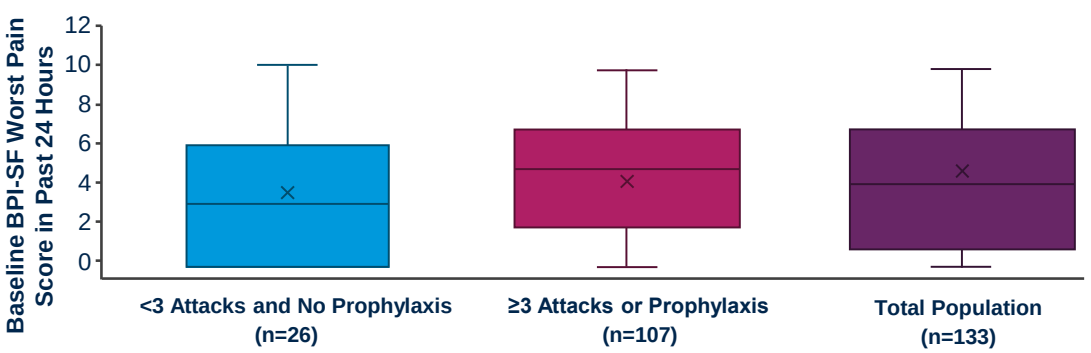
Alnylam®

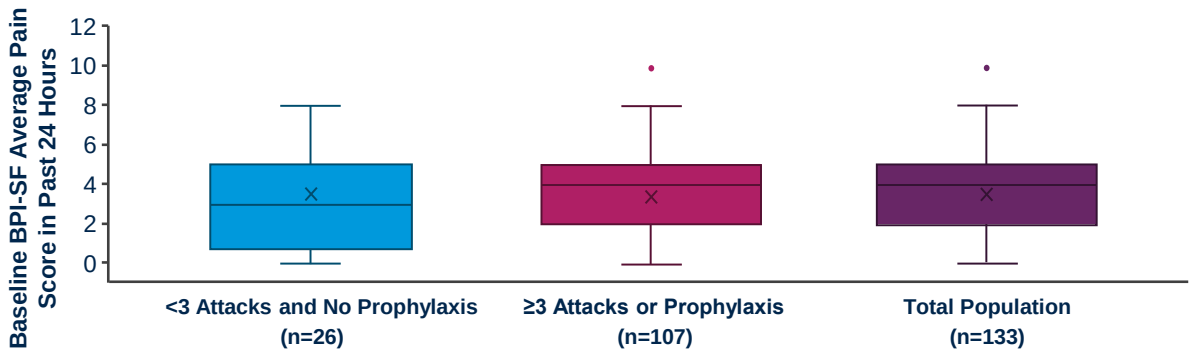
Pain is One of the Most Burdensome Symptoms of AHP[1–3] (3/3)

Pain Can Affect Patients with AHP, Regardless of Attack Frequency

- **Burden of pain was not affected by attack frequency** as demonstrated by comparable pain scores across all attack frequency subgroups assessed in the **EXPLORE B** natural history study as measured with the pain assessment tool BPI-SF, with a scale of 0–10 whereby a higher score denotes worse pain[1]
  - At baseline, mean (SD) worst pain scores in the past 24 hours were 3.5 (3.1), 4.5 (3.1), and 4.3 (3.1) in patients with <3 attacks and no prophylaxis, patients with ≥3 attacks or prophylaxis, and the total population, respectively[1]
  - At baseline, mean (SD) average pain scores in the past 24 hours were 3.3 (2.5), 3.7 (2.4), and 3.6 (2.4) in patients with <3 attacks and no prophylaxis, patients with ≥3 attacks or prophylaxis, and the total population, respectively[1]

Pain Intensity at Baseline as Assessed with BPI-SF Scores for Subgroups of Patients with <3 Attacks without Prophylaxis, ≥3 Attacks or Prophylaxis, and the Total Population[1,*]





*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.[1]
AHP, acute hepatic porphyria; BPI-SF, Brief Pain Inventory–Short Form; SD, standard deviation.

