Interim Analyses from the BEACON trial: A Phase 2, Randomized, Open-Label Trial of Bitopertin in Erythropoietic Protoporphyria

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BEACON

Bitopertin is an investigational agent and is not approved for use as a therapy in any jurisdiction worldwide.

Erythropoietic Protoporphyria (EPP)

- Rare condition affecting 7,000 to 8,000 individuals in the US and EU
- Debilitating condition characterized by extreme pain and damage to skin due to light exposure
- Deficient ferrochelatase enzyme causes pathologic accumulation of toxic metabolite, protoporphyrin IX
- Lifelong condition presents in early childhood
- Management includes lifestyle modifications, including sunlight avoidance and protective clothing

Image sources: *Daily Mail Australia* (2019); FDA Scientific Workshop on EPP (2016); Buonuomo et al. (2014) *Arch Dis Child*

Lecha et al. (2009). *Orphanet J Rare Dis*; *American Porphyria Foundation*; Dickey et al. (2021) *Genet Med*

Protoporphyrin IX (PPIX) is a Driver of Disease in EPP

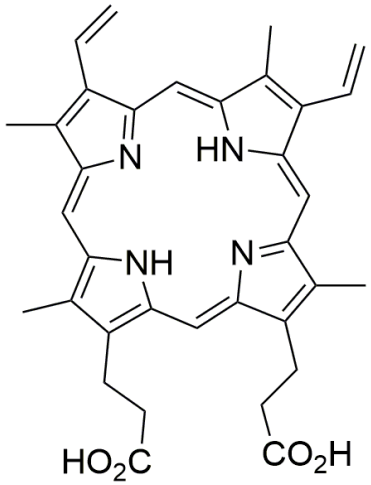
Accumulation of toxic, photoactive metabolite results in complications

Skin

- Porphyrin ring absorbs light and emits energy causing **cellular injury and inflammation**
- Burning and tingling (prodrome) experienced **within minutes of sunlight exposure**
- Phototoxic reactions cause **excruciating pain** and swelling and can lead to chronic skin lesions

Psychosocial

- Sun avoidance leads to **physical and social isolation**
- >40% of patients diagnosed with **anxiety or depression**



Protoporphyrin IX

Hepatobiliary

- ~25% of patients develop **cholelithiasis** requiring surgery or impairing liver function
- 2 to 5% progress to acute liver failure requiring **liver transplant**

