The Porphyrias

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Hematology Education, April 17, 2025

Disclosures

- Advisory board participation: Alnylam therapeutics, CRISPR therapeutics, Mitsubishi Tanabe, Disc Medicine, Bridge Bio
- Clinical trial support: Alnylam therapeutics, Mitsubishi-Tanabe, Disc Medicine
- Institutional disclosure:

The Icahn School of Medicine at Mount Sinai ("ISMMS") holds issued and pending patents related to the study drug Givosiran and has licensed these patents to Alnylam. As part of the license to Alnylam, ISMMS will receive payments from Alnylam, including a payment when Givosiran enters Phase 3 clinical studies, as well as future payments if Givosiran becomes a marketed treatment for Acute Hepatic Porphyria. ISMMS, as well as the ISMMS faculty that are named inventors on the licensed patents will benefit financially

Learning Objectives

- Understand the pathophysiology of the Acute Hepatic Porphyria and the Erythropoietic Protoporphyrias
- Understand the clinical manifestations and management of these disorders
- Recognize the key diagnostic tests
- Recognize the landscape of FDA approved therapies and emerging treatments in clinical development

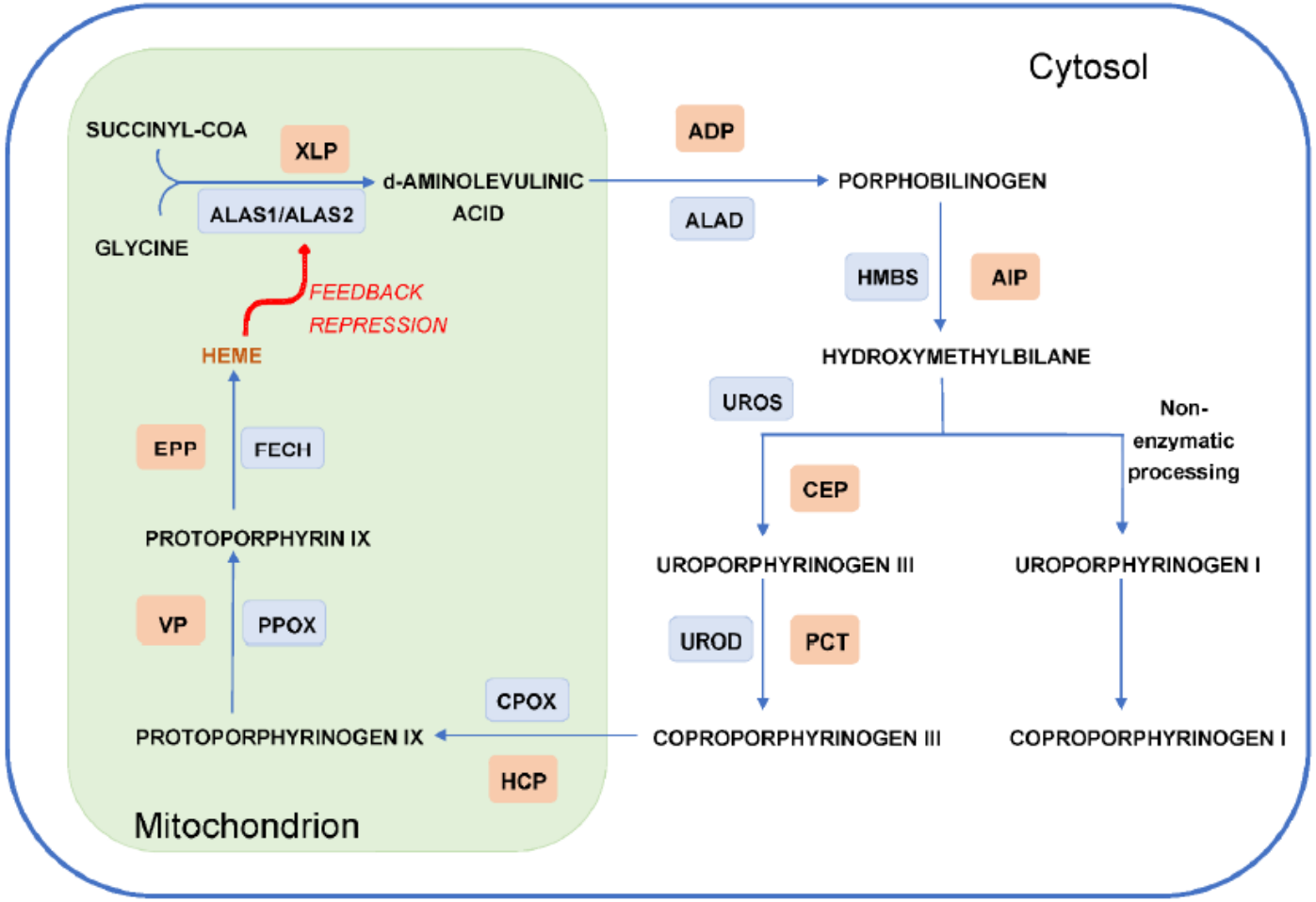
The Porphyrias

- Rare metabolic disorders of the heme-biosynthetic pathway
- Classified either based on the primary site of the enzymatic defect or clinical presentation

Acute
Acute Intermittent Porphyria (AIP)
Hereditary Coproporphyria* (HCP)
Variegate Porphyria* (VP)
ALAD Porphyria (ADP)
Cutaneous
Erythropoietic Protoporphyria (EPP)
X-linked Protoporphyria (XLP)
Congenital Erythropoietic Protoporphyria
Porphyria Cutanea Tarda (PCT)

Hepatic
Acute Intermittent Porphyria
Hereditary Coproporphyria*
Variegate Porphyria*
ALAD Porphyria
Porphyria Cutanea Tarda
Erythropoietic
Erythropoietic Protoporphyria
X-linked Protoporphyria
Congenital Erythropoietic Protoporphyria

The Porphyrias: Rare disorders of the heme biosynthetic pathway



- Eight enzymatic steps to the end product heme
- Heme exerts a negative feedback on the first enzyme of the heme biosynthetic pathway, ALAS1
- ALAS2, is erythroid specific and is regulated by erythroid-specific transcription factors

Erwin et al, Diagnostics 2021

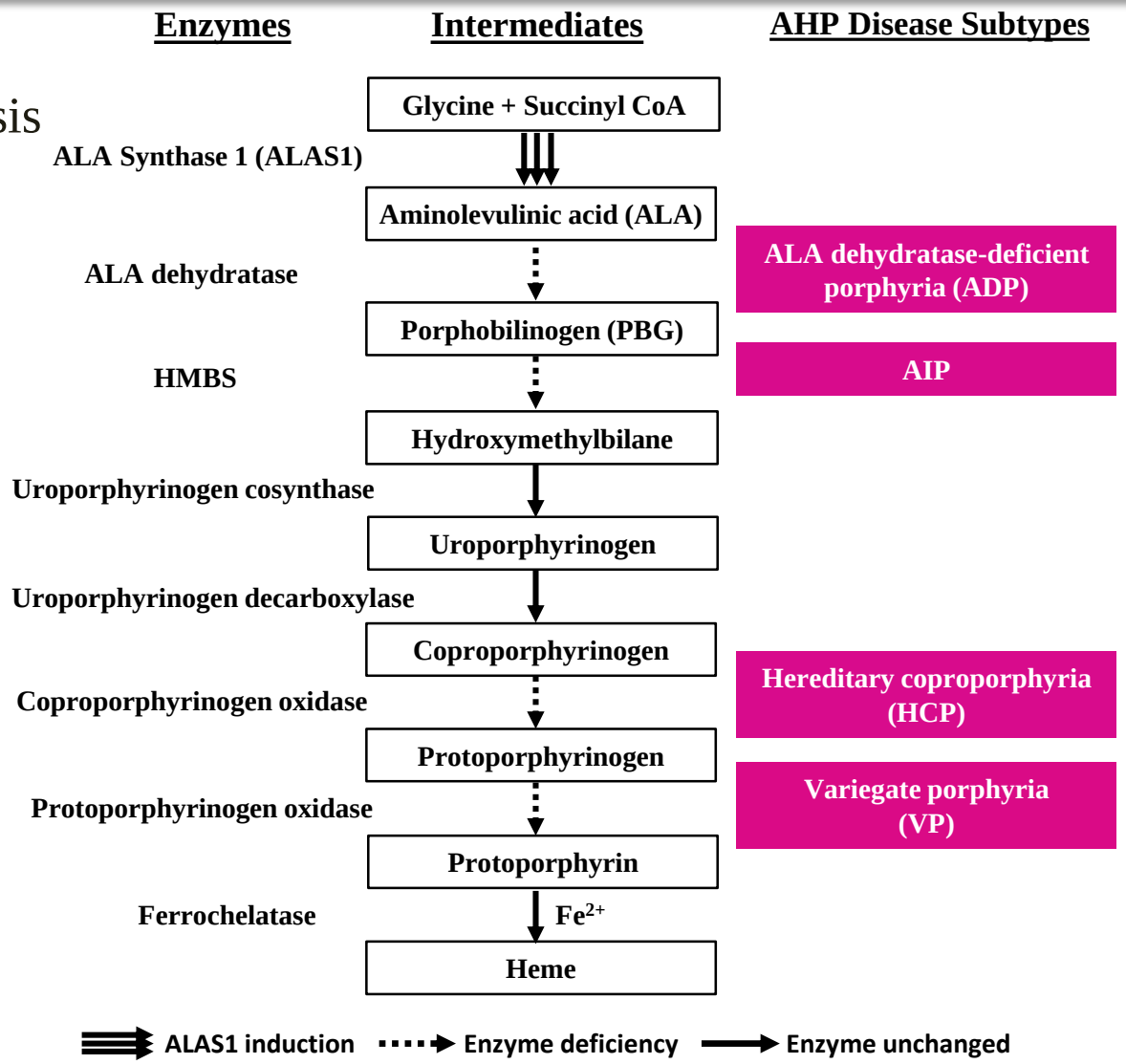
Acute Hepatic Porphyrias (AHP)

Disease Overview

- Deficiency in one of the enzymes in heme biosynthesis in liver
- Autosomal Dominant (except for ADP)
- Acute intermittent porphyria (AIP) most common, caused by pathogenic variants in the *HMBS* gene

Disease Pathophysiology

- Induction of ALAS1 leads to accumulation of neurotoxic heme intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG)
- ALA and PBG are factors associated with attacks or other disease manifestations of AHP



- 1. Bonkovsky et al. *Am J Med* 2014;127:1233–41; 2. Elder et al. *J Inherit Metab Dis* 2013;36:849–57; 3. Balwani et al. *Hepatology* 2017;66:1314–22; 4. Bonkovsky et al. *Mol Genet Metabo* 2019. doi: 10.1016/j.ymgme.2019.03.002. [Epub ahead of print]

AHP Patient Population

Female patients of childbearing age

HMBS Pathogenic Variant Prevalence

~1 in 1600–1700

Disease penetrance

~1%

(~20% in families of symptomatic AHP)

~10 in 1,000,000

people diagnosed with symptomatic AHP in the US[2]

Majority of patients are

age 18-45

at onset

Predominantly

female

- 1. Elder et al., 2013; 2 Nordmann et al. *J Intern Med* 1997;242:213–7; 3. Chen et al. *Hum Mutat* 2016;37:1215–222 4. Bissell DM et al. N Engl J Med. 2017;377:862-872 3. Lenglet H et al. Hum Mol Genet. 2018 Apr 1;27(7):1164-1173

AHP subtypes

AHP Type	Sex	Age of Onset	Typical Presenting Symptoms		Estimated % of AHP
			Acute attacks	Cutaneous	
AIP	Symptomatic patients are predominantly female	18–45 years	✓		Most Prevalent AHP Type (~80%)
VP			✓	✓	Less Prevalent
HCP			✓	✓	Less Prevalent
ADP	All recorded symptomatic patients have been male	Variable	✓		Least Prevalent <10 cases ever reported worldwide

More prevalent

- 1. Ramanujam & Anderson. *Curr Protoc Hum Genet* 2015;86:1–263; 2. Elder et al. *J Inherit Metab Dis* 2013;36:849–57

Pathophysiology

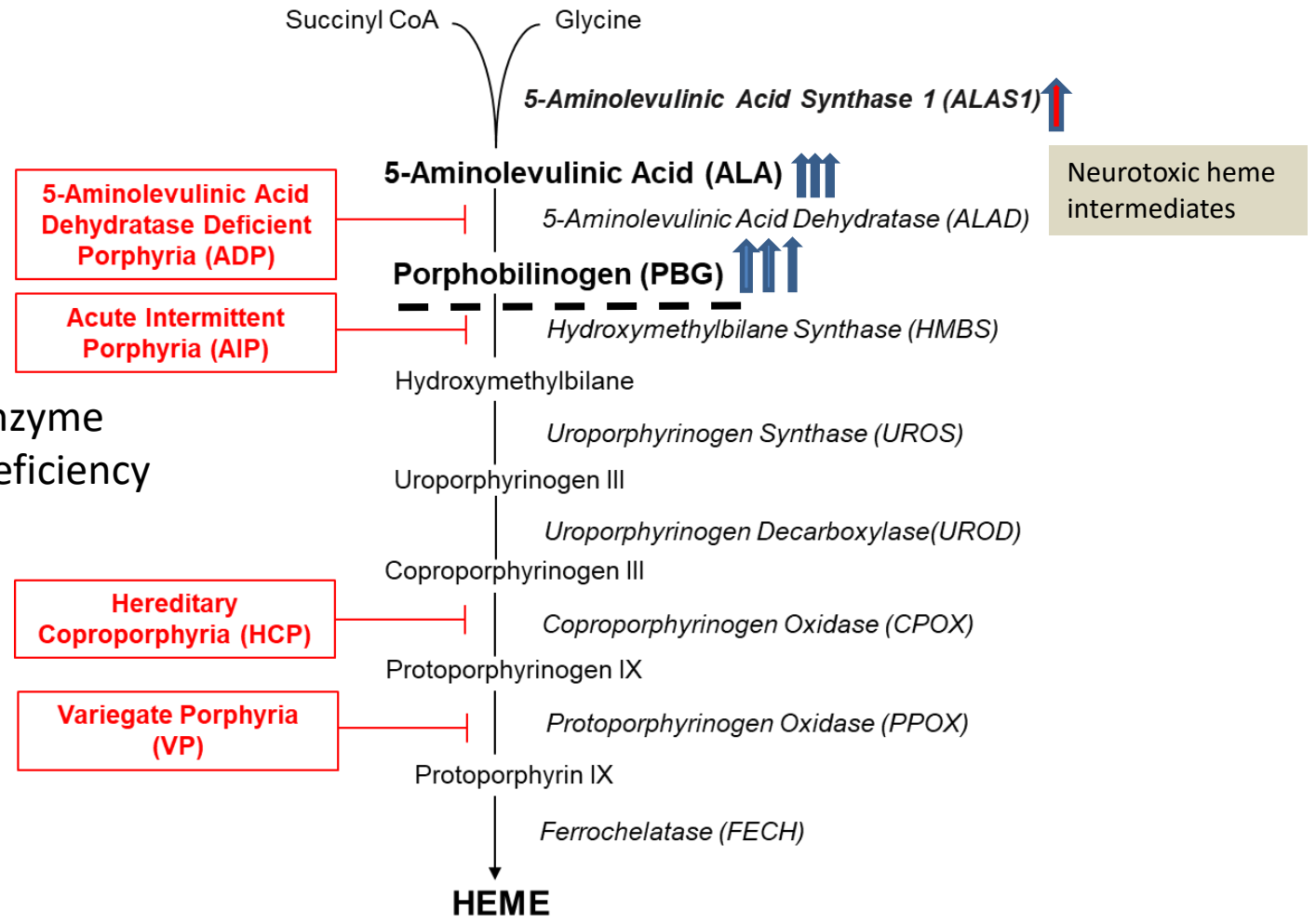
Direct or indirect ALAS1 induction

Promoting ALAS1 transcription
e.g Fasting or dieting
Alcohol

Increased Heme consumption
e.g cytochrome p-450 inducing drugs, infections, stress