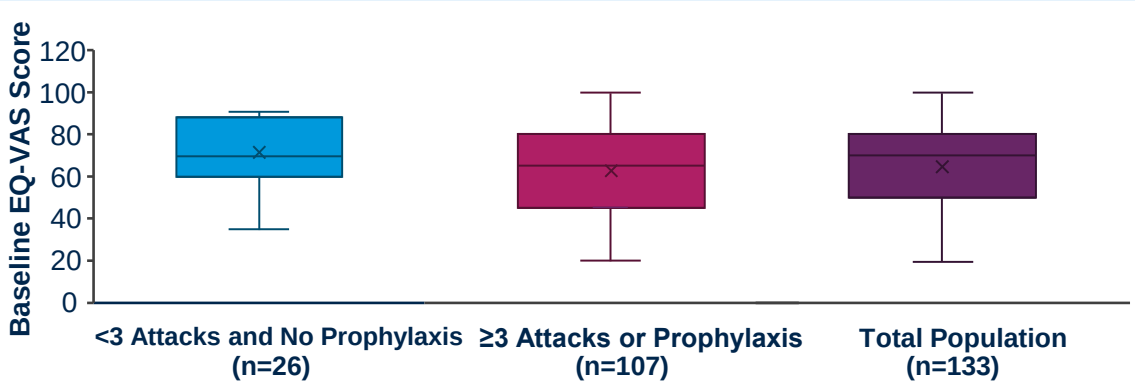
1. Cassiman D et al. *J Inherit Metab Dis* 2022;45:1163–1174; 2. Dickey A et al. *JIMD Rep* 2022;64:104–113; 3. Wheeden K et al. *Adv Ther* 2022;39:4330–4345.

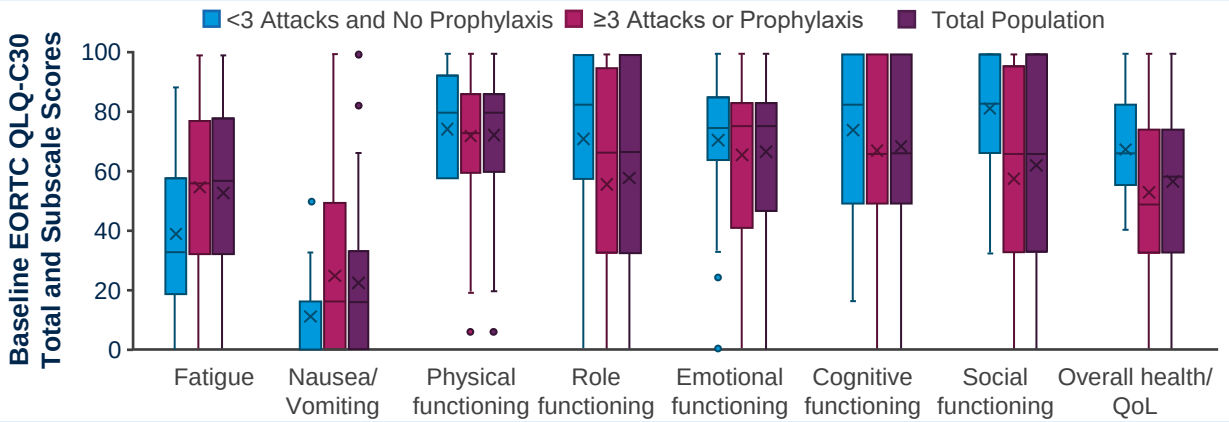
AHP is Associated with Poor QoL

QoL Can Be Affected in Patients with AHP Regardless of Attack Frequency

- QoL in patients with AHP was investigated in **EXPLORE** using EQ-5D-5L*,[1]
  - At baseline, the mean (SD) EQ-5D-5L* score of the AHP patient population with a median age of 38 was 0.78 (0.15), which is lower than the European population norm of 0.92 for the same age group[1]
- QoL was limited in patients with AHP **regardless of attack frequency** as identified in further QoL measures and subgroup analysis in **EXPLORE B**[2]
  - At baseline, EQ-VAS† scores (62.9–71.8) and EORTC‡ scores (53.8–68.0) remained similar across the different AHP subgroups[2]

