Initial Data 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)

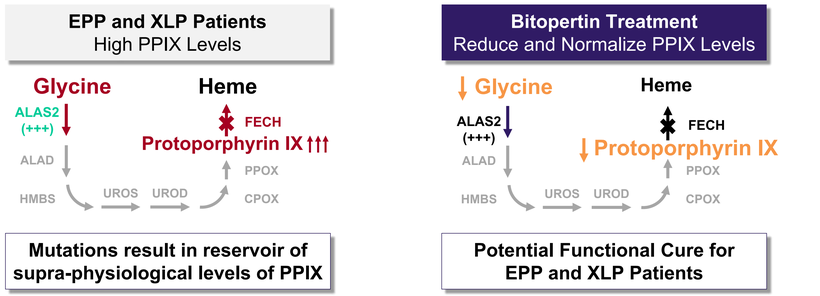
EPP and XLP are rare disorders caused by pathogenic variants in the ferrochelatase (*FECH*) or 5-aminolevulinate synthase 2 (*ALAS2*) genes, which result in accumulation of photoreactive protoporphyrin IX (PPIX). PPIX elevations cause debilitating phototoxic skin reactions following exposure to sunlight 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 subjects.

EFFECTS OF BITOPERTIN IN MOUSE MODELS OF EPP AND XLP[5]

Bitopertin lowered blood PPIX levels by >40% vs controls, was associated with decreased liver PPIX levels, and reduced histopathological evidence of liver cholestasis and fibrosis vs controls.[6,7]



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
- Enrolling 22 subjects with EPP or XLP

KEY ELIGIBILITY CRITERIA

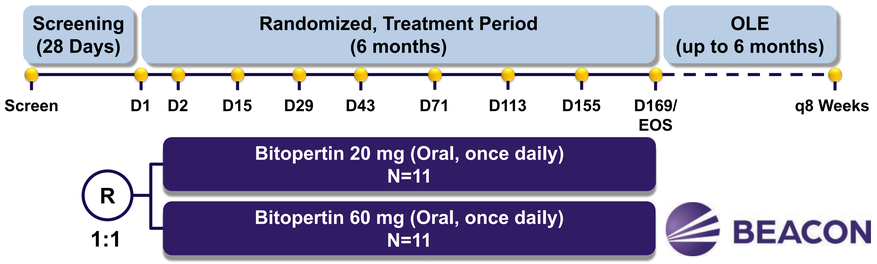
- ≥18 years of age
- Diagnosed by *FECH*/*ALAS2* genotyping or biochemical porphyrin analysis
- 2-month washout of afamelanotide or dersimelagon

ENDPOINTS

- **Primary:** Percent change in whole blood (WB) 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 (QOL)
- Liver fibrosis (FibroScan® or ARFI)



Bitopertin is an investigational drug and is not approved for use by any regulatory agency.

RESULTS - EFFICACY

DISPOSITION

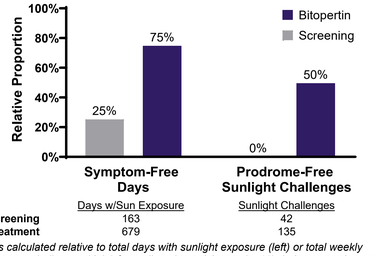
	Bitopertin 20 mg (n=8)	Bitopertin 60 mg (n=7)	Total (n=15)
Enrolled	8	7	15
Completed Day 43	5	4	9
Completed Study (Day 169)	0	1	1

Data as of 8 May 2023.

PRIMARY EFFICACY: CHANGES IN PPIX

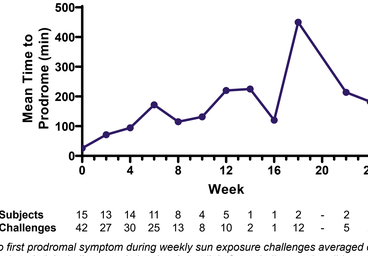
- ↓ WB metal-free PPIX across broad range of baseline PPIX levels (420-3410 µg/dL)
- Dose-dependent reductions

PPIX Changes Over Time



Data as of 7 April 2023

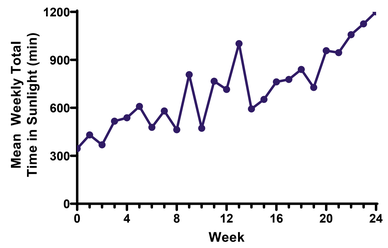
Individual PPIX Data



SECONDARY EFFICACY: LIGHT TOLERANCE

- ↑ Average weekly total time in sunlight
- ↑ Proportion of symptom-free days (no early warning symptoms or full reactions) with sun exposure
- ↑ Average time to prodrome and proportion of prodrome-free weekly sunlight exposure challenges
- ↓ Daily phototoxic reaction rate by 96% vs screening

