Results from the HELIOS Study: A Phase 2, Open-Label, Long-Term Extension Study of Bitopertin in Erythropoietic Protoporphyria

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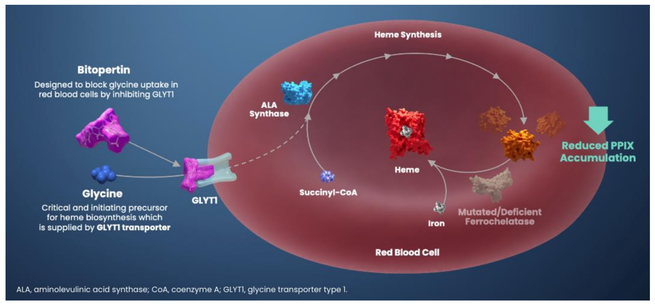
INTRODUCTION

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, respectively, 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. 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, oral, small molecule inhibitor of glycine transporter 1 (GlyT1). GlyT1 supplies extracellular glycine for the initial step of heme biosynthesis in erythroid cells.[4] GlyT1 inhibition results in modulation of the heme synthesis pathway to decrease intermediates, including PPIX.[5] Bitopertin has exhibited a favorable safety profile in prior clinical studies in other indications with cumulative enrollment of >4,000 participants.



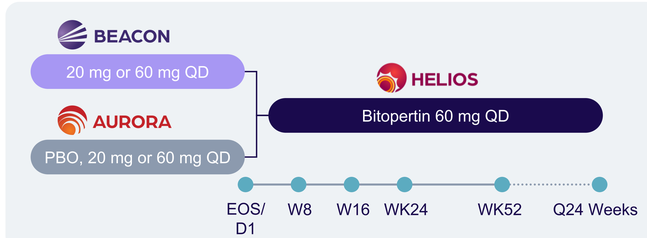
METHODS

Study Design

- Phase 2, randomized, open-label study
- Participants ≥12 years of age with EPP or XLP who completed prior bitopertin studies (AURORA or BEACON)

Endpoints

- Primary: Safety and tolerability
- Secondary: Percent change in whole blood metal-free PPIX
- Study Assessments: Daily sun exposure diary; patient-reported quality of life; liver fibrosis (FibroScan® or ARFI)



RESULTS

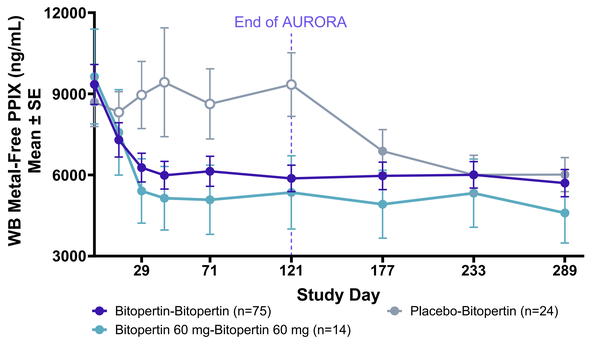
Disposition and Baseline Characteristics

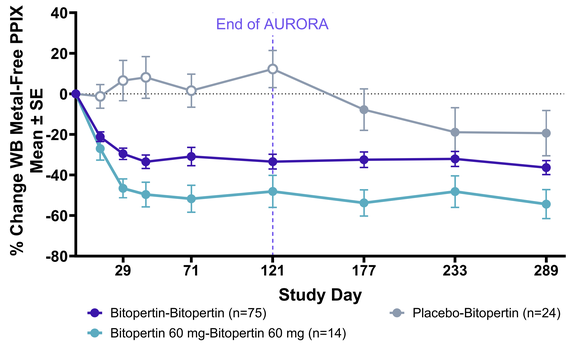
	PBO → Bitopertin (n=21)	Bitopertin → Bitopertin (n=65)	Total (n=86)
Enrolled	21	65	86
Discontinued Treatment	0	2 (3%)	2 (2%)
Completed Week 24	17 (81%)	50 (77%)	67 (78%)
Mean ± SD age, years	41.9 ± 11.1	46.2 ± 15.1	45.2 ± 14.3
Age <18	0	3 (5%)	3 (3%)
Male, n (%)	12 (57%)	31 (48%)	43 (50%)
White, n (%)	21 (100%)	63 (97%)	84 (98%)
EPP, n (%)	21 (100%)	64 (98%)	85 (99%)
XLP, n (%)	0	1 (2%)	1 (1%)
Mean ± SD Baseline PPIX (ng/mL)	8546 ± 6335	5990 ± 4185	6606 ± 4873
Mean ± SD Baseline ALT (U/L)	32.9 ± 15.1	32.8 ± 34.7	32.8 ± 31.0

Baseline defined as Day 1 of HELIOS. Abbreviations: PBO = placebo; SD = standard deviation; PPIX = protoporphyrin IX.