Mean EQ-VAS Scores and EORTC QLQ-C30 Total and Subscale Scores at Baseline for Subgroups of Patients with <3 Attacks without Prophylaxis, ≥3 Attacks or Prophylaxis, and the Total Population[2,†,‡,§]





*The EQ-5D-5L scale ranges 0–1 whereby higher score denotes better health;[3] †The EQ-VAS scale records an individual's rating of their overall current health-related QoL, ranging 0–100; higher scores denote better health state;[2] ‡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;[2] §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.[2]

AHP, acute hepatic porphyria; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire core 30; EQ-5D-5L, EuroQoL 5-dimension 5-level; EQ-VAS, EuroQol Visual Analog Scale; QoL, quality of life.

1. Gouya L et al. *Hepatology* 2020;71:1546–1558; 2. Cassiman D et al. *J Inherit Metab Dis* 2022;45:1163–1174; 3. Euroqol. Terminology – EQ-5D. Available at: https://euroqol.org/support/terminology/ (accessed October 2023).

AHP is Associated with a Change in Mental State

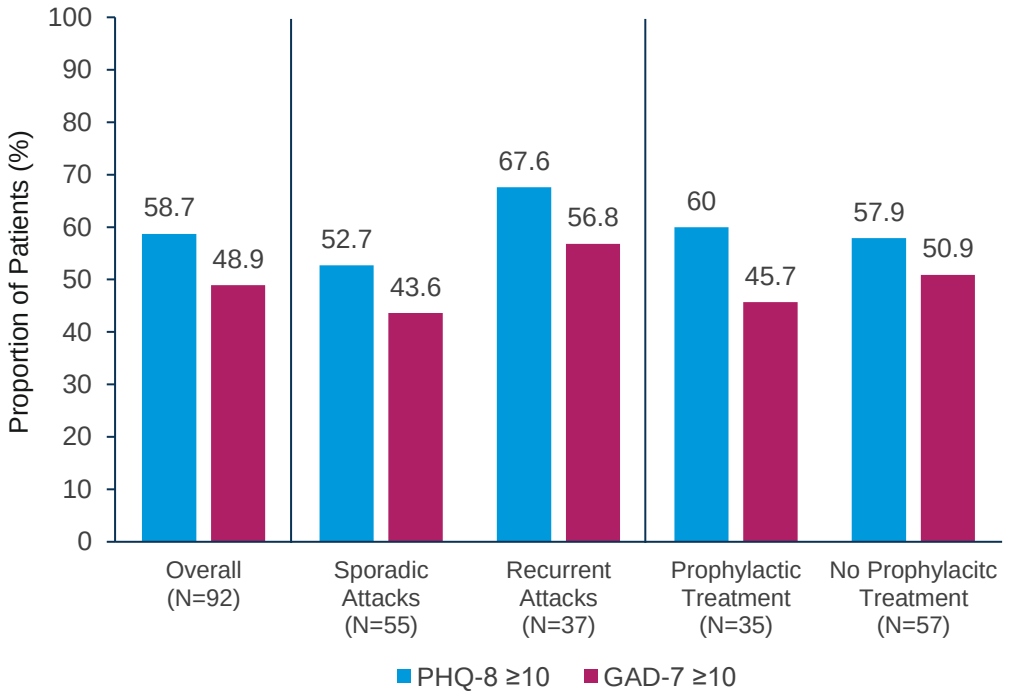
Anxiety and Depression are Common in Patients with AHP

- Patients with AHP can experience **mental status changes** during attacks (such as confusion, anxiety, and hallucinations), as well as anxiety, depression, and trouble sleeping on a chronic basis[1]

Moderate-to-severe depression and anxiety were reported in the multinational **POWER study** in 54 (58.7%) and 45 (48.9%) patients, respectively, as shown by a PHQ-8* or GAD-7† score of ≥10[2]