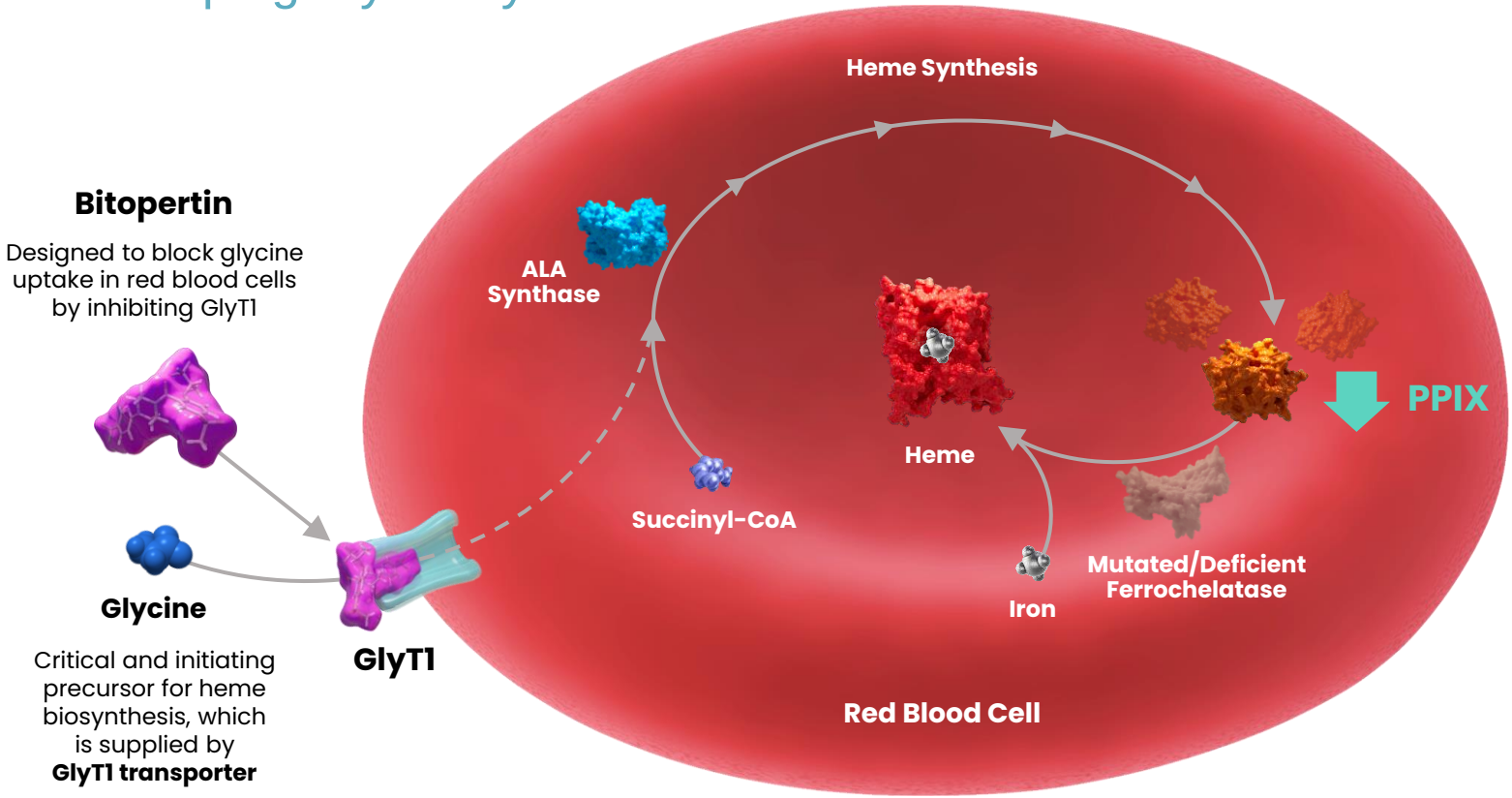
Other Complications

- Vitamin D deficiency resulting in osteoporosis and propensity for fractures; mild anemia
- Comorbidities contribute to higher rates of **ER visits and hospitalizations**

Naik et al. (2019) *JIMD Rep*; Levy (2023) *Gastroenterol Hepatol*; Obi et al. (2022) *Front Cell Dev Bio*; Di Pierro et al. (2022) *Diagnostics*.

Bitopertin: Investigational, Oral, Selective GlyT1 Inhibitor

Designed to reduce disease-causing PPIX by limiting uptake of glycine into developing erythrocytes



Abbreviations: ALA = aminolevulinic acid synthase; CoA = coenzyme A; GlyT1 = glycine transporter type 1

BEACON Trial Overview

Enrollment data as of 20 Oct 2023

Trial Endpoints: Changes in blood PPIX levels, light tolerance, time to prodromal symptom*, safety, tolerability, and PK

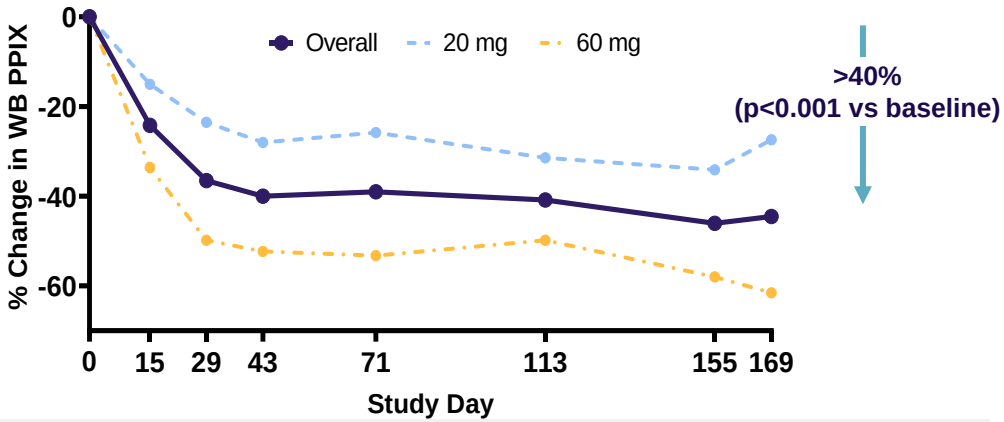
	Bitopertin 20 mg (n=11)	Bitopertin 60 mg (n=11)	Total (n=22)
Enrolled	11	11	22
Completed Day 43	11	11	22
Completed Day 113	9	8	17
Completed Treatment Period (Day 169)	7	7	14

