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

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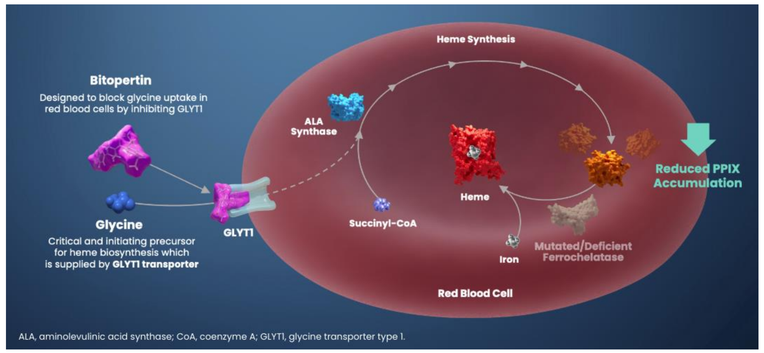
INTRODUCTION

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

EPP and XLP are rare disorders caused by pathogenic variants in the ferrochelatase (FECH) or 5-aminolevulinate synthase 2 (ALAS2) genes, which result in accumulation of photoreactive protoporphyrin IX (PPIX). PPIX elevations cause debilitating phototoxic skin reactions following exposure to sunlight and can cause potentially life-threatening hepatopathy in some patients. Higher PPIX reductions are associated with amelioration of disease in the settings of hematopoietic stem cell transplant, pregnancy, and extracorporeal photoinactivation.[1-3]

Mechanism of Disease and Bitopertin Treatment

Bitopertin is an investigational small molecule inhibitor of glycine transporter 1 (GlyT1). GlyT1 supplies extracellular glycine for the initial step of heme biosynthesis in erythroid cells.[4] It is hypothesized that GlyT1 inhibition can decrease PPIX accumulation and improve light tolerance.[5] Bitopertin has exhibited a favorable safety profile in prior clinical studies in other indications with cumulative enrollment of >4,000 participants.



ALA, aminolevulinic acid synthase; CoA, coenzyme A; GLYT1, glycine transporter type 1.

BEACON (ACTRN12622000799752) was designed to evaluate the safety, tolerability, and efficacy of bitopertin in individuals with EPP

METHODS

Study Design

- Phase 2, randomized, open-label, parallel-arm trial
- Enrolled 22 adults and 4 adolescents (12 - <18 years of age) with EPP or XLP

Key Eligibility Criteria

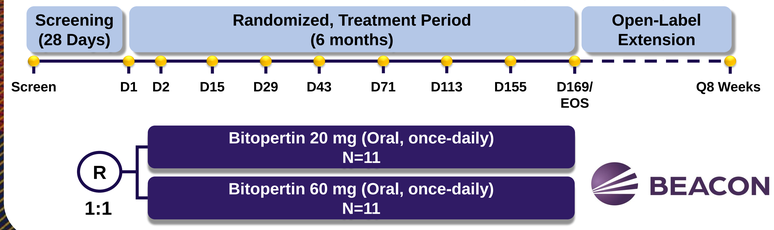
- Diagnosed by FECH/ALAS2 genotyping or biochemical porphyrin analysis
- 2-month washout of afamelanotide or dersimelagon

Endpoints

- Primary: Percent change in whole blood metal-free PPIX
- Key secondary: Total hours of sunlight exposure on days with no pain from 10:00 to 18:00 hours

Study Assessments

- Daily sun exposure diary
- Weekly sun exposure challenge (time to prodrome)
- PGIC/PGIS; patient-reported quality of life
- Liver fibrosis (FibroScan® or ARFI)



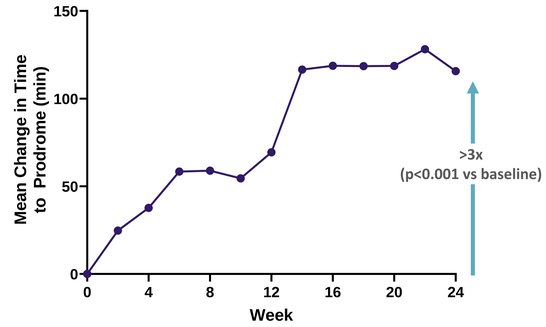
RESULTS

Disposition and Baseline Characteristics: Adult Population

	Bitopertin 20 mg (n=11)	Bitopertin 60 mg (n=11)
Randomized	11	11
Completed Study	10	11
Discontinued Prior to Day 169	1	0
Characteristic		
Mean Age, years	43.2	44.5
Female, n (%)	6 (55%)	8 (73%)
White, n (%)	11 (100%)	10 (91%)
EPP, n (%)	11 (100%)	10 (91%)
XLP, n (%)	0	1 (9%)
Baseline PPIX, Mean ± SD (ng/mL)	11920 ± 7495	8559.5 ± 6654
Time to Prodrome, n (%)		
< 30 min	7 (64%)	6 (55%)
≥ 30 min	4 (36%)	5 (46%)