- Moderate-to-severe rates of depression and anxiety remained high across each subgroup, suggesting that the AHP burden on patients' mental health was substantial **regardless of AHP attack rates or hemin prophylaxis[2]**
- Compared with the general population, these rates are **considerably higher than those in a 2019 US national survey** that used the same scales, in which 7% adults reported moderate-to-severe depression and 9.5%, 3.4%, and 2.7% reported mild, moderate, and severe anxiety symptoms, respectively[2]

Proportions of Patients with AHP and Moderate-to-Severe Depression and Anxiety[2,*,†]



A patient with AHP explained that there are days in which they feel so "lousy" they are unable to "get out of bed" to "go to the grocery store and get some chores done."[1]

*Moderate-to-severe depression was identified with a PHQ-8 cutoff score of ≥10; †Mild, moderate, and severe anxiety was identified with GAD-7 scores of 5, 10, and 15, respectively.
AHP, acute hepatic porphyria; PHQ-8, 8-item Patient Health Questionnaire Depression Scale; GAD-7, 7-item Generalized Anxiety Disorder Scale; US, United States.
1. Wheeden K et al. *Adv Ther* 2022;39:4330–4345; 2. Dickey A et al. *JIMD Rep* 2022;64:104–113.

Alnylam®

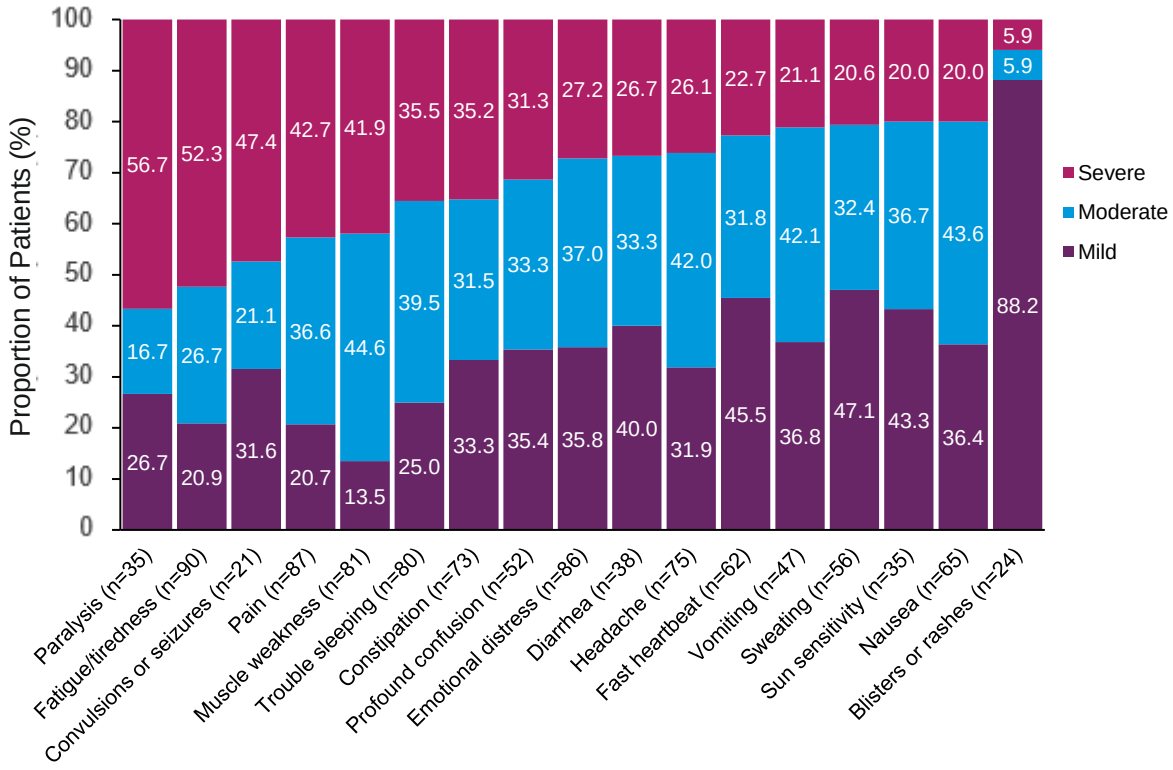
AHP Symptoms Affect Daily Life

The Acute and Chronic Symptoms of AHP Can Impact Daily Life

- Patients with AHP in the multinational **POWER study** (N=92) were asked to report on the **impact of specific symptoms** on their daily activities. Moderate-to-severe impact on daily activities was reported among:[1]
  - **79.3%** of patients who experienced chronic pain
  - **86.5%** of patients who experienced chronic muscle weakness
  - **79.0%** of patients who experienced chronic fatigue
  - **75.0%** of patients who experienced trouble sleeping
- AHP symptoms impacted the daily activities of 78.6% of patients with AHP in the **qualitative interview study** (N=14)[2]

"I try everything I can to try and get through the whole day and it's really hard to keep a full-time job and try to do normal daily activities due to the pain that I feel, as well as being tired." – Patient with AHP[2]