*Time to prodromal symptom = the time until a participant experiences an early warning signal of a phototoxic attack measured through a weekly sunlight challenge. If a participant is unable to elicit a prodrome during a sunlight challenge, the amount of time the participant chose to remain in light is recorded.
Abbreviations: D = day; EOS = end of study; OLE = open-label extension; PK = pharmacokinetics

Primary Endpoint: Percent Change in Whole-Blood PPIX

- Bitopertin significantly reduced whole-blood (WB) metal-free PPIX levels by >40%
- Dose-dependent reductions observed across broad range of baseline WB PPIX levels (144-3,410 µg/dL)

PPIX Changes Over Time

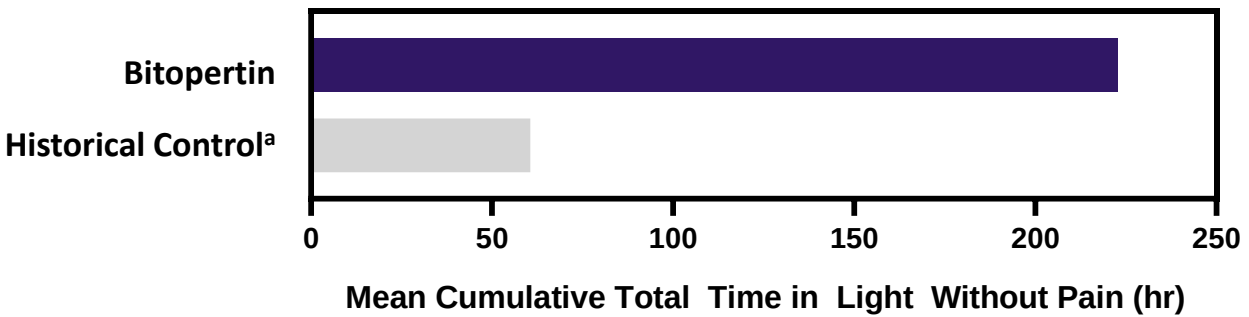


Overall N	22	22	20	22	16	16	13	8
20 mg	11	11	10	11	9	9	7	4
60 mg	11	11	10	11	7	7	6	4

PPIX data as of 18 September 2023. Least-squares means for percent changes in PPIX were analyzed using a mixed model for repeated measures.

Key Secondary Endpoint: Total Time in Light Without Pain

- Cumulative total time in light observed over 6-month treatment period with bitopertin represents >3x increase relative to historical control
- Time-dependent improvements in average daily light tolerance with bitopertin