Endogenous or exogenous progesterone

Enzyme Deficiency



Yasuda et al, Blood 2023

Acute Hepatic Porphyria

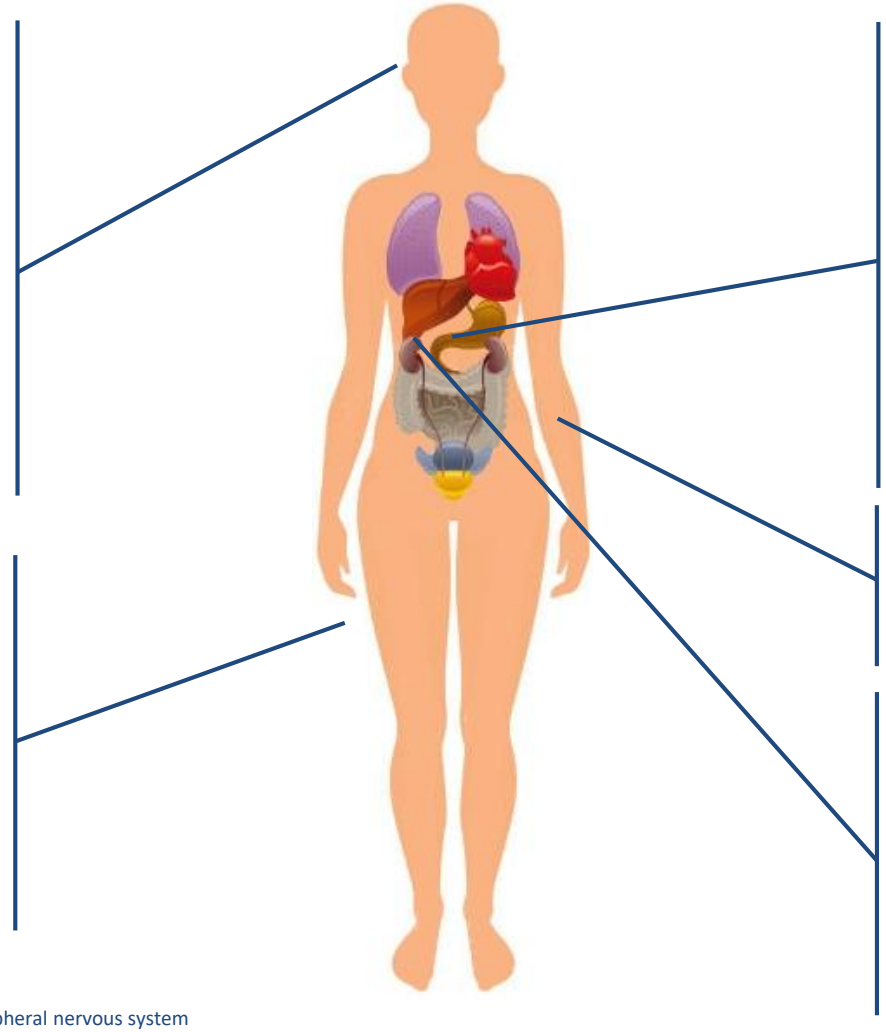
Clinical Characteristics

CNS Manifestations

- Confusion
- Anxiety
- Memory loss
- Depression
- Tiredness
- Hallucinations[a]
- Seizures[a]

PNS Manifestations

- Neuropathic pain
- Sensory loss
- Muscle weakness
- Paralysis[a]
- Respiratory failure[a]



ANS Manifestations

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

Cutaneous Manifestations[b]

- Lesions on sun-exposed skin

Long-Term Complications

- Hepatocellular carcinoma
- Chronic kidney disease (CKD)
- Neuronal damage
- Hypertension

- [a]Only occurs in severe cases. [b]Only occurs in VP and HCP
- ANS, autonomic nervous system; CNS, central nervous system; PNS, peripheral nervous system
- Anderson et al. *Ann Intern Med* 2005;142:439–50; Gouya et al. Presented at the International Liver Congress, April 2018; Pischik & Kauppinen. *Appl Clin Genet* 2015;8:201–14; Simon et al. *Patient* 2018;11:527–37

AHPs: Longitudinal study of the Porphyrias

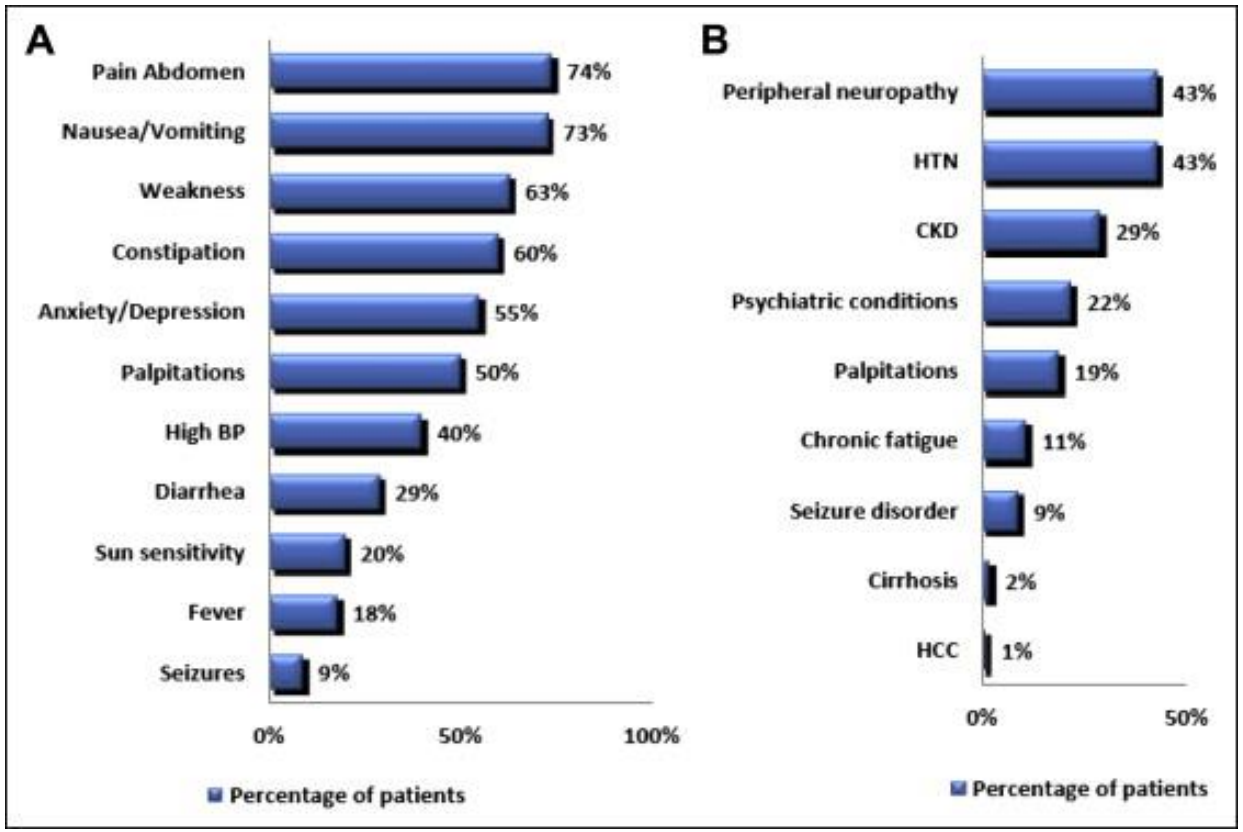


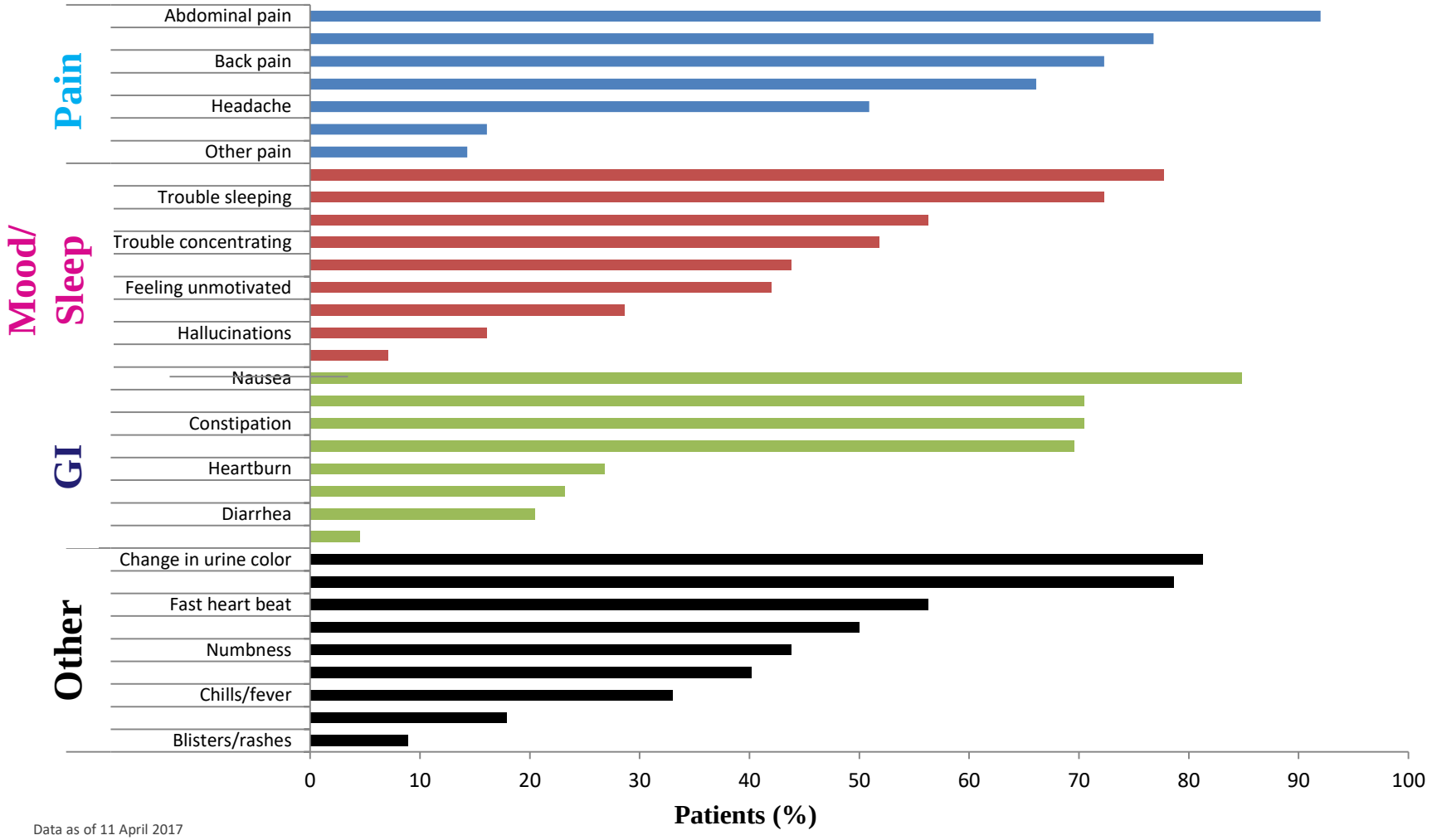
Figure 1. (A) Symptoms and signs during acute attacks in acute intermittent porphyria. (B) Medical conditions associated with acute intermittent porphyria. BP = blood pressure; CKD = chronic kidney disease; HCC = hepatocellular carcinoma; HTN = hypertension.

Bonkovsky HL et al, The Am Journal of Medicine, 2014

EXPLORE Natural History Study

Baseline Patient-Reported Attack Symptoms

- Symptoms reported by > 80% of patients: abdominal pain, nausea, change in urine color

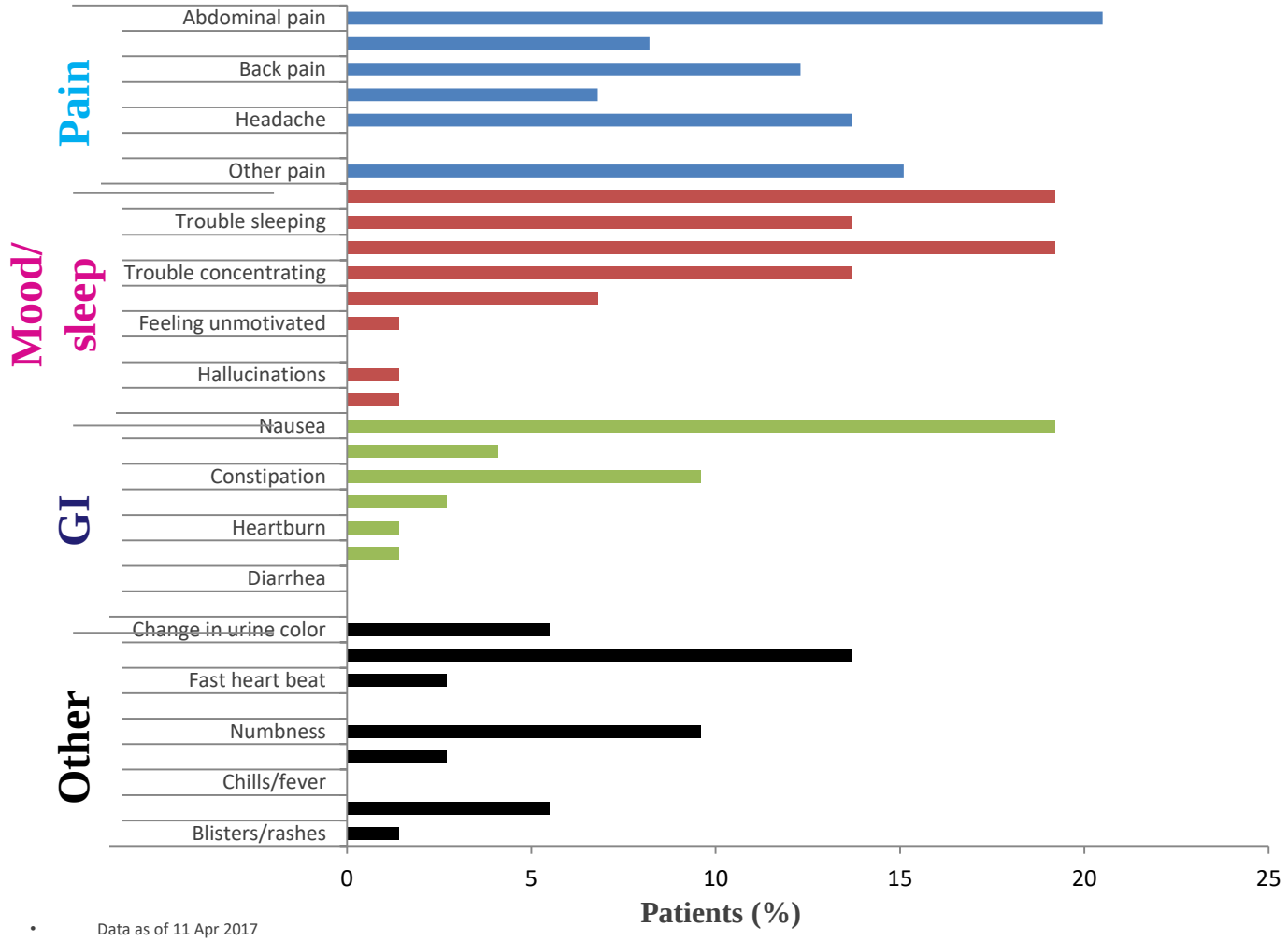


- Data as of 11 April 2017

EXPLORE Natural History Study

Baseline Patient-Reported Chronic Symptoms

- 65% patients with chronic symptoms, most commonly pain, tiredness, anxiety and nausea, with 46% reporting daily symptoms



- Data as of 11 Apr 2017

Symptoms during acute attacks

Symptoms during acute attacks[†]	Laboratory or Imaging findings
Abdominal pain	Elevated urine/plasma porphobilinogen and aminolevulinic acid[‡§]
Nausea	Elevated creatinine and BUN[ß]
Vomiting	Elevated liver enzymes[ß]
Constipation	Posterior reversible encephalopathy syndrome[ß]
Chest, back or leg pain	Hyponatremia[ß]
Hypertension	
Tachycardia	
Muscle weakness	
Fatigue	
Urinary retention	
Peripheral neuropathy	
Tonic-clonic seizures	
Confusion	
Hallucinations	

[†]Patients may present with a combination of symptoms, most commonly abdominal pain.
[‡]Seen in all patients during acute attacks with levels typically >10 times the upper limit of normal although in some cases, particularly with VP and HCP, elevations between 4-10 times upper limit of normal may be seen. In ADP, only urine and plasma ALA are elevated; PBG is normal. [§]Samples should be corrected to urine creatinine.
[ß]May or may not be present during acute attacks.