Patients Reporting Mild, Moderate, or Severe Impact of Symptoms on Daily Activities[1]



AHP, acute hepatic porphyria.

1. Dickey A et al. *JIMD Rep* 2022;64:104–113; 2. Wheeden K et al. *Adv Ther* 2022;39:4330–4345.

Cost Implications of AHP

AHP Can Impact Healthcare Utilization and Work

Patients with AHP reported a high-level of healthcare utilization during EXPLORE

- In **EXPLORE A** (N=112), 88% of patients experienced a total of 483 AHP attacks[1]
  - 77% of AHP attacks required **urgent medical treatment in a hospital or healthcare facility** and/or treatment with intravenous hemin[1]
  - The unpredictable nature of AHP attacks mean that patients must always be prepared for a hospital visit[1]
- In **EXPLORE B**, patients with AHP (N=136) reported a mean of **4.1 emergency department visits** and **4.2 overnight stays in a hospital** during the 12 months prior to baseline[2]

Participants with AHP reported that it is **"really hard to keep a full-time job,"** that they are **"no longer able to work,"** and whatever work they do **"has to be extremely flexible."**[3]

"…I got my dream job with [company] and then I had my second attack. And then I had recurrent attacks after that, and **[the company] said they would never have me again**. That's what I trained for, for many years and had been my lifelong ambition." – Patient with AHP[3]

AHP Can Affect a Patient's Ability to Work

- In **EXPLORE B** (N=136), only one-third of patients were employed in full-time work at baseline[2]
  - Of those patients working full time, **36% of patients (n=49) missed workdays** in the past 12 months due to an attack[2]
- In **POWER study** (N=92), a majority of patients with AHP agreed or strongly agreed that:[4]
  - **AHP affected their ability to keep a job,** as reported by 60.9% of patients[4]
  - **AHP stopped them from working to their full potential,** as reported by 72.9% of patients[4]

AHP, acute hepatic porphyria.

1. Gouya L et al. *Hepatology* 2020;71:1546–1558; 2. Cassiman D et al. *J Inherit Metab Dis* 2022;45:1163–1174; 3. Wheeden K et al. *Adv Ther* 2022;39:4330–4345; 4. Dickey A et al. *JIMD Rep* 2022;64:104–113.