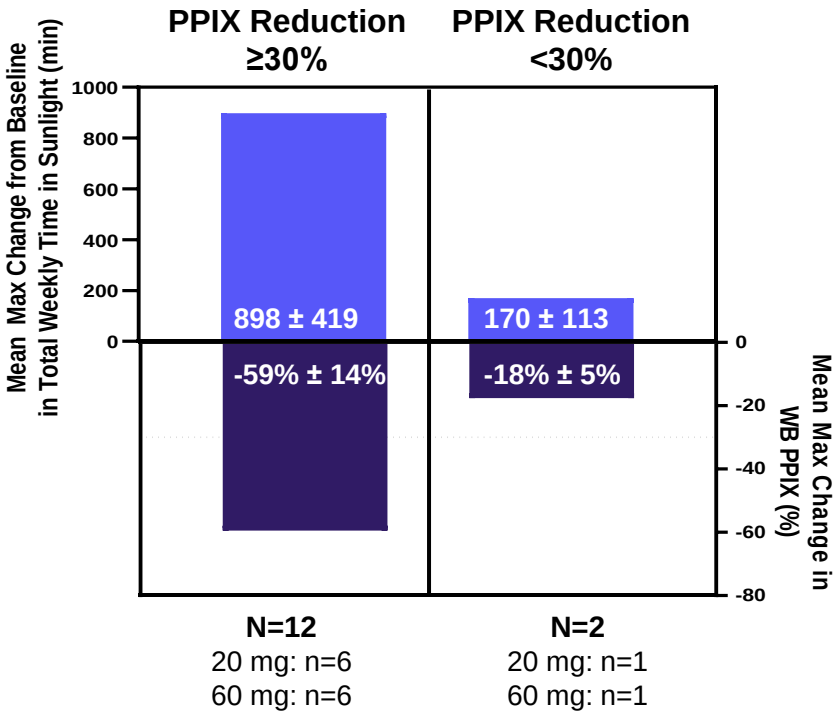
Cumulative 6-month Total Time in Light Without Pain (hr)

n	Mean ± SD	Median
14[b]	222.6 ± 129.3	178.2
43	60.6 ± 60.6	40.8

[a] Placebo arm from prior Phase 3 study in EPP (Langendonk et al. [2015] NEJM). [b] Includes data from participants who completed EOS visit (D169).

Association Between PPIX and Light Tolerance

Greatest improvements in light tolerance seen in participants with PPIX reductions ≥30%

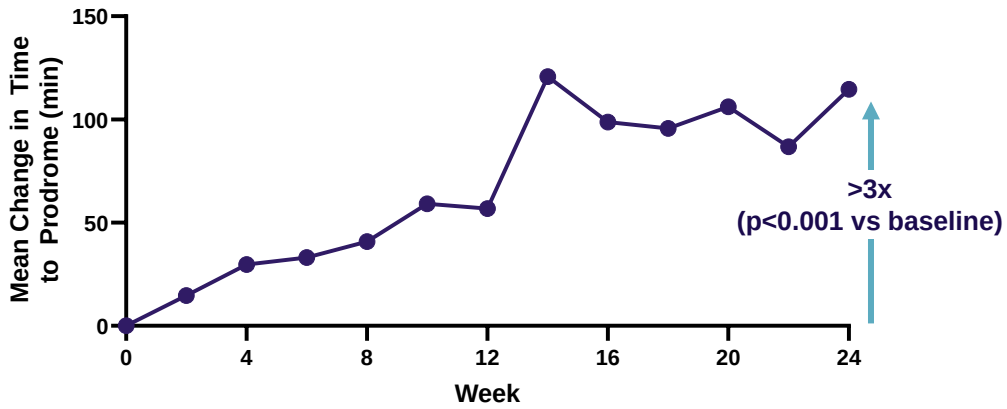


Maximum changes from baseline in weekly total time in sunlight as assessed with a daily diary. Includes only participants who have completed through Day 169/EOS.

Secondary Endpoint: Time to Prodrome

- Significant, time-dependent improvements in light tolerance during sunlight-exposure challenges