PPIX Profile with Long-Term Bitopertin Treatment (All Doses)

- Sustained reductions in PPIX with continued bitopertin treatment (20/60 mg doses)
- Greater PPIX decreases in participants who received continuous treatment with 60 mg of bitopertin
- Bitopertin treatment in HELIOS reduced PPIX in participants initially randomized to placebo in AURORA

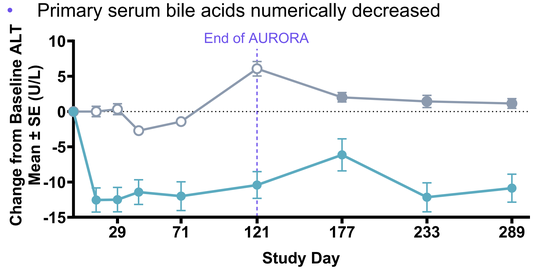




Bitopertin-Bitopertin: participants initially randomized to bitopertin (20 or 60 mg dose) in AURORA or BEACON; Bitopertin 60 mg-Bitopertin 60 mg: subset of participants who received 60 mg of bitopertin continuously in AURORA or BEACON and HELIOS. Bitopertin-Placebo: participants initially randomized to placebo in AURORA. Study day calculated relative to Day 1 of AURORA or BEACON. Percent change from baseline calculated relative to baseline in AURORA or BEACON. Abbreviations: PPIX = protoporphyrin IX; SE = standard error; WB = whole-blood

Exploratory Hepatobiliary Biomarkers

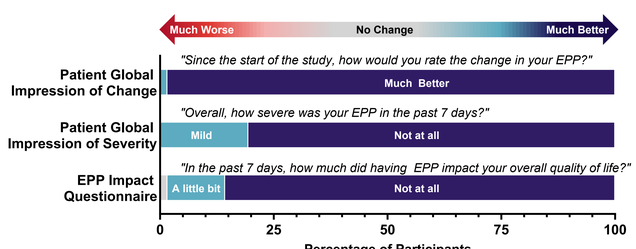
- Continued treatment with 60 mg of bitopertin reduced ALT
- Primary serum bile acids numerically decreased



Data from subset of participants who received 60 mg of bitopertin continuously in AURORA or BEACON and HELIOS or were randomized to placebo in AURORA and received bitopertin 60 mg in HELIOS. Study day calculated relative to Day 1 of AURORA or BEACON. Change from baseline calculated relative to baseline in AURORA or BEACON. Abbreviations: ALT = alanine aminotransferase; SE = standard error

Quality of Life Measures

- Nearly all participants reported improvements in quality of life (QOL) measures through Week 24 of HELIOS



Percentage calculated relative to number of participants with data at Week 24 in HELIOS: n=62 for PGIC, PGIS and n=63 for EPP Impact Questionnaire. Abbreviations: EPP = erythropoietic protoporphyria; PGIC = patient global impression of change; PGIS = patient global impression of severity

Safety

- Median exposure: 18.1 months (range: 5.9 to 28.7 months)
- 1 participant reported SAEs (unrelated) due to motor vehicle accident
- 1 Grade 3 TEAE (unrelated): hypertransaminasaemia
- All other TEAEs mild or moderate in severity
- Safety profile similar across adults and adolescents

	Adults (n=83)	Adolescents (n=3)	Total (n=86)
Any TEAE	41 (49%)	2 (67%)	43 (50%)
Grade 3 TEAE	2 (2%)	0	2 (2%)
Discontinuation due to AE	2 (2%)	0	2 (2%)
SAE	1 (1%)	0	1 (1%)
Common TEAEs (reported in ≥ 5% of participants)			
COVID-19	6 (7%)	1 (33%)	7 (8%)

Abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event

Conclusions

- Bitopertin exhibits a **favorable longer-term safety profile** (up to 2+ years exposure)
- Bitopertin **safety profile is similar across adults and adolescents** with EPP or XLP
- Longer-term treatment with bitopertin is associated with **sustained reductions in PPIX**
- Consistent with prior EPP studies, bitopertin is associated with **improvements in QOL**
- Longer-term treatment with 60 mg of bitopertin **reduced ALT and improved other exploratory hepatobiliary biomarkers**

References

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