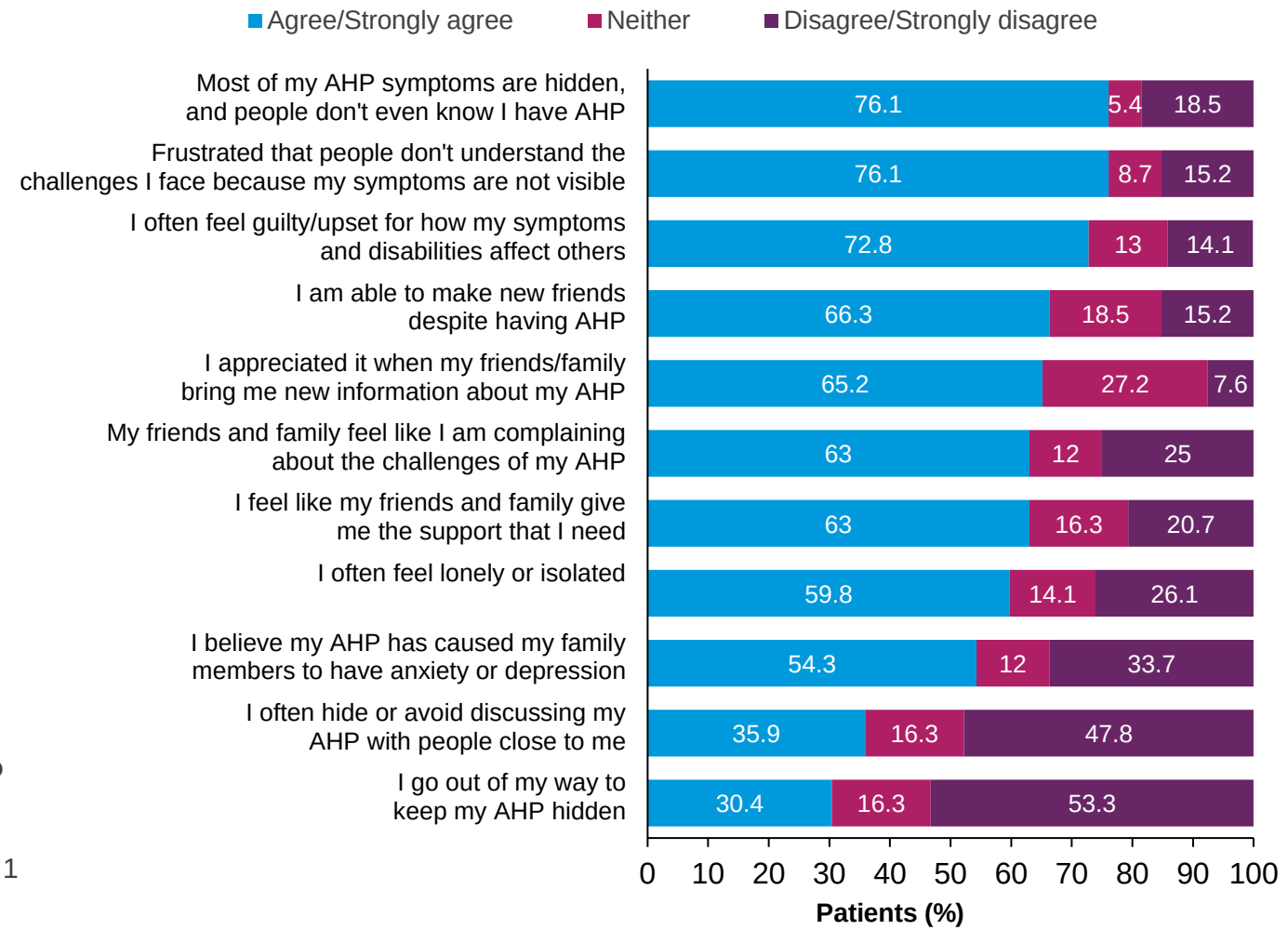
Alnylam®

Social Implications of AHP

AHP Can Have a Negative Impact on the Social Lives of Patients

- The multinational **POWER study** (N=92) included unique survey questions to investigate the impact of AHP on patients' **social life**[1]
  - A large proportion of patients with AHP (59.8%) reported often feeling **lonely** or **isolated**[1]
  - As AHP is rare and not externally visible:
    - Many patients (72.8%) reported feeling **guilty** and **upset** about how their symptoms and disabilities affected those around them
    - 76.1% of patients reported frustrations that **others did not understand** the challenges that they face[1]
  - The importance of a support network was highlighted, with 63.0% of patients with AHP disclosing that their **friends and family** provided them with the support they needed[1]

Impact of AHP on Social Life[2]



AHP, acute hepatic porphyria.

1. Dickey A et al. *JIMD Rep* 2022;64:104–113; 2. Lombardelli S et al. Presented at the International Congress of Porphyrins and Porphyrias, September 4–7, 2022, Sofia, Bulgaria. Poster.