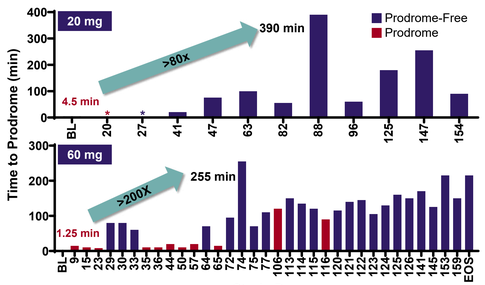
Weekly Total Time in Sunlight



No. of Subjects	15	14	13	11	8	5	4	3	2	2	2	2	1
No. of Diary Entries	163	55	64	39	28	20	21	13	12	13	11	11	7

Average total time in sun recorded in daily sun exposure diaries over a one-week period for 20 mg and 60 mg bitopertin dose groups combined. Incomplete diary entries counted as zero minutes.

Individual Sunlight Exposure Challenges



Time to prodrome data for individual participants receiving 20 mg or 60 mg bitopertin. More than 1 challenge could be completed each week. Additional post-baseline (BL) data not visible due to y-axis scale: prodrome (*) after 2 min and prodrome-free (*) challenge with 4 min of sunlight.

Symptom-Free Sunlight Exposure

	Days w/Sun Exposure	Sunlight Challenges
Screening	163	42
On-Treatment	679	135

Percentages calculated relative to total days with sunlight exposure (left) or total weekly sunlight exposure challenges (right) from all study participants (n=15) during screening or while receiving bitopertin (combined 20/60 mg doses); 88% of days were symptom-free post-Day 29.

Time to Prodrome

No. of Subjects	15	13	14	11	8	4	5	1	1	2	-	2	1
No. of Challenges	42	27	30	25	13	8	10	2	1	12	-	5	2

Time to first prodromal symptom during weekly sun exposure challenges averaged over a two-week period, including cumulative time in sunlight from challenges that did not elicit a prodrome. Data are averaged for 20 mg and 60 mg bitopertin dose groups combined.

RESULTS - QUALITY OF LIFE

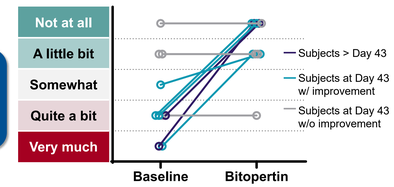
PATIENT GLOBAL IMPRESSION OF CHANGE/SEVERITY[a]

- PGIC: 10/10 participants reported their EPP was **much better** (n=8) or **a little better** (n=2) in the last 7 days at Day 43
- PGIS: 9/10 participants reported **severity** of their EPP was **mild** (n=3) or **not at all** (n=6) in the last 7 days at Day 43

EPP IMPACT QUESTIONNAIRE (EPIQ)

- Improvements in novel EPP-specific PRO assessing QOL[a,b]

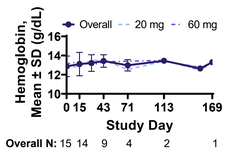
"In the past 7 days, how much did having EPP impact your overall quality of life?"



[a] QOL data may be entered at Day 43 ± 3 days and includes data from 1 participant who had not completed Day 43 visit
[b] Responses at baseline or most recent visit while receiving bitopertin (combined 20/60 mg doses, n=10); relative improvements noted in green and no change in grey.

RESULTS - SAFETY

- No serious adverse events
- No discontinuations or dose reductions
- All TEAEs Grade 1 in severity and transient[a]
- No changes in mean hemoglobin levels



	Bitopertin 20 mg (n=8)	Bitopertin 60 mg (n=7)	Total (n=15)
Total number of TEAEs	8	8	16
Subjects with any TEAE	6 (75%)	6 (86%)	12 (80%)
TEAES reported in >1 subject			
Dizziness	4 (50%)	5 (71%)	9 (60%)
Headache	2 (25%)	1 (14%)	3 (20%)

Data as of 8 May 2023. Summaries include uncoded TEAEs categorized by verbatim terms. [a] Mean time to resolution: 2 days.

CONCLUSIONS

- Initial data establishes proof of concept that bitopertin targets underlying EPP pathophysiology by reducing whole-blood PPIX levels
- Functional benefit observed with bitopertin, including prolonged symptom-free periods of sun exposure and prodrome-free sunlight challenges
- Consistent improvements in multiple measures of light tolerance also associated with quality-of-life improvements
- Bitopertin has been well tolerated to date with no changes in hemoglobin
- Safety profile in EPP consistent with prior studies in >4,000 individuals

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