Balwani et al, Liver Int, in press

Most common misdiagnoses

Urinary tract infection
Appendicitis
Acute pancreatitis
Cholecystitis
Irritable bowel syndrome
Ovarian cyst
Endometriosis
Gastrointestinal illness

Appendectomy
Cholecystectomy
Laparoscopic surgery
Colonoscopy
Endoscopy
CT scan abdomen/pelvis
MRI abdomen
MRI brain

Diagnostic testing

Biochemical Testing

- **AHP is diagnosed with random (spot) urine tests for ALA, Porphobilinogen (PBG)***
- 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
- Additional biochemical tests can be performed to confirm diagnosis and AHP type

Genetic Testing

- Genetic testing can be performed to 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 creatine

➢ 1. Bonkovsky et al. *Am J Med* 2014;127:1233–41; 2. Anderson et al. *Ann Intern Med* 2005;142:439–50; 3. Whatley & Badminton. Acute Intermittent Porphyria. In: GeneReviews. Seattle, WA: University of Washington, Seattle; Updated 2013

Report

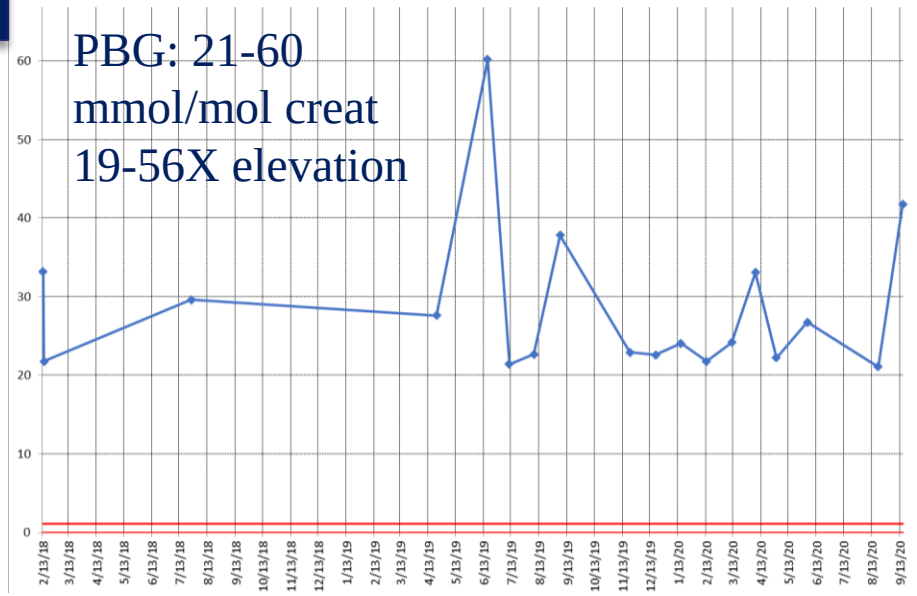
RESULT SUMMARY

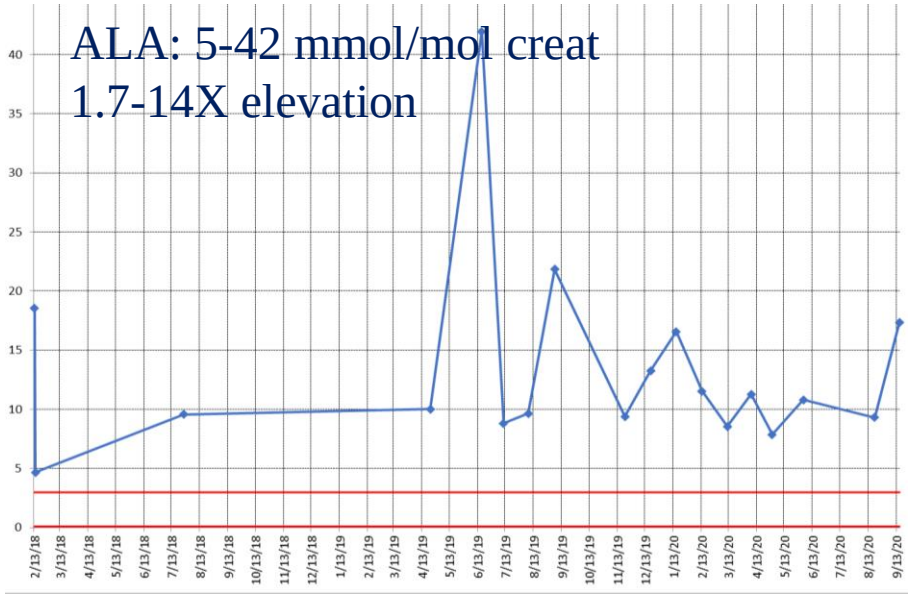
	mmol/mol creat.	Normal	Note
Aminolevulinic Acid	41.97	0.09 - 2.97	HH
Porphobilinogen	60.17	0 - 1.08	HH

HH –very high, H –high, L-low, ND-not detected

Interpretation
Follow up study of a known AIP patient. Urinary 5-aminolevulinic acid (ALA) and porphobilinogen (PBG) levels are highly elevated and higher than previous. Recommend clinical correlation.

Test Method and Comments
5-aminolevulinic acid (ALA) and porphobilinogen (PBG) levels are measured by a liquid chromatography tandem mass spectrometry (LC-MS/MS) method. The test is clinically utilized for screening patients suspected of acute porphyria, as well as long term monitoring of confirmed porphyria patients for management.





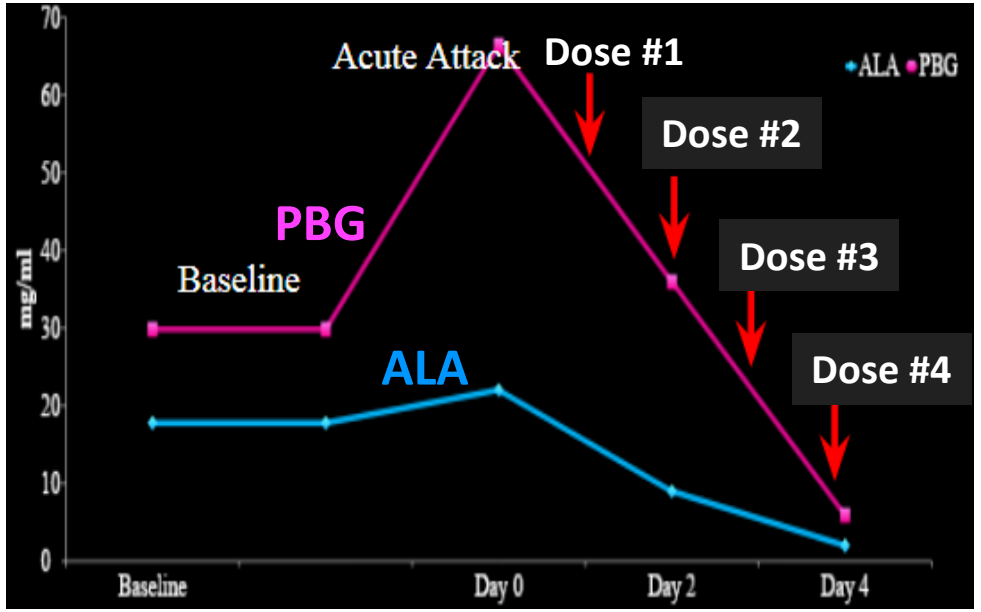
EPIC order:
Aminolevulinic Acid (ALA) and Porphobilinogen (PBG), Urine
Alias: Urine ALA and PBG
Collect 5 mL random urine in amber cup or tube, minimum of 0.5 mL

Inpatient Management

- Identify and remove known triggers
- Check drug database prior to administering new medication
- Send urine porphobilinogen and blood work
- Supportive care including pain medications
- **Start hemin:** First-line treatment for acute attacks
- **Hemin (Panhematin®) dose:** 3-4mg/kg daily x 4 days or accordingly based on clinical response
- **Start IV dextrose:** D5 or D10 ½ NS (300 gm/24 hr) while waiting for hemin

Hemin therapy

- Heme-arginate in Europe (Normosang®)
- Lyophylized hemin in USA (Panhematin®)
- Indication - acute attacks
- Albumin stabilizes hemin & reduces side effects
- Adverse effects
  - Thrombophlebitis
    - Large bore IV or CVC
  - Coagulation abnormalities
  - Secondary iron overload
    - 100 mg contains ~ 8 mg elemental iron



Bonkovsky HL. et al. PNAS 1971:68.
Lamon JM. et al. Lancet 1978:312.
Anderson KE. et al. Intern Med 2006:144.

Management approaches for AHPs

Symptomatic and supportive management

Treatment of AHP symptoms

Patients with AHP often receive medications for symptoms including but not limited to, nausea, hypertension, neuropathy, anxiety, and depression

Pain medications

Patients with AHP are commonly prescribed opioid and non-opioid pain medications

Hormone therapy

GnRH agonists may be used chronically for women experiencing an acute attack related to their menstrual cycles

- GnRH, gonadotropin-releasing hormone
- 1. Balwani M, et al. *Hepatology.* 2017;66(4):1314-1322. 2. Wang. Acute Hepatic Porphyrias: Review and Recent Progress. Hepatol Commun. 2018 Dec 20;3(2):193-206. 3. PANHEMATIN [Package Insert]. Lebanon, NJ: Recordati Rare Diseases, Inc; 2017. 4. Anderson, KE. *Mol Genet and Metab*, https://doi.org/10.1016/j.ymgme.2019.07.002.

Management approaches for AHPs

Disease specific treatment

Hemin

Approved for the treatment of AHP attacks and is also used on-demand or prophylactically

Givosiran

Small interfering RNA indicated for the treatment of adults with AHP

Liver transplantation

Liver transplantation is reserved for patients with intractable acute attacks which are not responsive to other therapies

Hemin therapy

Hemin therapy

Challenges

Difficult to set up infusion locally

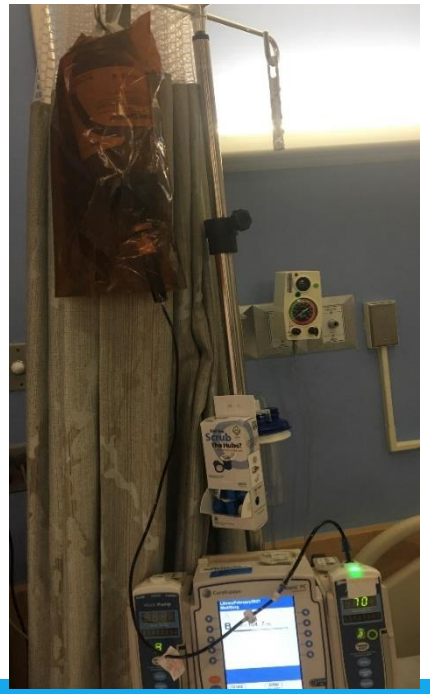
Not available at all ED/hospitals

Long-term complications: iron overload and hepatic fibrosis

Monitoring

Ferritin

Liver enzymes



Outpatient vs. Inpatient Hemin Therapy

OUTPATIENT

- Patients who can identify prodromal symptoms
- Abdominal pain
- Nausea without vomiting

INPATIENT

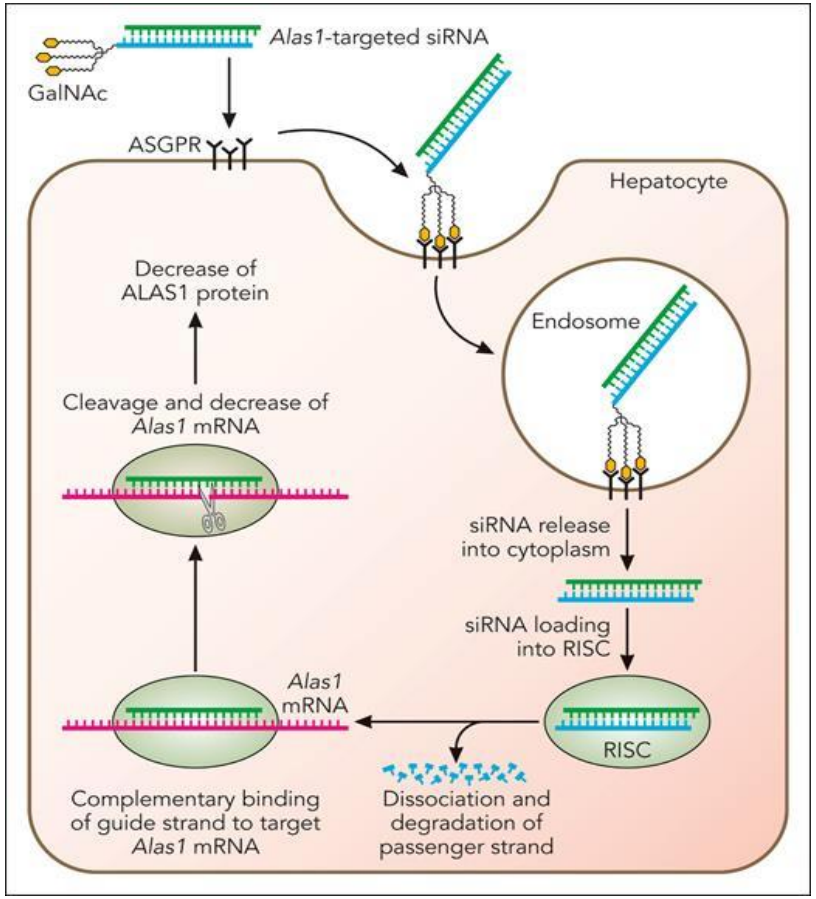
- Severe abdominal pain
- Requiring opioid analgesic
- Vomiting
- Hypertension
- Tachycardia

Frequency of Acute Neurovisceral Attacks

- **Recurrent attacks**: >4 attacks/year
  - Can have monthly attacks (women during the luteal phase of menstrual cycle)
- **Sporadic Attacks:** < 4 attacks/year
- **Asymptomatic High Excretors (ASHE)/Chronic High Excretors (CHE):**
  - Clinically asymptomatic with high levels of ALA and PBG (may have a history of previous attack)
- **Latent:**
  - Normal ALA and PBG levels