Alnylam®

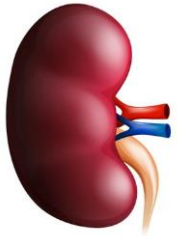
Potential Long-Term Complications of AHP

Potential for Liver and Kidney Disease, Hypertension, and Chronic Neuropathy in Patients with AHP

Liver Disease

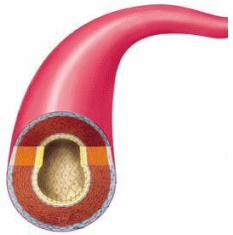
- AHP has been identified as a risk factor for PLC, especially hepatocellular carcinoma[1]
  - In a population-based study, the annual incidence of PLC was 0.35% in individuals with AHP—108-fold higher compared with 0.003% in the reference population[2]

Kidney Disease



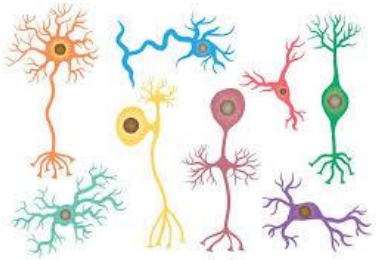
- Studies have found high levels of CKD in patients with AHP[3]
- In total, 59% of patients with symptomatic AIP have been observed to have CKD (eGFR <60 mL/min/1.73 m^2)[4]
- Patients with sporadic AIP (<4 attacks/year) have been observed to have a significantly increased risk of CKD compared with patients with latent AIP (p=0.018)*,[5]

Hypertension



- Patients with AHP may have an increased risk of chronic sustained hypertension[3,6,7]
  - As the risk of hypertension is high in the general population, further research is required to detect the true excess risk in patients with AHP[6]

Chronic Neuropathy



- Patients with AHP can develop chronic pain associated with axonal motor polyneuropathy[7]
  - Chronic pain symptoms can lead to severe depression and anxiety, which may necessitate psychiatric care[7]
- Suicidality has also been observed in patients with AHP[8,9]
- Permanent quadriplegia may rarely occur as a result of severe attacks[10]

*Patients with sporadic AIP were defined as having had at least one previous neurovisceral attack and an annual rate of attacks lower than four per year. A neurovisceral attack was considered to have been suffered when the patient was admitted to hospital due to clinical compatible symptoms with raised urinary porphobilinogen levels and received specific treatment. Latent AIP status was defined when there was no neurovisceral attack background.
AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PLC, primary liver cancer.

1. Peoc'h K et al. *Mol Genet Metab* 2018;128:236–241; 2. Baravelli CM et al. *J Intern Med* 2017;282:229–240; 3. Pallet N et al. *Clin Kidney J* 2018;11:191–197; 4. Pallet N et al. *Kidney Int* 2015;88:386–395; 5. Buendia-Martinez J et al. *Orphanet J Rare Dis* 2021;16:106; 6. Stewart MF. *J Clin Pathol* 2012;65:976–980; 7. Wang B et al. *Hepatol Commun* 2019;3:193–206; 8. Jeans JB. *Am J Med Genet* 1996;65:269–273; 9. Neeleman RA et al. *J Inherit Metab Dis* 2018;41:809–817; 10. Wikberg A et al. *J Intern Med* 2000;248:27–32.

Alnylam®

AHP Disease Burden Summary

Click for further information

- Patients with AHP can experience both unpredictable attacks and chronic symptoms[1]
- Chronic symptoms can vary in intensity and duration; some patients with AHP may experience “flare-ups” or “episodes”[2]
- Pain is one of the most burdensome symptoms of AHP, and patients can experience acute and/or chronic pain in a variety of areas[2,3]
- AHP is associated with poor QoL (regardless of attack frequency) and a change in mental state; rates of moderate-to-severe anxiety and depression are considerably higher in patients with AHP compared with the general population[3–5]
- Acute and chronic symptoms can impact daily activities[2,5]
- There can be cost implications of AHP; AHP can impact healthcare utilization and work[2,4]

AHP, acute hepatic porphyria; QoL, quality of life.