Time to Prodrome

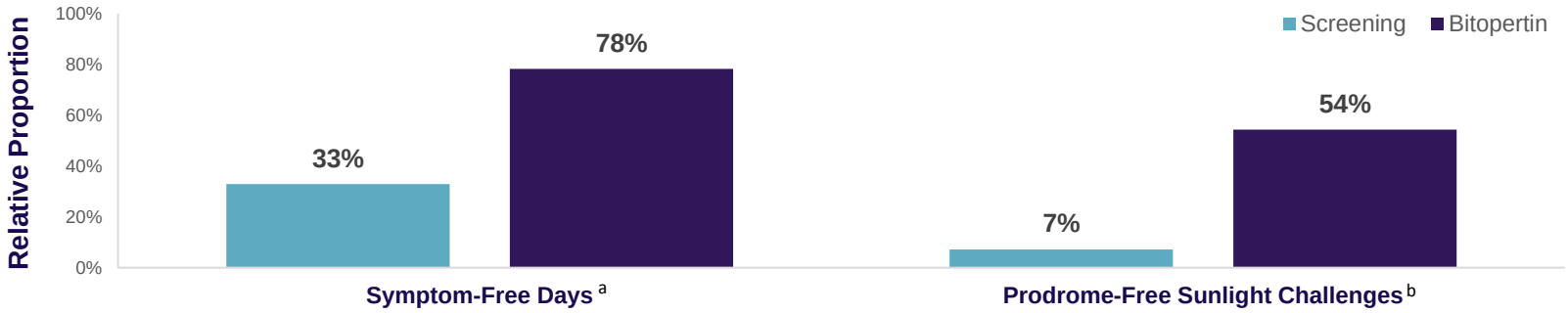


No. of Participants[a]	22	19	21	20	19	18	21	15	15	17	14	16	14
No. of Challenges	69	45	46	43	44	42	40	32	35	46	32	47	33

[a] The number of subjects with at least 1 sunlight-exposure challenge during a 2-week period. Time to prodrome data from weekly sunlight-exposure challenges were averaged over a 2-week period, including cumulative time in sunlight challenges where the participant did not report a prodrome, and were analyzed using MMRM for both 20 mg and 60 mg bitopertin dose groups combined.

Light Tolerance: Days Without Symptoms or Prodromes

- 92% reduction in patient-reported full phototoxic reactions[a]
- An increase in the proportion of total symptom-free days (no prodrome / early warning symptoms or full phototoxic reactions) with sunlight exposure was observed