Givosiran: siRNA-mediated silencing of hepatocyte Alas1

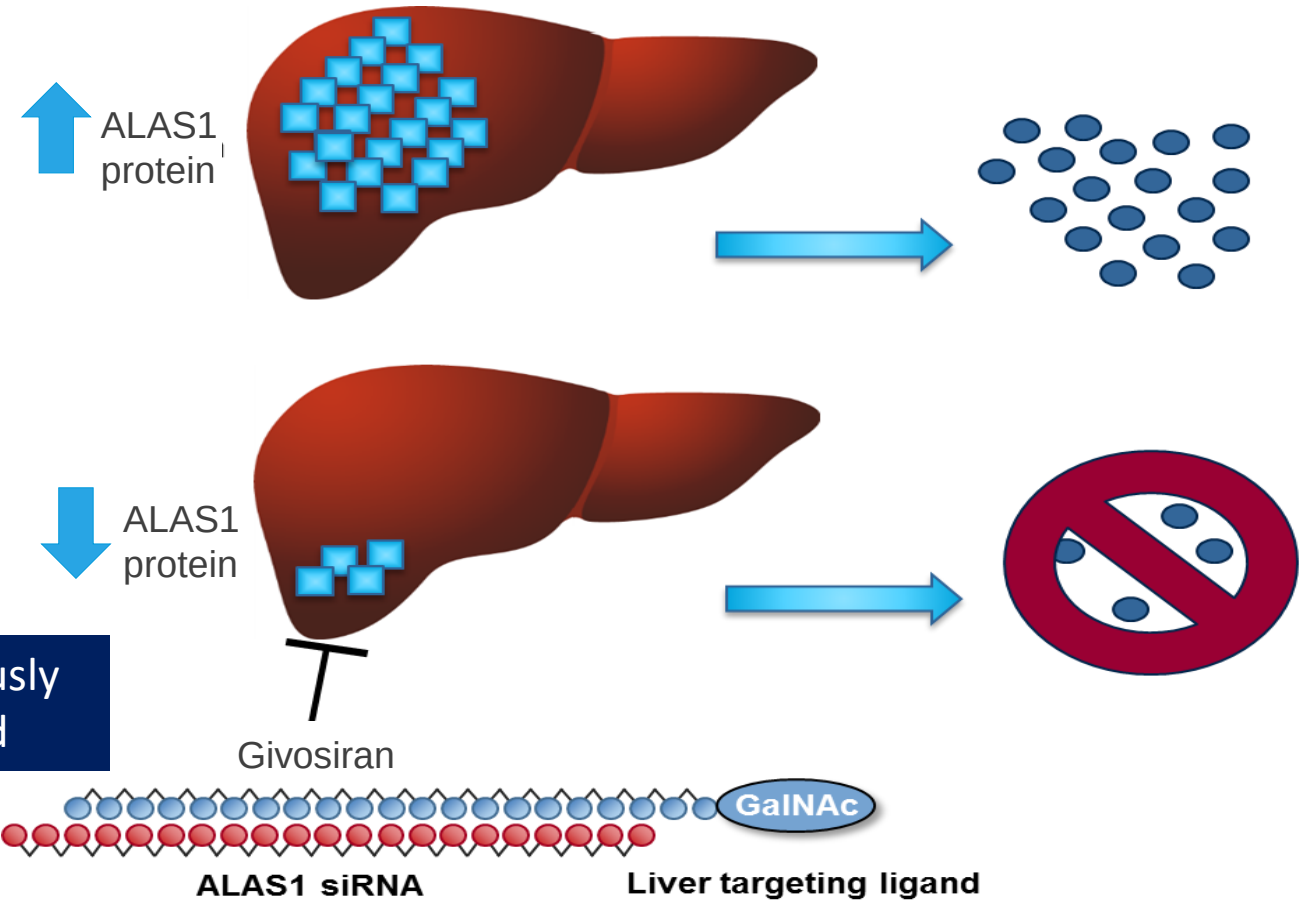
Givosiran is a double-stranded small interfering RNA that causes degradation of aminolevulinate synthase 1 (*ALAS1*) mRNA in hepatocytes through RNA interference



- RNAi is a natural biological process that regulates gene expression by "interfering" with messenger RNA (mRNA)
- RNAi therapeutics mimic this process by delivering specially designed small interfering RNAs (siRNAs) which bind to target disease-causing mRNA and guide their destruction

Makiko Yasuda,Siobán Keel,Manisha Balwani, RNA interference therapy in acute hepatic porphyrias, Blood, 2023

Mechanism of action of Givosiran

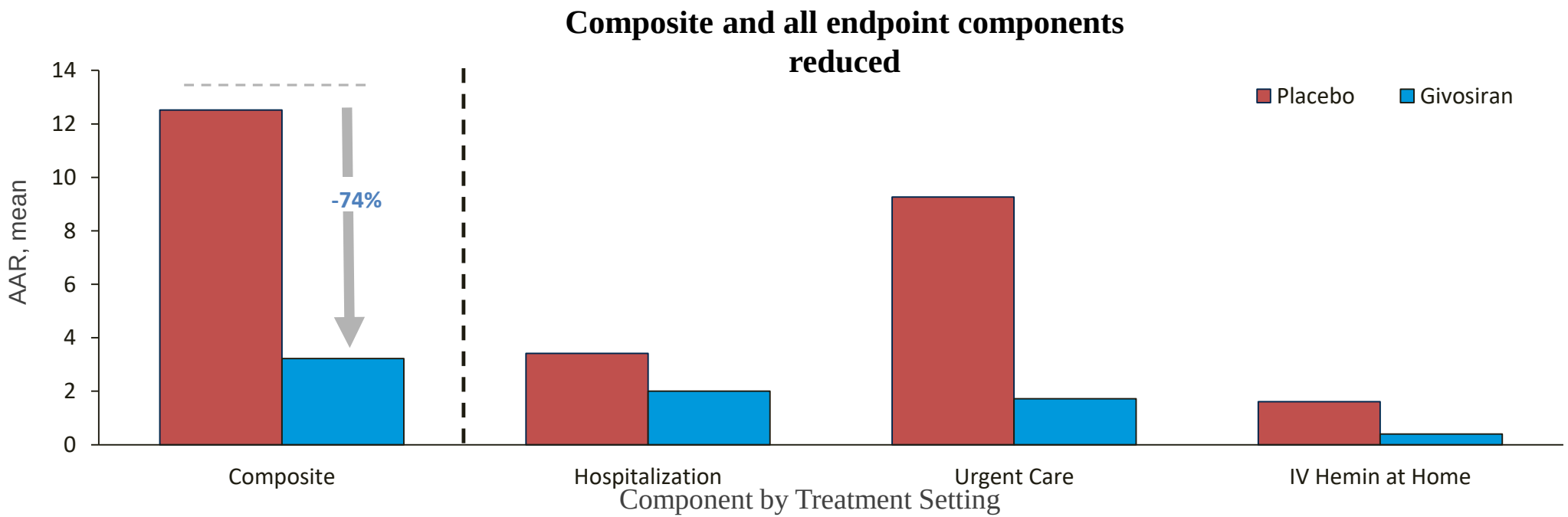


ALA and PBG are neurotoxic intermediates associated with attacks or other disease manifestations

Givosiran reduces the elevated levels of liver ALAS1 mRNA. This leads to reduced circulating levels of ALA and PBG

Phase 3 clinical trial: Primary Efficacy Endpoint: Annualized Attack Rate (AAR) in Patients with AIP

Primary Endpoint	Givosiran (N=46)	Placebo (N=43)	Rate Ratio (95% CI) (givosiran vs placebo)	P-Value
Composite AAR, mean (95% CI)	3.2 (2.25, 4.59)	12.5 (9.35, 16.76)	0.26 (0.16, 0.41)	6.04×10^{-9}



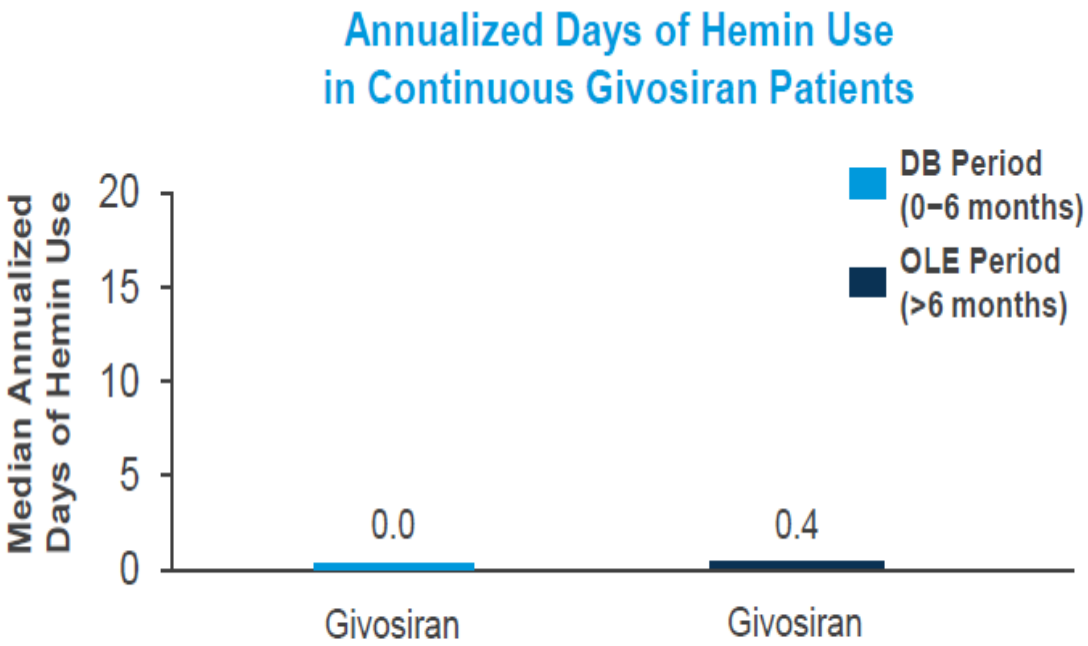
The efficacy data described above, based on data from the ENVISION study as reported in September 2019, may differ from the efficacy data contained in the U.S. Prescribing Information for GIVLAARI

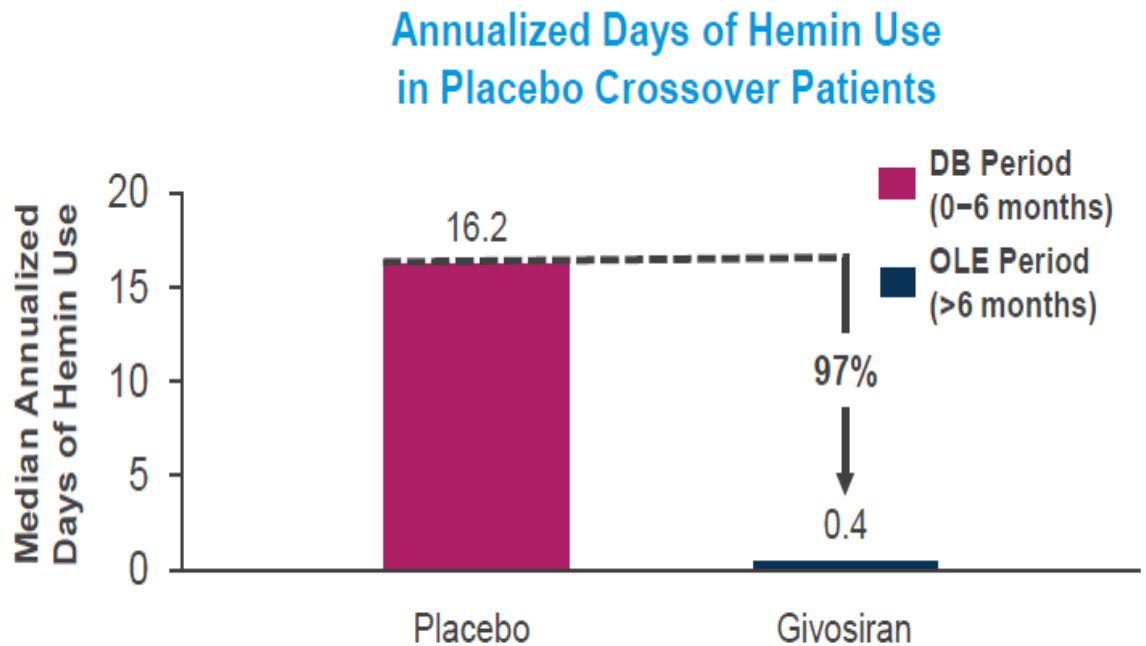
Mean AAR was derived using the negative binomial regression model; mean AAR for components was duration-weighted AAR; median AAR was calculated from the individual's patient's AAR

Gouya et al. Presented at the International Congress on Porphyrins and Porphyrias, September 2019

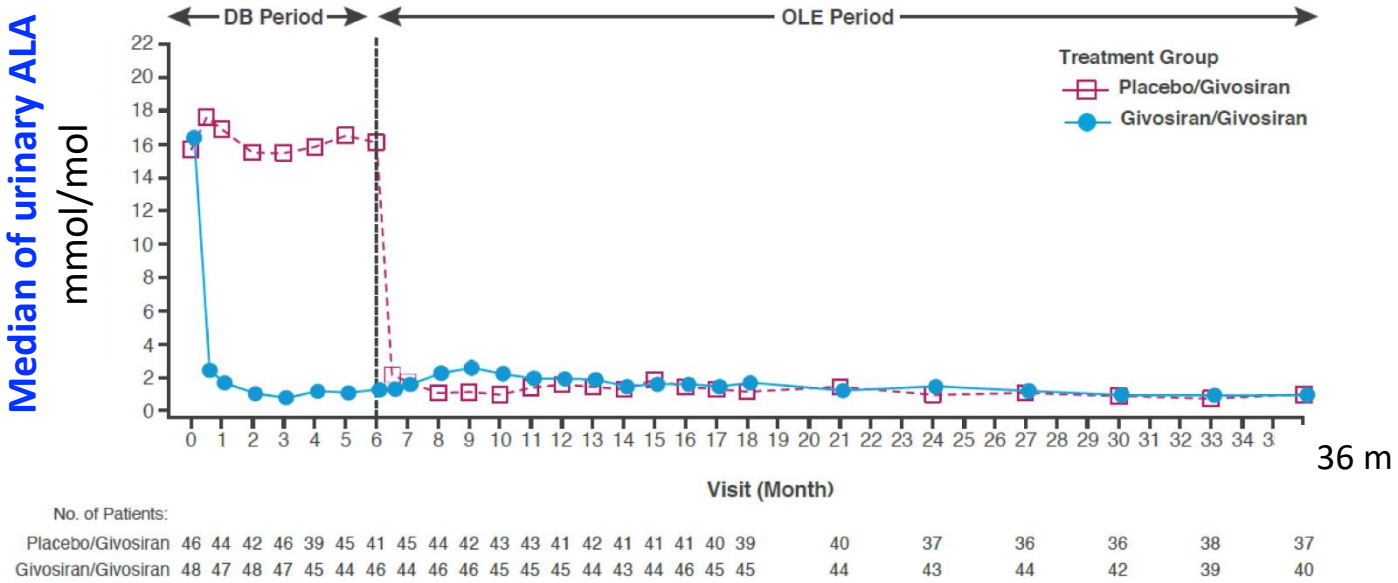
Results: Hemin Use

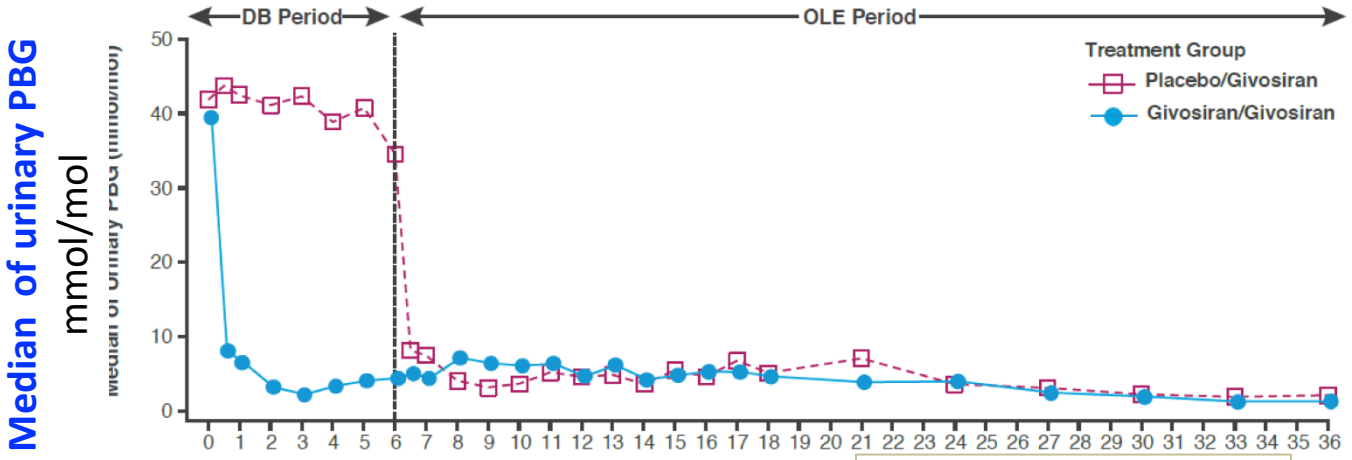
The proportion of patients with no days of hemin use increased over time in the continuous givosiran group and placebo crossover group



