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

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1093

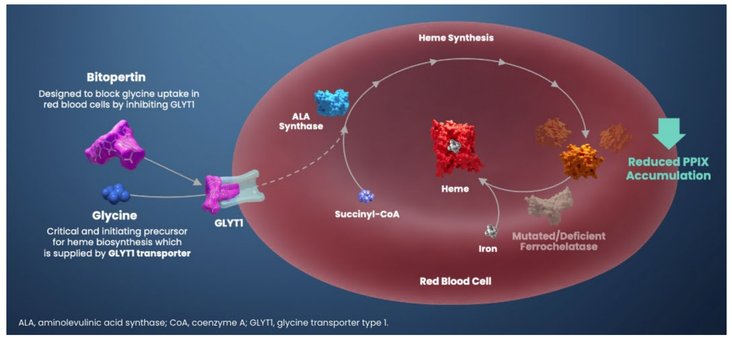
INTRODUCTION

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.



BEACON (ACTRN12622000799752) was designed to evaluate the safety, tolerability, and efficacy of bitopertin in adults and adolescents 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

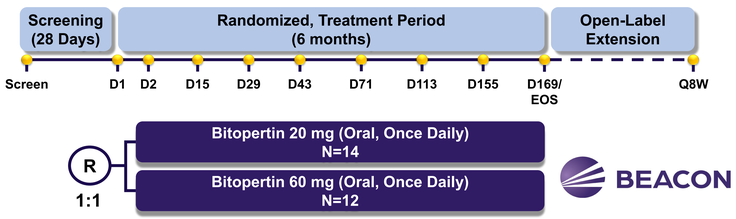
- Diagnosed by FECH/ALAS2 genotyping or biochemical porphyrin analysis
- 2-month washout of afamelanotide or dersimelagon

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)



ARFI=acoustic radiation force impulse; D=day; EOS=end of study; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; Q8W=every 8 weeks; R=randomization

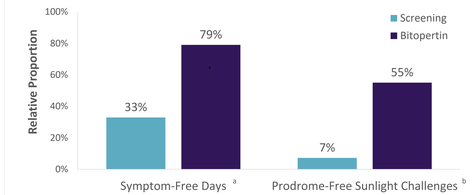
RESULTS

Disposition and Baseline Characteristics:

	Adult Population		Adolescent Population	
	Bitopertin 20 mg (n=11)	Bitopertin 60 mg (n=11)	Bitopertin 20 mg (n=3)	Bitopertin 60 mg (n=1)
Randomized	11	11	3	1
Completed Study	10	11	2	1
Discontinued Prior to Day 169	1	0	1	0
Characteristic				
Mean Age, years	43.2	44.5	14.3	14.0
Female, n (%)	6 (55%)	8 (73%)	2 (67%)	0 (0%)
White, n (%)	11 (100%)	10 (91%)	3 (100%)	1 (100%)
EPP, n (%)	11 (100%)	10 (91%)	3 (100%)	1 (100%)
XLP, n (%)	0	1 (9%)	0	0
Baseline PPIX, Mean ± SD (ng/mL)	11920 ± 7495	8559.5 ± 6654	4537 ± 1245	3570
Time to Prodrome, n (%)				
< 30 min	7 (64%)	6 (55%)	0	0
≥ 30 min	4 (36%)	5 (46%)	3 (100%)	1 (100%)

Light Tolerance: Days without Symptoms or Prodromes

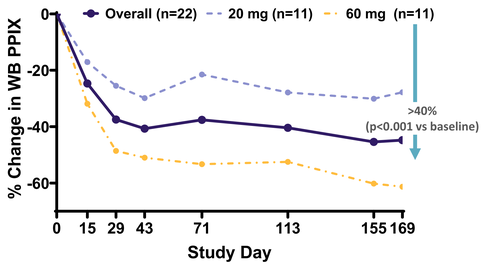
- 92% reduction vs screening in patient-reported full phototoxic reactions
- Increase in proportion of total symptom-free days (no prodrome or full phototoxic reaction) with sun exposure

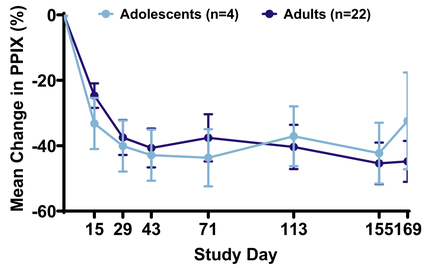


	Days w/ Sunlight Exposure [c]	Sunlight Challenges [c]
Screening	231	69
On-Treatment	2338	694

[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)

Primary Endpoint: Percent Changes in Whole Blood PPIX

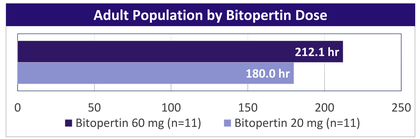


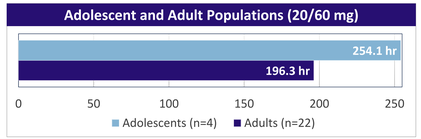


Least-squares means and p-value for percent changes in PPIX analyzed using a mixed model for repeated measures (MMRM). WB = whole blood

Key Secondary Endpoint: Cumulative Total Time in Light

- Dose-dependent improvement in light tolerance endpoint
- Similar light tolerance benefit observed in adult and adolescent populations





Least-squares means for cumulative time in light measured via daily diary, adding all time in light between the hours of 10:00 am and 6:00 pm on days without any pain, and analyzed using an analysis of variance model.

Associations between PPIX Reductions and Light Tolerance

Tertiles of PPIX Change

PPIX Increased ← → PPIX Decreased

Light Tolerance Measure (Mean ± SD)	Tertile 3 (-43% to 25%)	Tertile 2 (-53% to -43%)	Tertile 1 (-98% to -53%)
Cumulative total time in sunlight without pain (h)	145.6 ± 99.5	190.5 ± 111.6	262.1 ± 160.6
Average time in sunlight without pain (h)	0.86 ± 0.6	1.1 ± 0.7	1.6 ± 1.0
Change from baseline in time to prodrome (min)	85.3 ± 78.8	96.0± 109.0	165.5 ± 128.8

Safety

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

	Adults		Adolescents	
	Bitopertin 20 mg (n=11)	Bitopertin 60 mg (n=11)	Bitopertin 20 mg (n=3)	Bitopertin 60 mg (n=1)
Subjects with any TEAE	9 (82%)	11 (100%)	3 (100%)	1 (100%)
TEAEs leading to discontinuation	1 (9%)	0	1 (33%)	0
TEAEs reported in >2 subjects				
Dizziness	6 (55%)	7 (64%)	3 (100%)	1 (100%)
Headache	3 (27%)	1 (9%)	0	0
Nausea	1 (9%)	2 (18%)	0	0

CONCLUSIONS

- Bitopertin targets underlying EPP pathophysiology by significantly reducing PPIX at low and high doses and in both adults and adolescent populations
- Reductions in PPIX were associated with improvements in multiple measures of sunlight tolerance
- Similar light tolerance benefit observed across adult and adolescent populations
- Bitopertin was well tolerated in adults and adolescents 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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