1. Simon A et al. *Patient* 2018;11:527–537; 2. Wheeden K et al. *Adv Ther* 2022;39:4330–4345; 3. Gouya L et al. *Hepatology* 2020;71:1546–1558; 4. Cassiman D et al. *J Inher Metab Dis* 2022;45:1163–1174; 5. Dickey A et al. *JIMD Rep* 2022;64:104–113.

Alnylam®

Acute Hepatic Porphyria: Management Options

Alnylam®

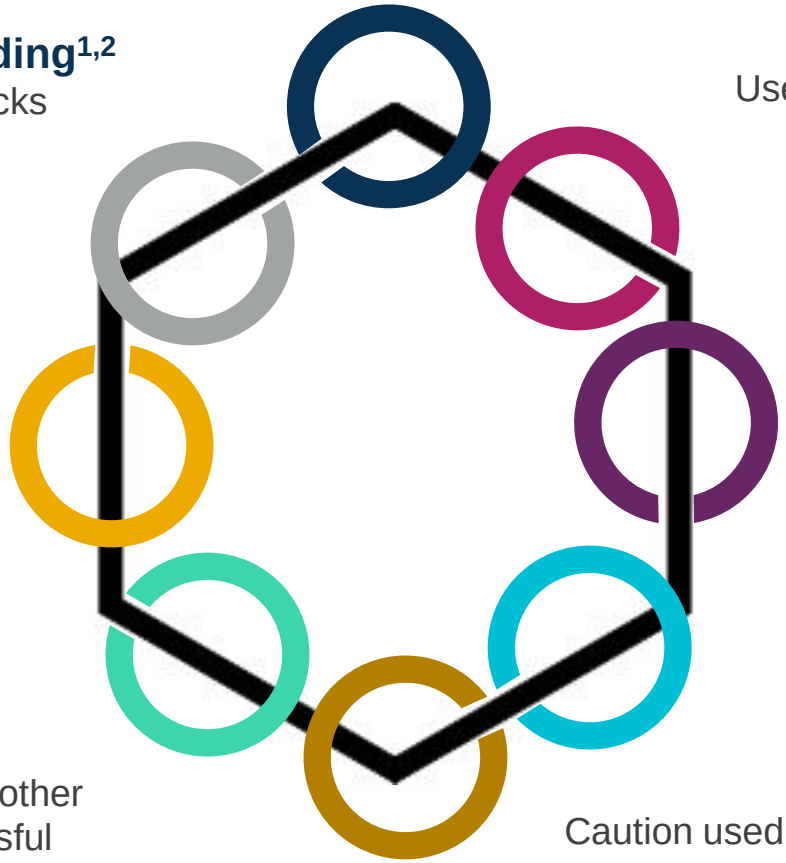
Management Options for AHP

Glucose and Carbohydrate Loading[1,2]
Used for the treatment of AHP attacks

Hemin[3]
Used for the treatment of attacks

Hormone Therapy (GnRH analogs)[1,5]
Used for patients experiencing AHP attacks related to their menstrual cycles

Liver Transplantation[3,5]
Used rarely in severe cases where other approaches have been unsuccessful



Medications to Treat Pain[1,4]
Used to manage painful AHP symptoms

Medications to Treat Symptoms[3]
Used to treat and reduce AHP symptoms like nausea, constipation, tachycardia (fast heartbeat), and seizures

RNA Interference Therapy[5]
Used for the treatment of adults with AHP

Trigger Avoidance[5]
Caution used with certain foods, drugs, and behaviors that may increase the risk of AHP attacks

AHP, acute hepatic porphyria; GnRH, gonadotropin-releasing hormone; RNA, ribonucleic acid; RNAi, RNA interference.

1. Wang B et al. *Hepatol Commun* 2019;3:193–206; 2. Pischik E & Kauppinen R. *Appl Clin Genet* 2015;8:201–214; 3. Anderson KE et al. *Ann Intern Med* 2005;142:439–450; 4. Puy H et al. *Lancet* 2010;375:924–937; 5. Balwani M et al. *Hepatology* 2017;66:1314–1322.

Alnylam®

Thank you!