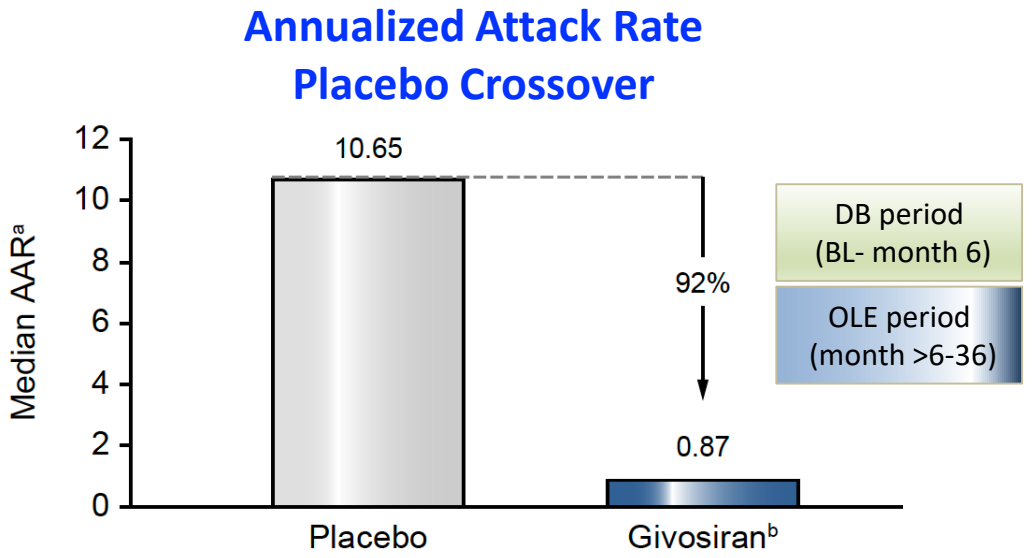


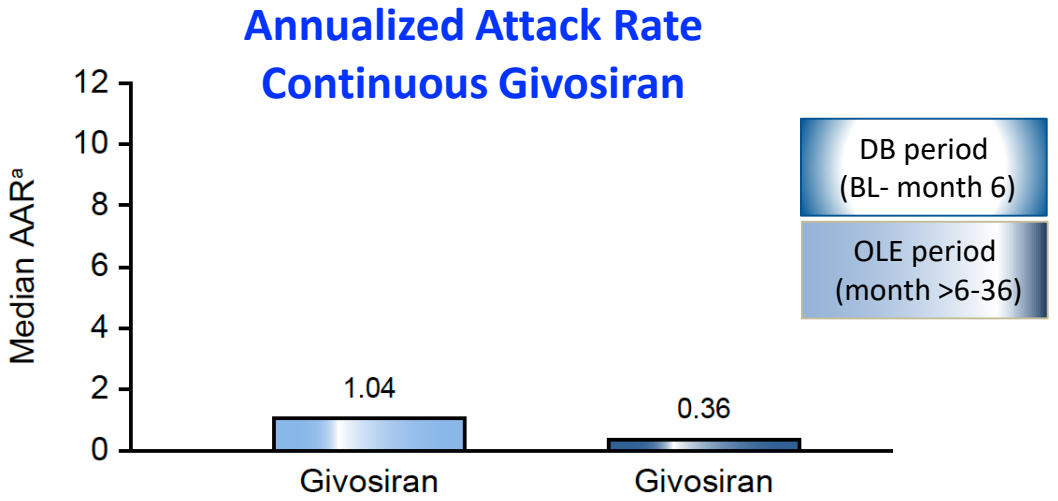
Givosiran biochemical and clinical responses





Reference ranges
ALA ULN 1.47 mmol/mol Cr
PBG ULN 0.137 mmol/mol Cr



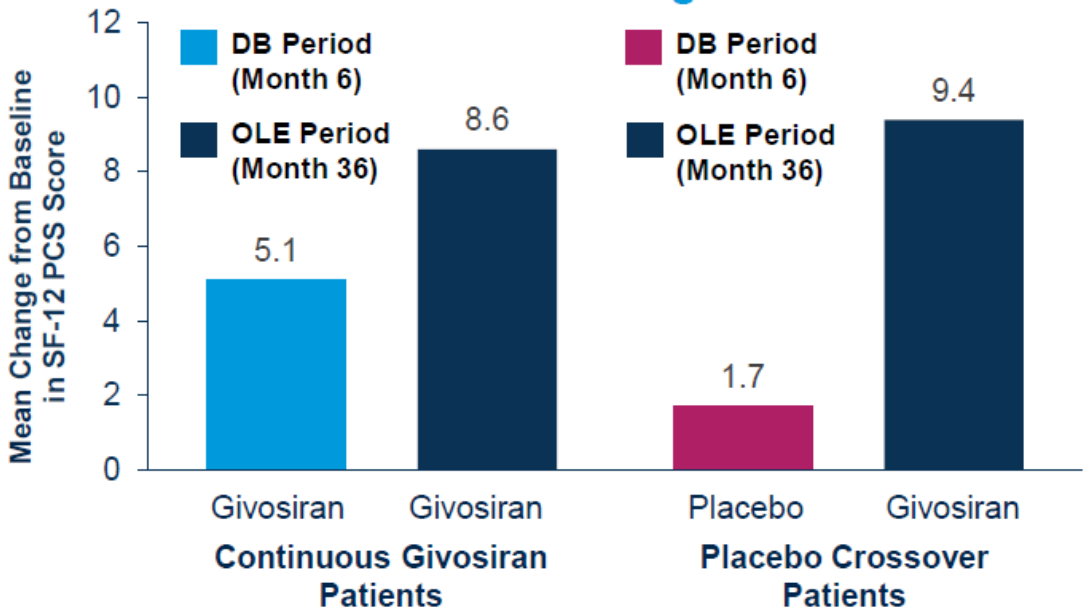


Adapted from Kuter D. et al. Hepatology 2023:

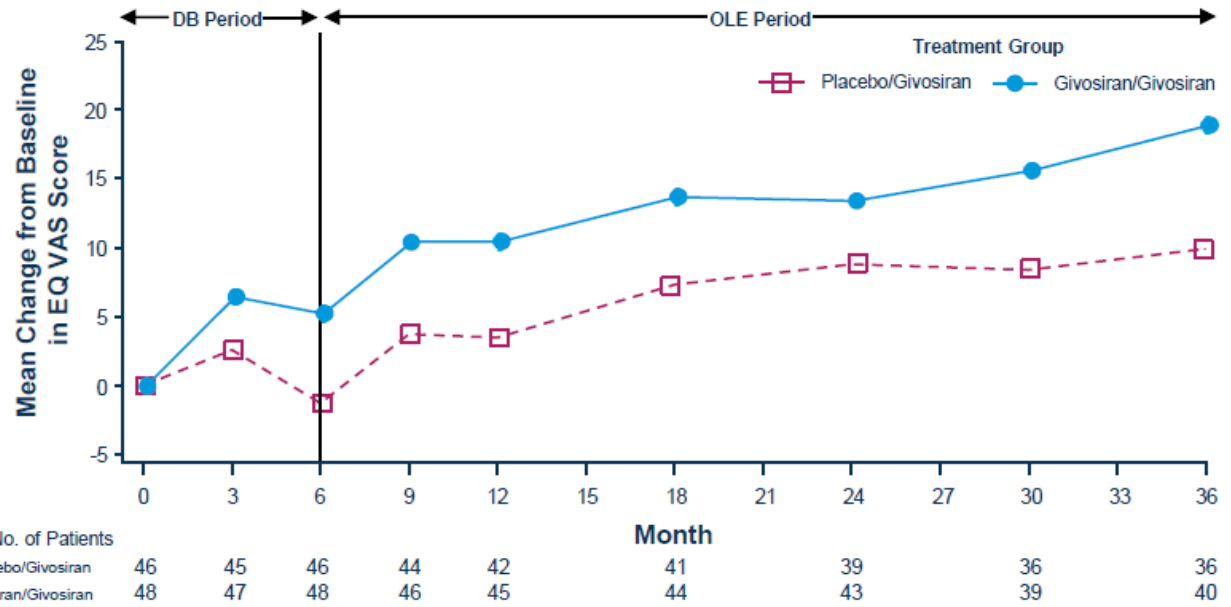
Results: Quality of Life

With givosiran, patients experienced improvements in QOL, as reflected in SF-12 PCS scores and EQ-VAS scores

Mean Change in SF-12 PCS Scores from Baseline through OLE Period[a]



Mean Change in EQ-VAS Scores from Baseline through OLE Period[b]



[a]Estimates for the clinically meaningful difference are ≥2 to 5 points for SF-12 PCS, based on published data for other chronic diseases.[1,2]
[b]Estimates for the clinically meaningful difference are ≥7 to 8 points for EQ-VAS, based on published data for other chronic diseases.[3,4]

DB, double-blind; EQ-VAS, EuroQol visual analog scale; OLE, open-label extension; PCS, Physical Component Summary; QOL, quality of life; SF-12, Short Form (12-item) Health Survey.

1. Clement ND, et al. *Knee Surg Sports Traumatol Arthrosc*. 2014;22(8):1933-1939. **2.** Parker SL, et al. *J Neurosurg Spine*. 2012;16(5):471-478.
3. Zanini A, et al. *Respir Care*. 2015;60(1):88-95. **4.** Nolan CM, et al. *Thorax*. 2016;71(6):493-500.

Side effects of givosiran

Potential side-effects	Givosiran vs. Placebo treated
Nausea	27% vs. 11%
Injection site reactions	25% vs. 0%
ALT>3X ULN	15% vs. 2%
Increased creatinine or decreased eGFR	15% vs. 4%
Elevated homocysteine	Not reported in this study
Drug-drug interactions	Not reported in this study

Adapted from Balwani M. et al. NEJM 2020: 382.

- **Drug interactions:**

CYP1A2 and CYP2D6 substrates

- **Not recommended in pregnancy or in breast feeding individuals**

*FULL PRESCRIBING INFORMATION:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/0212194s000lbl.pdf

Sardh E. et al. NEJM 2019:380.
Balwani M.,…, Keel SB, et al. 2020:382.
Kuter D. et al. Hepatology 2023: Online ahead of print
Agarwal S. et al. Clinic Pharm Ther 2020:108.

Liver enzyme abnormalities

- **ENVISION long-term follow-up (36 months)**
  - 11% (10/94) had ALT >3X ULN and 3% (3/94) had ALT >5X ULN
  - Generally occurred after ~ 3-6 months of therapy and resolved over time
- **Real world experience**

  French retrospective study of 25 AIP patient (7/25 on ENVISION)
  - ALT elevations in 32% (8/25)
    - 5 ≤ 2 X ULN; 2, 4-5 X ULN; 1, 2, 5X ULN
  - If ALT elevations ≤ 5X ULN →

    all resolved with continued dosing

Kuter D. et al. Hepatology 2023: Online ahead of print.
Poli A. et al. Molec Genet and Metab 2022:135.

Renal function abnormalities

- **ENVISION long-term follow-up (36 months)**

DB period @ 3 months:
Median creatinine rise
0.07 mg/dL in givosiran tx

OLE @ 36 months
No renal AE led to tx discontinuation

eGFR

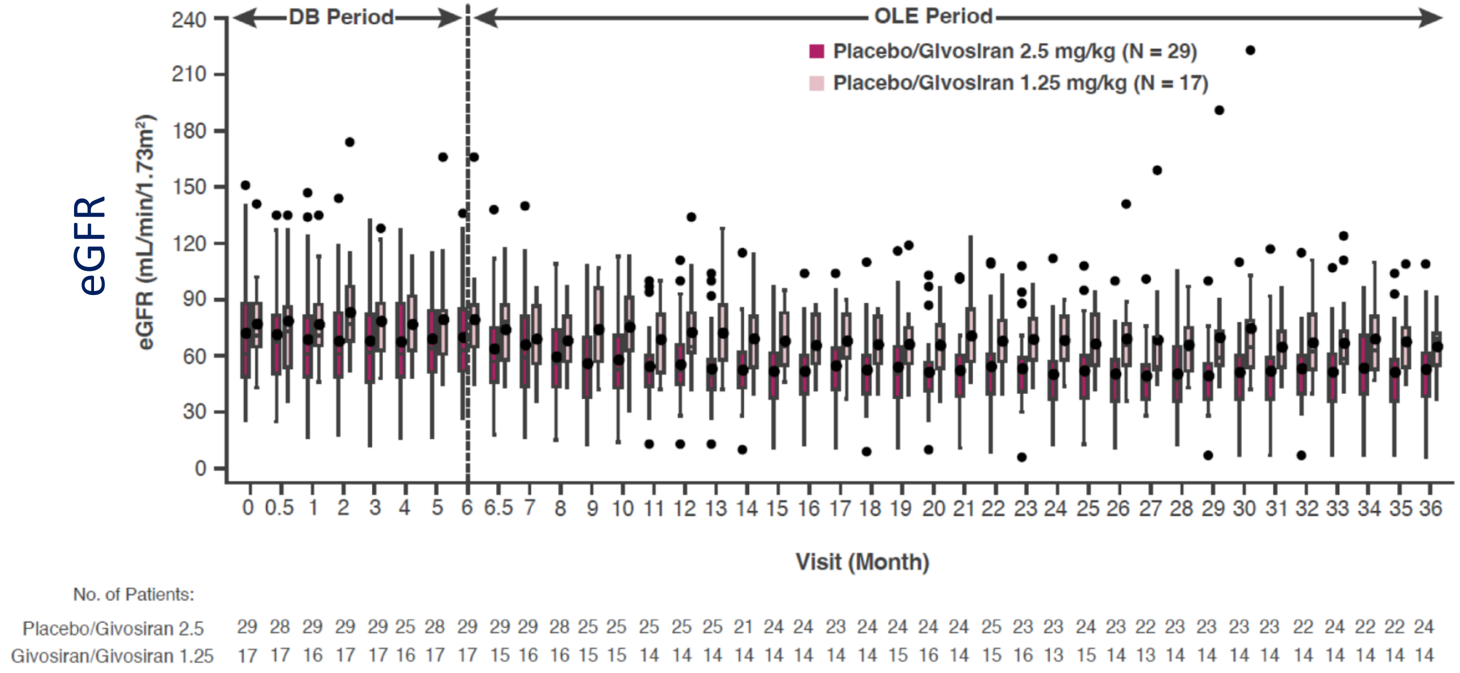


Figure adapted from Kuter D. et al. Hepatology 2023: Online ahead of print
Balwani M. et al. NEJM 2020: 382

- **Real world experience**

  French retrospective study of 20 AIP patients (7/20 on ENVISION)

  – Transient decline in renal function in 90% (18/20) within 3 m therapy

  – **Suggestion those with baseline renal dysfunction may face a higher risk**

Kuter D. et al. Hepatology 2023: Online ahead of print.
Lazareth H. et al. Kidney Int Rep 2021:6.

Unanswered Questions

- *Are there negative consequences of sustained ALAS1 suppression?*
- *Why are plasma homocysteine levels elevated in AHP patients, how does givosiran impact homocysteine metabolism, and what is the clinical significance of this hyperhomocysteinemia?*
- *Will givosiran impact the long-term complications of chronic pain and chronic kidney and liver disease in the AHPs?*
- *Is there a role for givosiran in the treatment of acute attacks in patients with AHP?*
- *Can givosiran be safely administered to pregnant individuals*?