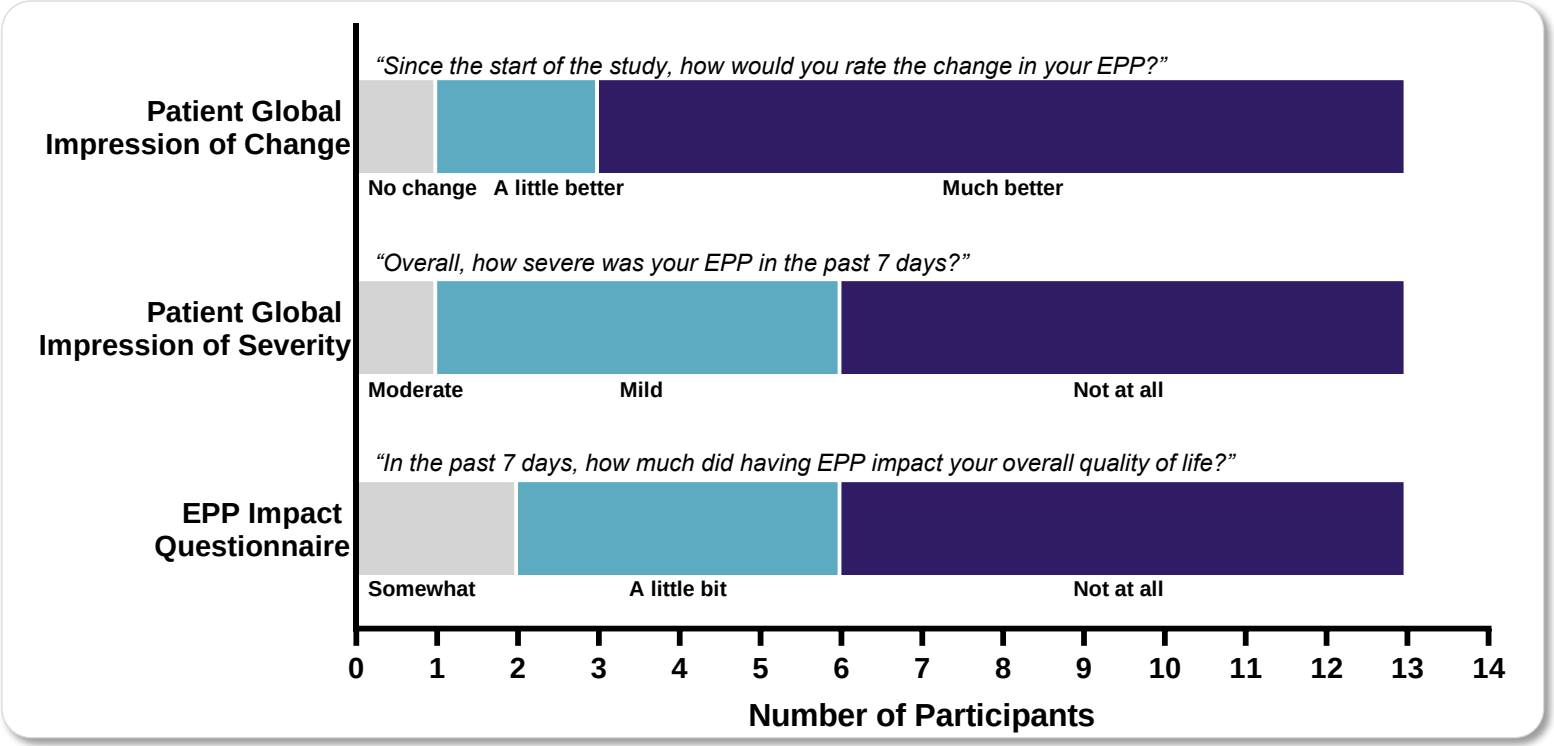


	Days w/ Sunlight Exposure[c]	Sunlight Challenges[c]
Screening	231	69
On-Treatment	2138	623

[a] As assessed with a daily diary; [b] As assessed with a weekly sunlight challenge; [c] Summed across all participants. Percentages calculated relative to total number of days with sunlight exposure (left) or total number of weekly sunlight exposure challenges (right) from all study participants (n=22) during screening or while receiving bitopertin (20 mg and 60 mg dose groups combined).

Measures of Quality of Life

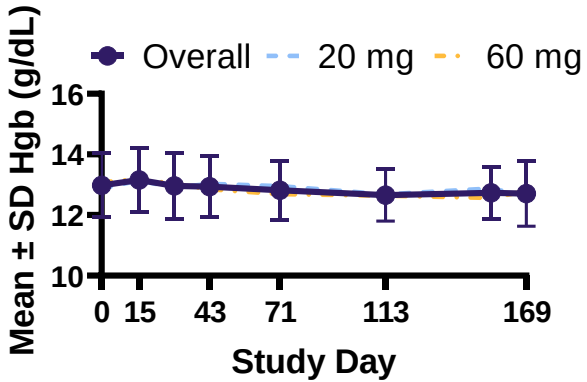
- Nearly all participants reported improvements in multiple quality-of-life measures at end of study



Only 13 participants who completed through Day 169/EOS with QOL responses.

Safety and Tolerability

- No serious adverse events
- Stable mean Hgb levels; no anemia AEs reported
- Favorable safety profile consistent with prior studies enrolling >4000 participants
- Safety profile supports enrollment of adolescents



	Bitopertin 20 mg (n=11)	Bitopertin 60 mg (n=11)	Total (n=22)
Subjects with any TEAE	9 (82%)	9 (82%)	18 (82%)
TEAEs leading to discontinuation	1 (9%)[a]	0	1 (5%)
TEAEs reported in >1 subject			
Dizziness	3 (27%)	4 (36%)	7 (32%)
Lightheadedness	3 (27%)	2 (18%)	5 (23%)
Headache	3 (27%)	1 (9%)	4 (18%)
Nausea	1 (9%)	2 (18%)	3 (14%)

Includes all coded AE data as of 20 October 2023. [a] Grade 3 TEAE reported as "localized headache."
Abbreviations: AE = adverse event; Hgb = hemoglobin; TEAE = treatment-emergent adverse event

Conclusions

Proof of Concept

Significant reduction in PPIX at low and high doses

Functional Outcomes

Significant improvement in sunlight tolerance

Quality of Life Impact

Patients reported an improved quality of life

Safety

No meaningful change in hemoglobin observed with bitopertin

Thank You