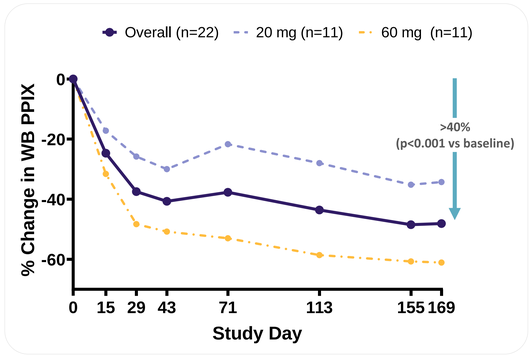
Secondary Endpoint: Time to Prodrome

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



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 (n=22).

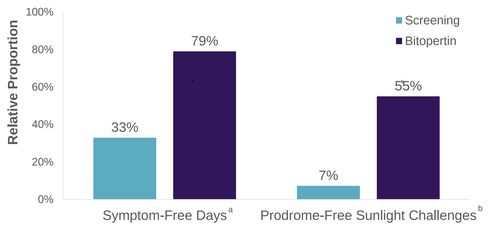
Primary Endpoint: Percent Changes in Whole Blood PPIX



Least-squares means and p-value for percent changes in PPIX analyzed using a mixed model for repeated measures (MMRM). WB = Whole Blood

Light Tolerance: Days without Symptoms or Prodromes

- 92% reduction vs screening in patient-reported full phototoxic reactions
- Increase in proportion of total symptom-free days (no prodrome or full phototoxic reaction) with sun exposure

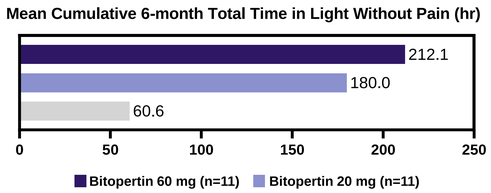


	Days w/ Sunlight Exposure [c]	Sunlight Challenges [c]
Screening	231	69
On-Treatment	2338	694

[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)

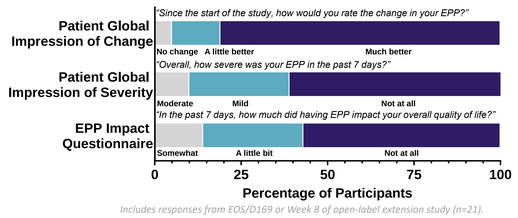
Key Secondary Endpoint: Cumulative Total Time in Light

- Dose-dependent improvement in light tolerance endpoint



Quality of Life Measures

- Nearly all participants reported improvements in QOL measures at end of study



Includes responses from EOS/D169 or Week 8 of open-label extension study (n=21).

Safety

- No serious adverse events (AEs)
- Stable mean hemoglobin levels; no anemia AEs

	Bitopertin 20 mg (n=11)	Bitopertin 60 mg (n=11)	Total (n=22)
Subjects with any TEAE	9 (82%)	11 (100%)	20 (91%)
TEAEs leading to discontinuation	1 (9%)[a]	0	1 (5%)
TEAEs reported in >2 subjects			
Dizziness	6 (55%)	7 (64%)	13 (59%)
Headache	3 (27%)	1 (9%)	4 (18%)
Nausea	1 (9%)	2 (18%)	3 (14%)

[a] Grade 3 TEAE of cluster headache

CONCLUSIONS

- Bitopertin targets underlying EPP pathophysiology by significantly reducing PPIX at low and high doses
- Functional benefit observed with significant improvement in multiple measures of sunlight tolerance
- Consistent improvements in multiple measures of light tolerance associated with improvement in quality of life measures
- Bitopertin was well tolerated with no meaningful changes in hemoglobin
- Safety profile in EPP consistent with prior studies in other indications enrolling >4,000 participants

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