Yasuda et al. Blood 2023

Long Term Complications: Kidney disease

- Porphyria associated kidney disease (PAKD) occurs in >50% of symptomatic patients.
  -60% of pts with PAKD have HTN
- PEPT2 1*1* variant predicts increased risk of renal disease
- Pathology: chronic tubulo-interstitial changes
- Kidney transplant is well tolerated in patients with ESRD
- Acute attack symptoms can improve after kidney transplant

1. Pallet N, Karras A, Thervet E, Gouya L, Karim Z, Puy H. Porphyria and kidney diseases. Clinical kidney journal. 2018;11(2):191-197. doi:10.1093/ckj/sfx146
2. Tchernitchko D, Tavernier Q, Lamoril J, et al. A Variant of Peptide Transporter 2 Predicts the Severity of Porphyria-Associated Kidney Disease. Journal of the American Society of Nephrology. 2017;28(6):1924-1932. doi:10.1681/asn.2016080918
3. Lazareth H, Talbi N, Kamar N, Levi C, Moulin B, Caillard S, Frimat L, Chemouny J, Chatelet V, Vachey C, Snanoudj R, Lefebvre T, Karras A, Gouya L, Schmitt C, Puy H, Pallet N. Kidney transplantation improves the clinical outcomes of Acute Intermittent Porphyria. Mol Genet Metab. 2020 Sep-Oct;131(1-2):259-266

Long Term Complications: Liver Disease

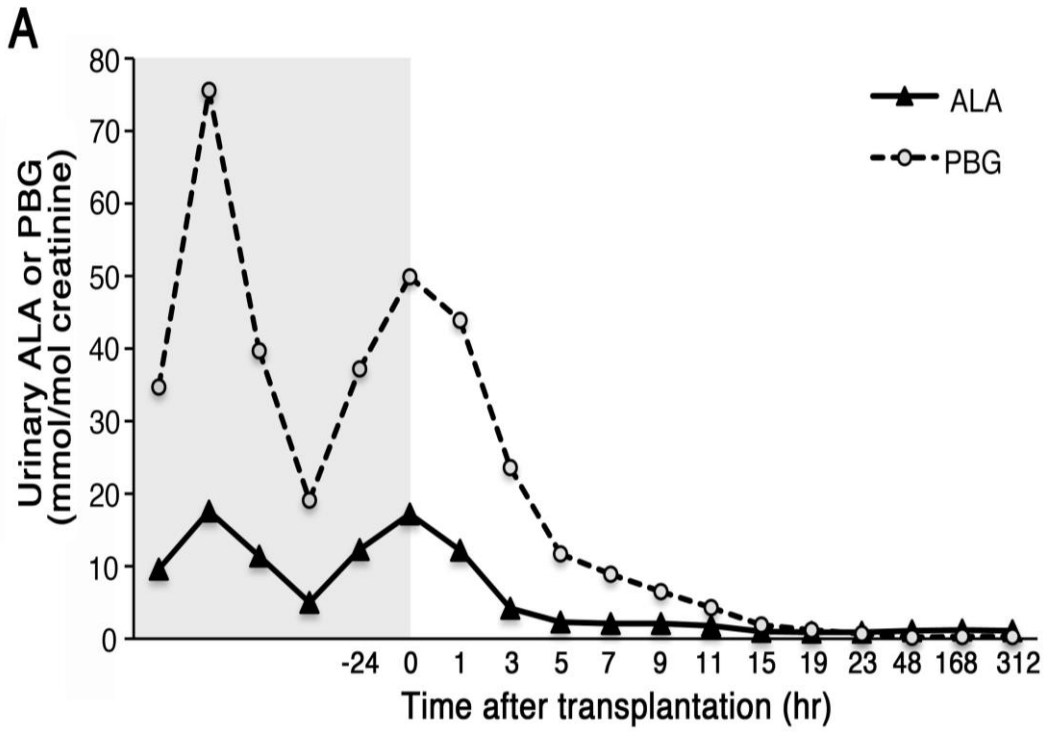
Liver disease

- Increased risk of developing Primary Liver Cancer
- Chronic increased ALA levels could lead to free radical generation → hepatic carcinogenesis
- Increased risk of HCC (1.5%) in a US study
  - Occurred in the absence of cirrhosis or fibrosis
- HCC surveillance recommended starting at age 50
- Risk of fibrosis and chronic inflammatory hepatic disease with frequent hemin use

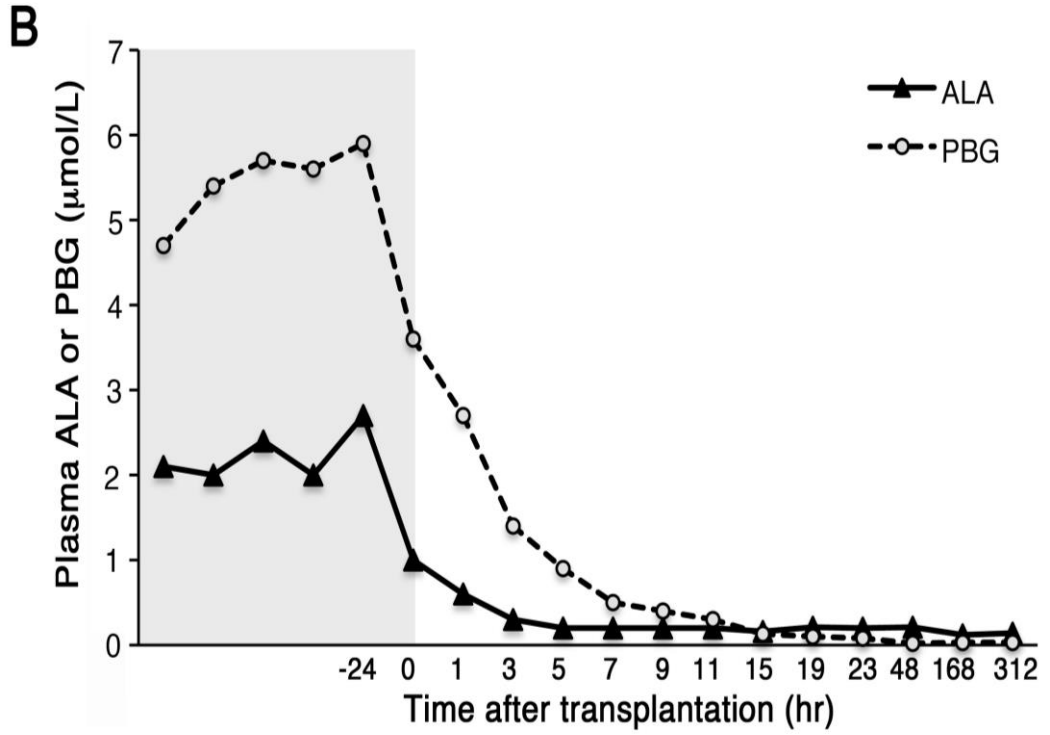
1. Andant C, Puy H, Bogard C, et al. Hepatocellular carcinoma in patients with acute hepatic porphyria: frequency of occurrence and related factors. Journal of hepatology. 2000;32(6):933-939. doi:10.1016/S0168-8278(00)80097-5
2. Saberi B, Naik H, Overbey JR, et al. Hepatocellular Carcinoma in Acute Hepatic Porphyrias: Results from the Longitudinal Study of the U.S. Porphyrias Consortium. Hepatology (Baltimore, Md). Published online July 18, 2020. doi:10.1002/hep.31460
3. Schmitt C, Lenglet H, Yu A, et al. Recurrent attacks of acute hepatic porphyria: major role of the chronic inflammatory response in the liver. Journal of internal medicine. 2018;284(1):78-91. doi:10.1111/joim.12750
4. Katell Peoc'h, Hana Manceau, Zoubida Karim, Staffan Wahlin, Laurent Gouya, Hervé Puy, Jean-Charles Deybach,Hepatocellular carcinoma in acute hepatic porphyrias: A Damocles Sword, Molecular Genetics and Metabolism, Volume 128, Issue 3, 2019,

Liver Transplantation Rapidly Normalized Plasma and Urinary ALA & PBG

Liver Transplant



Liver Transplant



Yasuda M, Erwin AL, Liu LU, et al. Liver Transplantation for Acute Intermittent Porphyria: Biochemical and Pathologic Studies of the Explanted Liver. Mol Med. 2015;21(1):487-495. Published 2015 Jun 5. doi:10.2119/molmed.2015.00099

Recommendations for Follow Up

Acute Hepatic Porphyrias: Recommendations for Evaluation and Long Term Management

Manisha Balwani, MD, MS[1], Bruce Wang, MD[2], Karl E. Anderson, MD[3], Joseph R. Bloomer, MD[4], D. Montgomery Bissell, MD[2], Herbert L. Bonkovsky, MD[5], John D. Phillips, PhD[6], and Robert J. Desnick, PhD, MD[1] for the Porphyrias Consortium of the Rare Diseases Clinical Research Network

TABLE 2. Follow-Up Assessments

			Sporadic and Recurrent Attacks		
	Latent	ASHE Every 12 Months	Every 3 Months	Every 6 Months	Every 12 Months
Medical history	As clinically indicated	X			X
Physical examination		X			X
Medication review		X			X
Quality of life		X			X
Biochemical tests					
Urine ALA and PBG		X			X
Additional laboratory tests					
CBC		X			X
CMP with eGFR		X			X
Hepatic function panel		X			X
Monitoring for HCC (>50 years)					
Liver US		X		X	
AFP		X		X	

CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Diagnosis and Management of Acute Hepatic Porphyrias: Expert Review

Bruce Wang,[1] Herbert L. Bonkovsky,[2] Joseph K. Lim,[3] and Manisha Balwani[4]

Table 2. Testing Recommendations for Acute Hepatic Porphyrias

Diagnostic biochemical testing	Confirmatory testing	Annual Monitoring	Monitoring on hemin[a]	Monitoring on givosiran[a,b]
Random urine PBG, ALA, and creatinine[c]	Genetic testing by sequencing *ALAD*, *HMBS*, *CPOX*, and *PPOX*	Liver enzymes, creatinine and eGFR, liver ultrasound, and α-fetoprotein every 6 mo after age 50 y	Iron, ferritin	Comprehensive metabolic panel, plasma homocysteine urinalysis; urinary protein to creatinine ratio, B12/folate, amylase/lipase

[a]Additional tests for patients receiving prophylactic hemin therapy or givosiran.
[b]We advise that the listed tests be performed before the start of givosiran and again just before each monthly injection of givosiran for 3 months. If the laboratory test results are stable and the drug is being well-tolerated, we advise that laboratory monitoring be repeated once every 3 months for the next year and at least once every 6 months thereafter.
[c]Sample should be normalized to creatinine, levels should be >5-fold the upper limit of normal for diagnosis. In 5-aminolevulinic acid dehydratase only ALA is elevated.

Balwani et al Hepatology 2017, Wang et al Gastroenterology 2023

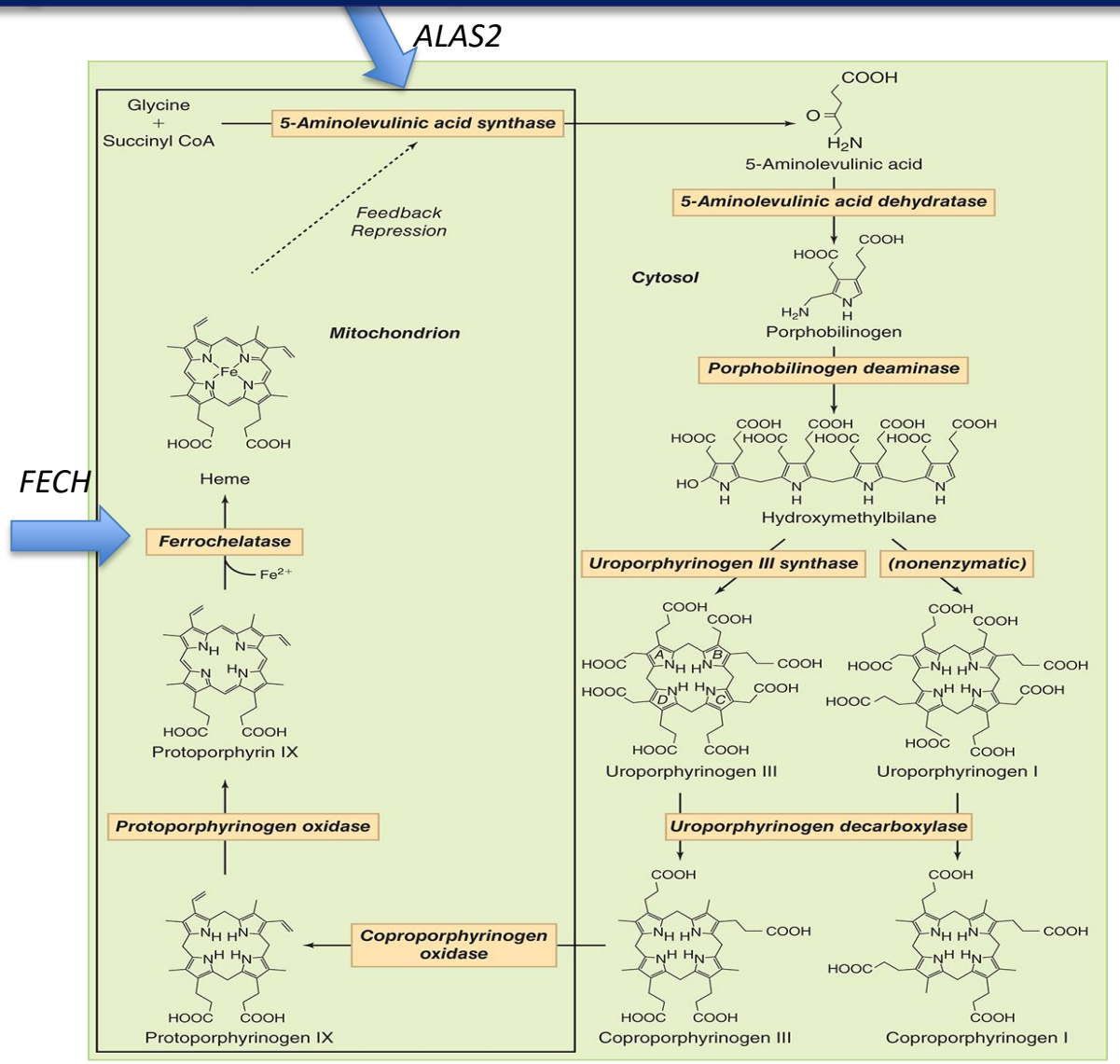
Summary

- The AHPs are a group of rare disorders, each occurring due to a deficiency in one of the enzymes of the heme-biosynthesis pathway
- Clinical manifestations are diverse including effects on the autonomic, central and peripheral systems
- Long term complications include neuropathy, chronic kidney disease and increase risk of HCC
- Diagnosis is made by biochemical testing on a **spot sample of urine for PBG**
- Genetic testing is useful for confirmation, identifying type of AHP and testing of family members
- Patients with recurrent attacks will need active medical management and monitoring

Cutaneous Porphyrias

Erythropoietic Protoporphyria (EPP) and X-linked Protoporhyria (XLP)

- Most common cutaneous porphyria in children
- Deficiency of ferrochelatase (FECH) or ALAS2 gain of function
- Accumulation of protoporphyrin (PROTO) in bone marrow reticulocytes, plasma, and liver
- Diagnosed significantly elevated levels of protoporphyrins in erythrocytes, with predominantly metal-protoporphyrin
- Genetic testing should be used to confirm the diagnosis



EPP Prevalence

- Prevalence estimates range from 1:75,000 in the Netherlands to 1: 180,000 in Sweden
- Prevalence in the US is unknown
- Recent study from the UK Biobank showed that EPP was 1.7 to 3 times more common than previously estimated
- Average diagnostic delay is over a decade

Average age of symptom onset is **3-4 years**

EPP is fully penetrant

Males and Females equally affected in EPP

Males more severely affected than females in XLP

Lala S, J. Pediatr 2018,
Balwani, M, JAMA Derm 2017

Acquired EPP and XLP

- Typically later onset > 40 years
- Associated with myelodysplastic or myeloproliferative syndromes
- Results from a somatic mutation or deletion in the ferrochelatase gene in hematopoietic cells
- Acquired XLP has been reported in one case with somatic mosaicism in the bone marrow for a known pathogenic variant in *ALAS2* (p.Q548X)

D. Blagojevic et a; Ann. Hematol., 89 (2010), pp. 743-744, C. Aplin et al J Invest Dermatol, 117 (2001), pp. 1647-1649C.B. Livideanu et al J Invest Dermatol, 133 (2013), pp. 1688-1690

Pathophysiology

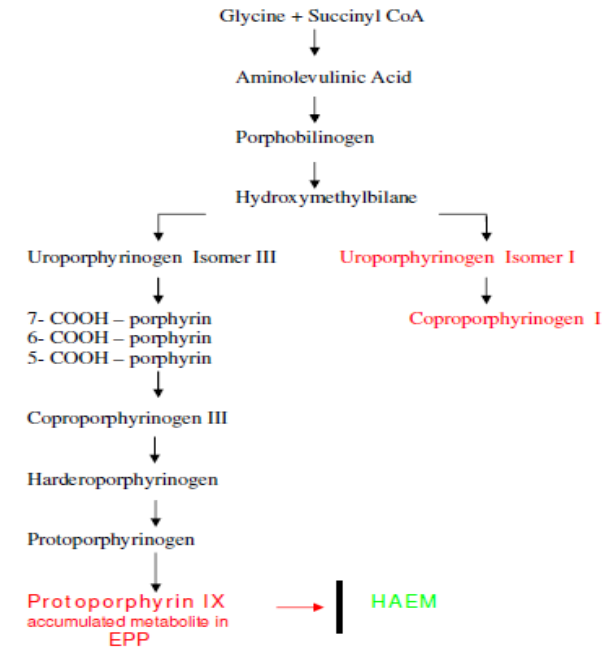


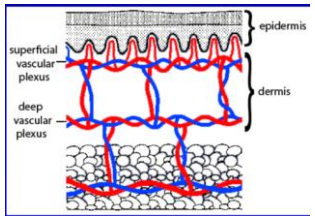
Figure I
The haem biosynthesis pathway.

Bone marrow

Circulating RBCs Plasma

Liver

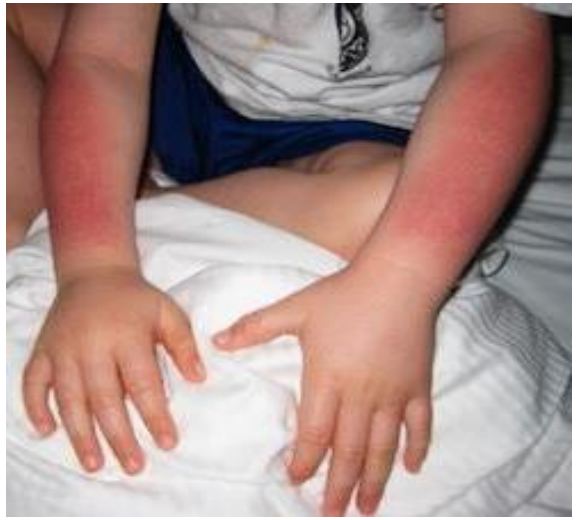
Vascular endothelium

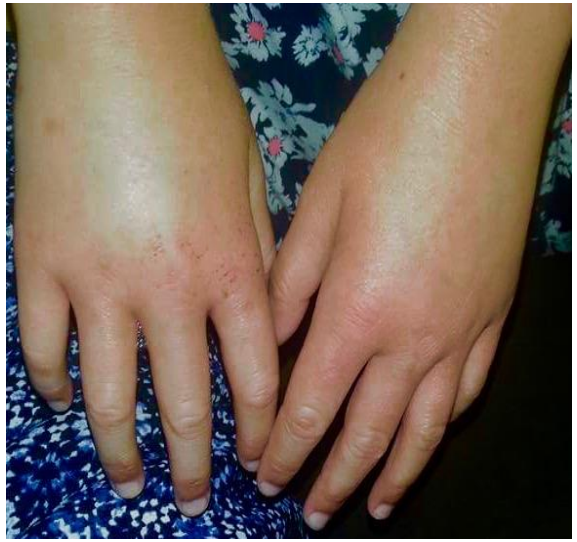


RBCs in skin blood vessels

Fig: Lecha M, Orphanet 2009

Clinical manifestations

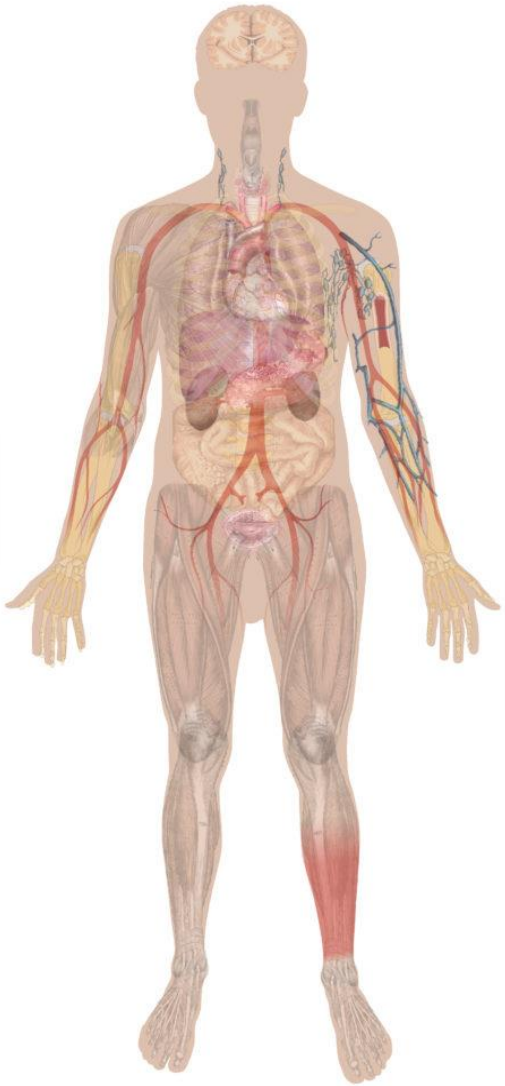




- **Acute, painful phototoxicity within minutes of sun-exposure**
- **Prodromal symptoms-tingling, burning, itching**
- **Erythema and Edema**
- **Recovery takes several days**
- **No blistering**

Multi-Systemic Involvement

Organ system	Signs and Symptoms
Liver	Elevated liver enzymes Cholestasis Gallstones Liver failure
Spleen	
Bone marrow	Anemia Thrombocytopenia Iron deficiency
Skin	Phototoxicity Lichenification Palmar Keratoderma
Skeletal	Vitamin D deficiency Osteopenia



Liver Disease in EPP/XLP

Longitudinal study of the PC

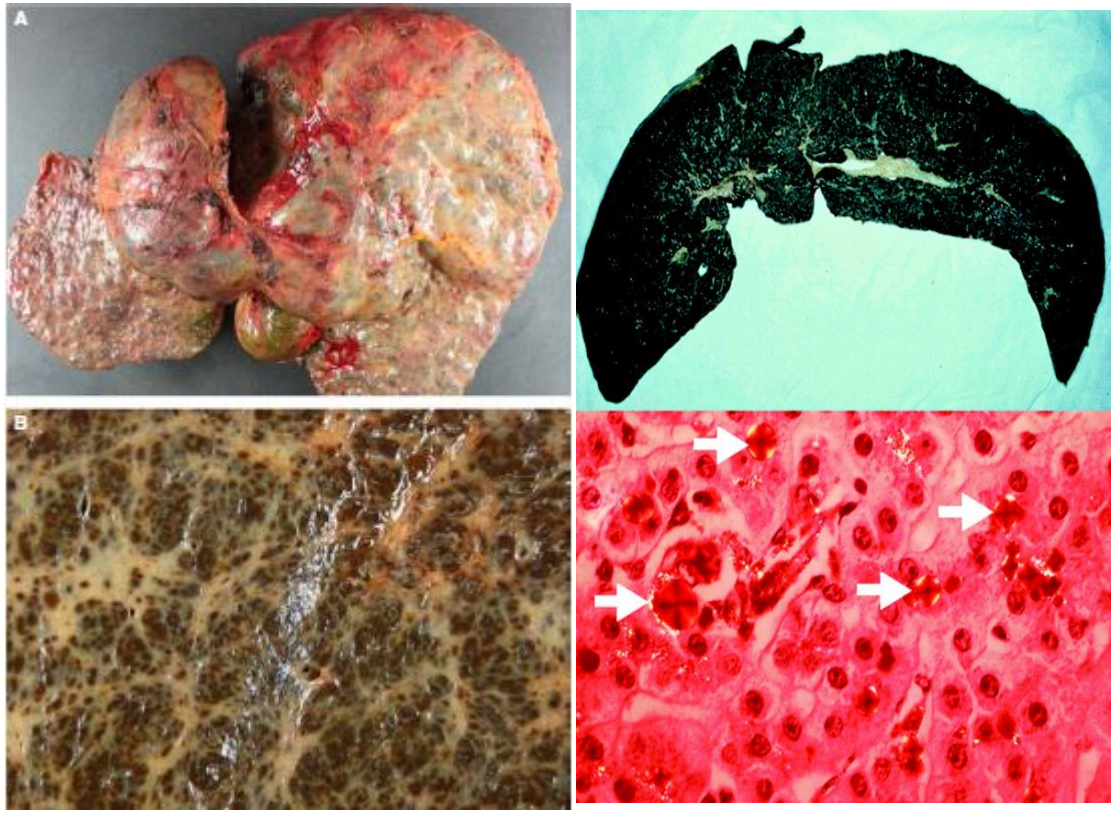
- 27% of patients with h/o abnormal liver enzymes
- 23.5% of patients with Gallstones

Single site data from Netherlands

- 29% of patients with hepatic steatosis
- 9.6% with fibrosis

Determinants of Risk

- Higher protoporphyrin levels
- Biallelic pathogenic variants in FECH
- Male patients with XLP
- Comorbid conditions?



Pic: Windon et al 2017

Balwani et al 2017, Wensink et al 2021

Management Approaches for EPP/XLP

Focused primarily on symptom avoidance and symptomatic management

Avoidance of phototoxic reactions
Sun protective clothing including long sleeves, gloves, and wide-brimmed hats
Sunscreens containing physical reflecting agents, window tints

Non-pharmacologic management of symptoms
Cold compresses, aloe, cold lotions, Ice packs, cold air, CBD

Use of supplements and medications
Vitamin C, Beta-carotene,
N-acetyl cysteine, Cimetidine

Management of progressive liver disease
Hemin, Plasmapheresis, Cholestyramine,
Ursodeoxycholic acid (UCDA)

Liver transplantation
End-stage liver disease
Not curative
High risk of morbidity and mortality

Bone marrow transplantation
Curative
+/- with Liver transplantation
High risk of morbidity and mortality

Pharmacologic management
Scenesse, subcutaneously administered α-MSH analogue

Afamelanotide (Scenesse)

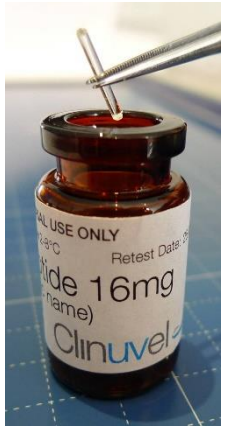
ORIGINAL ARTICLE

Afamelanotide for Erythropoietic Protoporphyria

J.G. Langendonk, M. Balwani, K.E. Anderson, H.L. Bonkovsky, A.V. Anstey, D.M. Bissell, J. Bloomer, C. Edwards, N.J. Neumann, C. Parker, J.D. Phillips, H.W. Lim, I. Hamzavi, J.-C. Deybach, R. Kauppinen, L.E. Rhodes, J. Frank, G.M. Murphy, F.P.J. Karstens, E.J.G. Sijbrands, F.W.M. de Rooij, M. Lebwohl, H. Naik, C.R. Goding, J.H.P. Wilson, and R.J. Desnick

- US trial (6 months) :
  Increased pain free sun exposure in afamelanotide group vs placebo (median, 69.4 hours vs 40.8 hours, p=0.04)
- European Union study (9 months)
  Increased pain free sun exposure in afamelanotide group vs placebo (median 6.0 hours vs 0.8 hours; p=0.005)
  Decreased number of phototoxic reactions (77 vs 146, p=0.04)

Improved quality of life in both studies

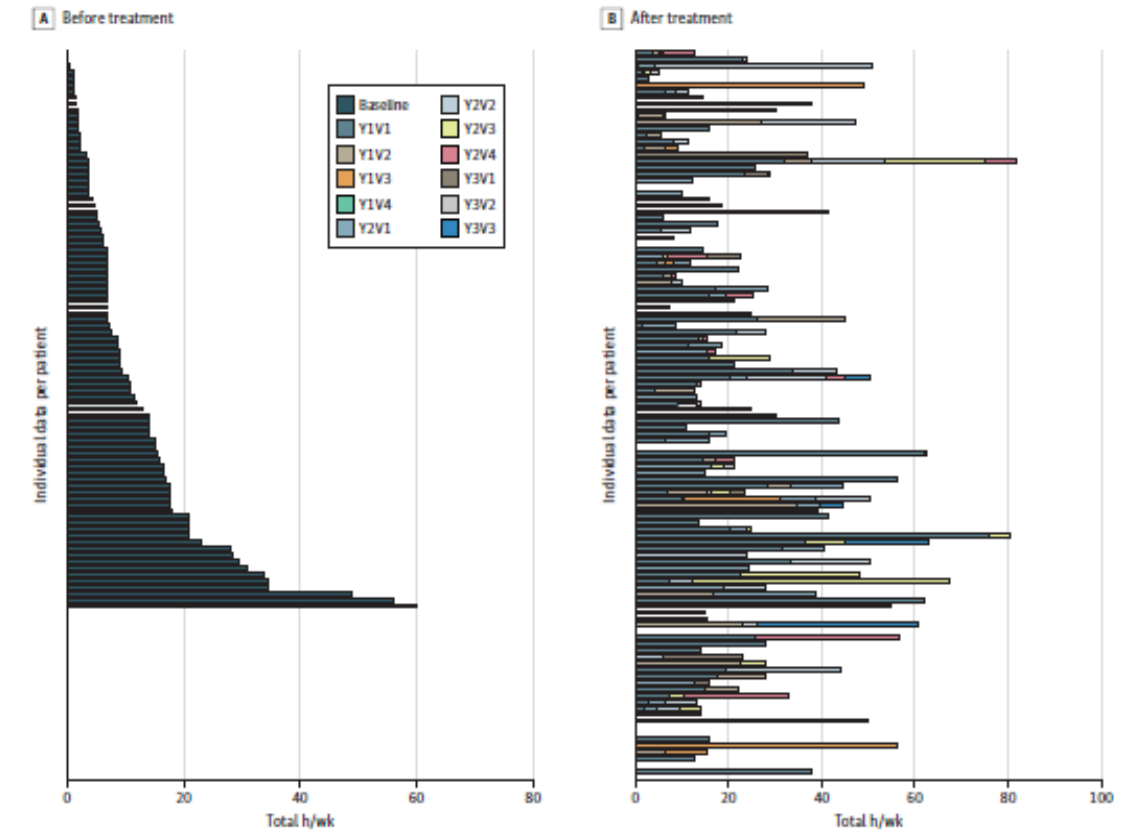


Afamelanotide (α-MSH stimulating analogue)

Approved by the EMA in 2014 and FDA in 2019

Afamelanotide in clinical practice: single site data

Figure. Individual Patient-Reported Time Outside



Before (A) and after (B) treatment with afamelanotide, displayed as total hours spent outside during a week for their best treated period. In panel B, the total length of the bar represents the total hours in the week in which time spent outside was the longest (maximum). The colors provide information on how time spent outside increases over the subsequent visits, until it reaches its maximum. For patients with missing data, before or after treatment, the value 0 was filled in. Each line of data represents the same patient in panel A and panel B. Y indicates year; V, visit.

- Improved clinical outcomes
- Less painful phototoxic reactions
- Improved quality of life
- Minor self limiting adverse events
- Improved outcomes with longer treatment duration
- 98% continuation rate
- Treatment response varied between individuals
- Mean time spent outside during treatment increased significantly by an added 6.1 hours per week compared to baseline

Wensink D et al, JAMA Dermatol. 2020 May 1;156(5):570-575

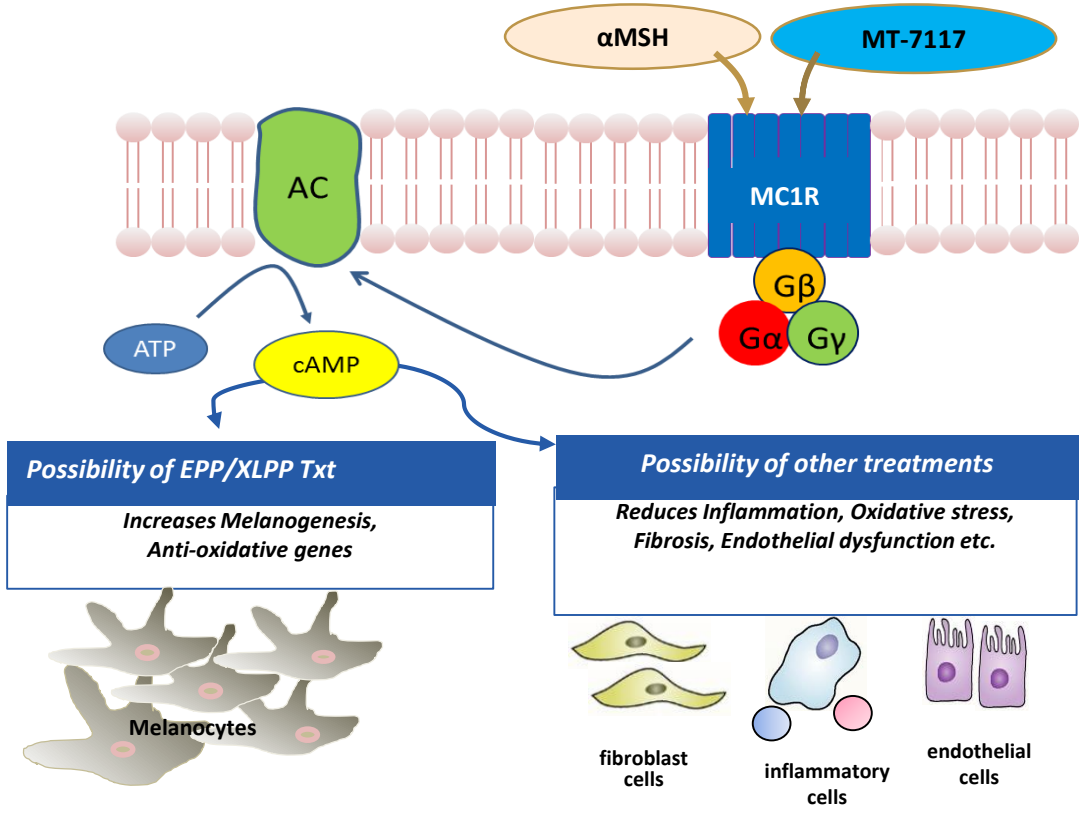
Investigational Therapies

MT-7117 (Dersimelagon) Proposed Mechanism of Action

MT-7117 is a synthetic, orally-administered, small molecule agonist of the melanocortin-1 receptor (MC1R)

Proposed Mechanisms of MC1R Agonism in EPP/XLP

1. Activation of MC1R, coupled to the cAMP signaling pathway, leads to stimulation of melanogenesis and a switch from the pheomelanin synthesis to the production of eumelanin pigments (protective)
2. Increased melanin reduces penetration of the damaging UV and visible light
3. MC1R agonists may also:
   - Enhance DNA repair
   - Upregulate antioxidant enzymes
   - Reduce production of pro-inflammatory cytokines (minimizing the PPIX-mediated damage and resulting pain)

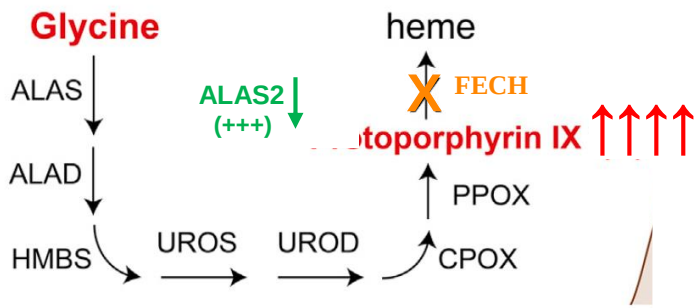


Ahmed TJ, et al. *Intl J Inflamm.* 2013;Article ID 985815:1-10; Brzoska T, et al. *Endocrine Reviews.* 2008;29(5):581-602.

Bitopertin: Highly selective glycine reuptake inhibitor (GlyT-1)

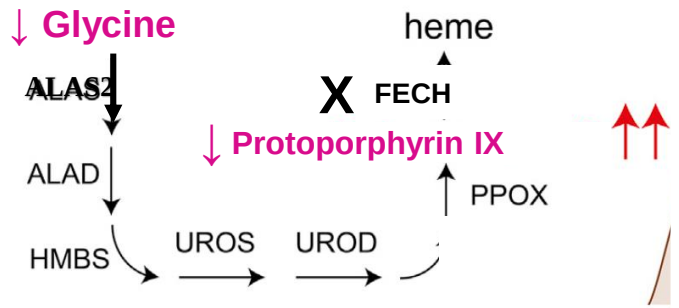
Reduce disease-causing PPIX by limiting uptake of glycine in developing erythrocytes

EPP and XLPP Patients
High PPIX Levels



Mutations result in reservoir of supra-physiologic levels of PPIX

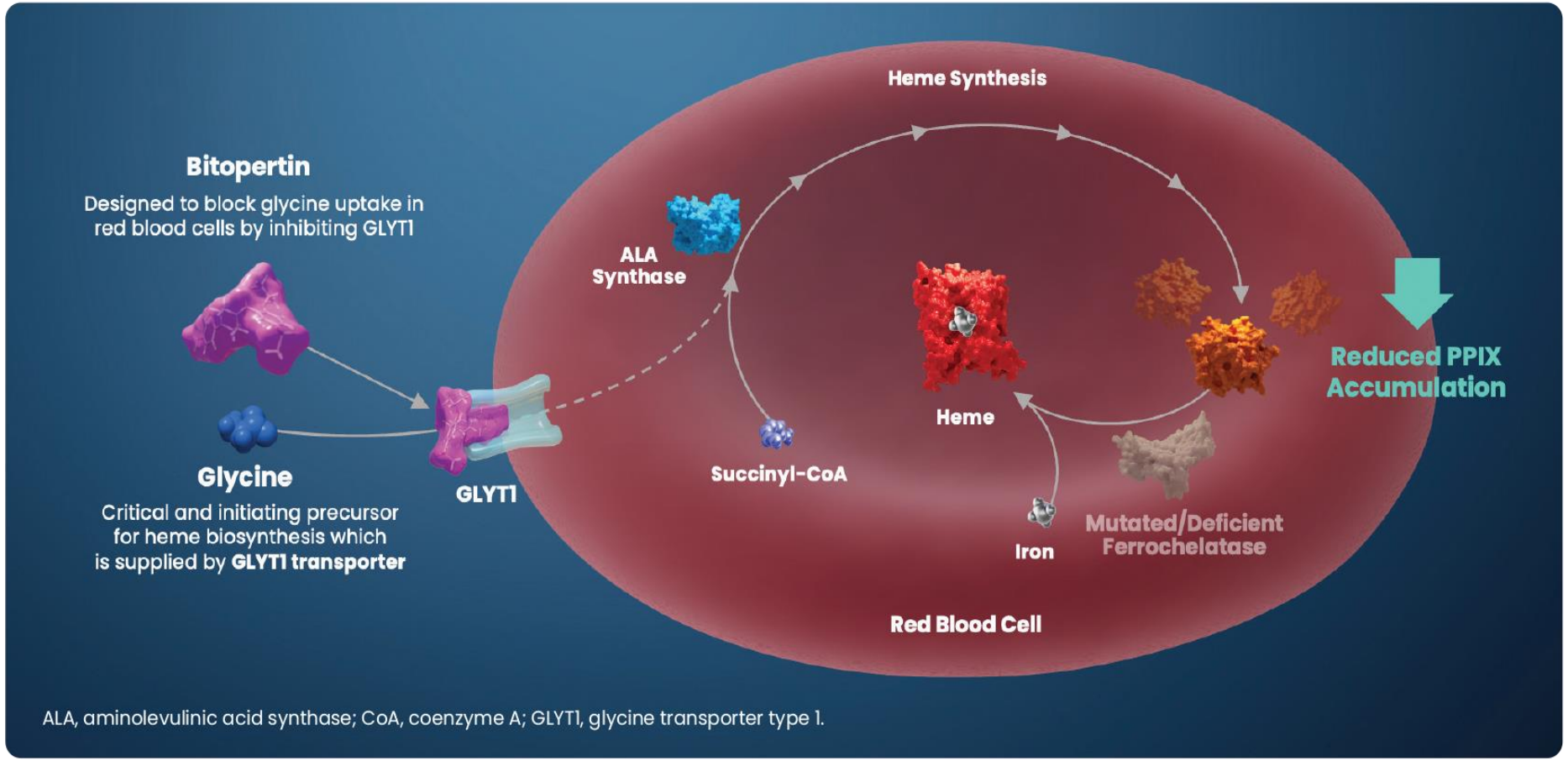
Bitopertin Treatment
Reduce and Normalize PPIX Levels



Potential Functional Cure for EPP and XLPP Patients

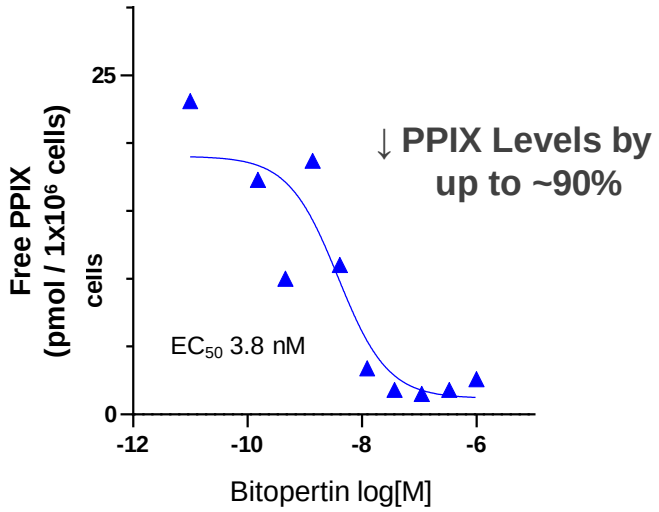
Bitopertin: GlyT1 receptor inhibitor

Erythropoietic Protoporphyria and X-Linked Protoporphyria

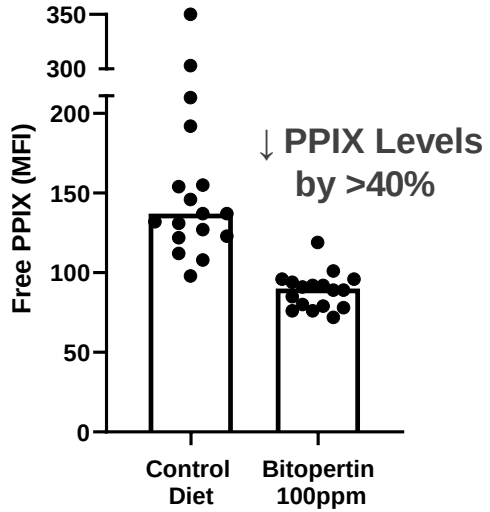


Bitopertin Reduced PPIX in Models of EPP and XLP

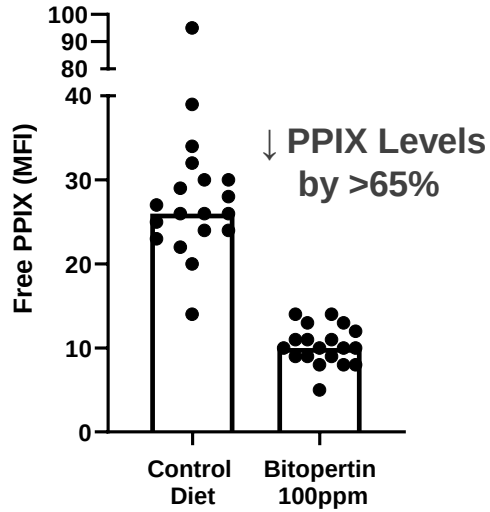
In vitro – EPP Model (K562 Cell)
FECH$^{IVS3\text{-}48C/KO}$ Mutation



In vivo - EPP Model (Mouse)
FECH^{m1pas} Missense Mutation



In vivo - XLP Model (Mouse)
ALAS2^{Q548X} Gain-of-Function Mutation

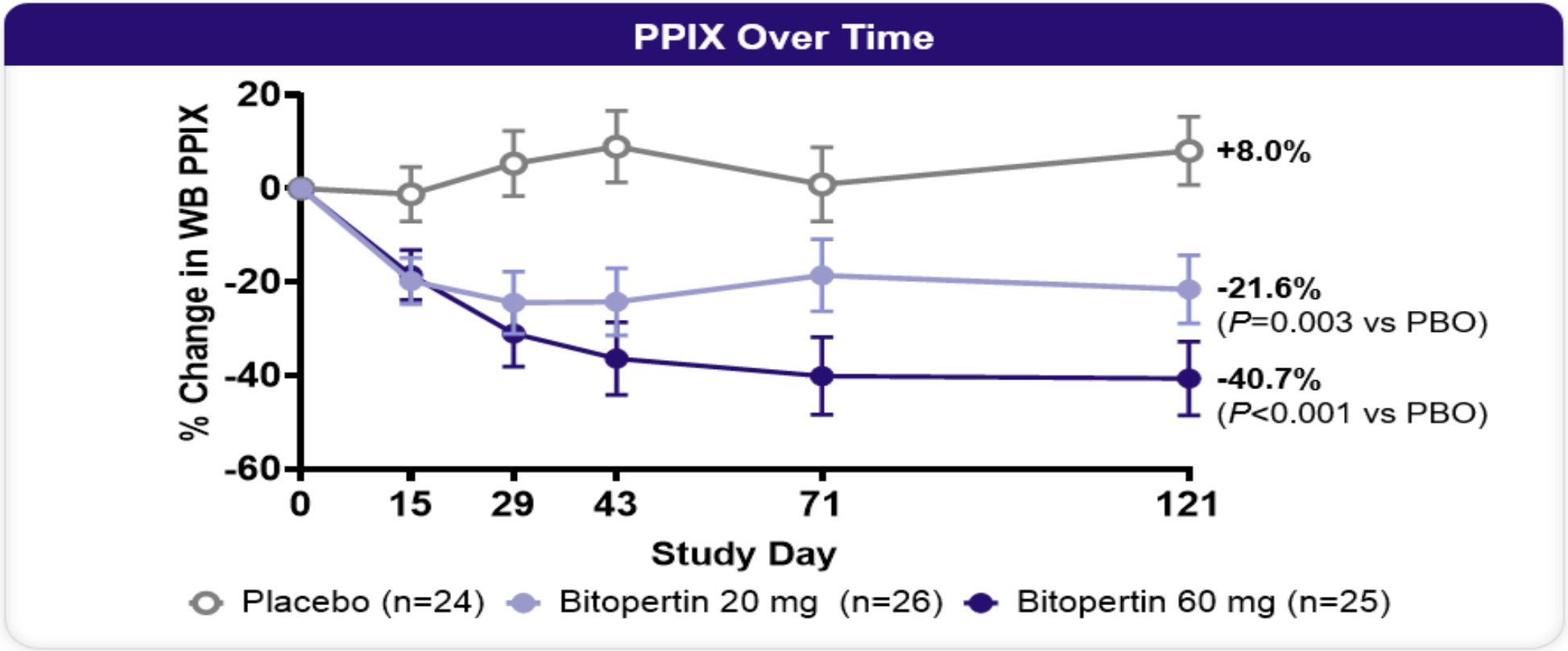


Data presented at the 63rd ASH Annual Meeting (December 2021); Studies performed in collaboration with Boston Children's Hospital (PI: Paul Schmidt, Advisor: Mark Fleming)

Phase 2 clinical trial (AURORA) met its primary endpoint

- Bitopertin reduced PPIX levels, taking ~6-8 weeks to reach max reduction
- Significant reductions observed in both 20 mg and 60 mg doses

Orally administered once daily



MMRM, mixed model repeated measures; PBO, placebo; WB, whole blood.
Least-squares means and *P* values for percent changes in PPIX analyzed using a MMRM to compare 20 mg and 60 mg bitopertin dose groups vs placebo.

Acknowledgements

Patients and their families

Study investigators and coordinators

Alnylam, Mitsubishi, Disc for sharing slides