Results from the AURORA Trial: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial of Bitopertin in Erythropoietic Protoporphyria

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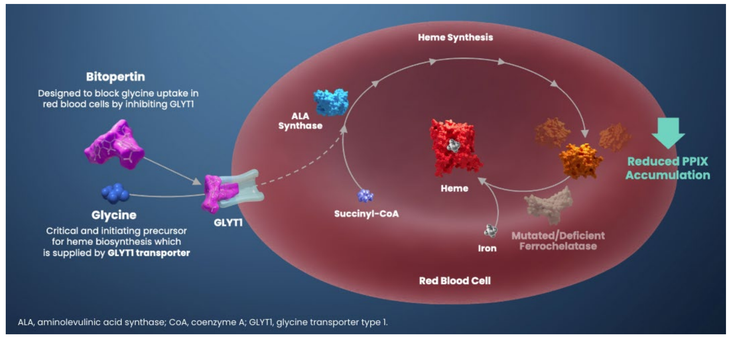
INTRODUCTION

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.



AURORA (NCT05308472) was designed to evaluate the safety, tolerability, and efficacy of bitopertin in adults with EPP

METHODS

AURORA

Study Design

- Phase 2, randomized, placebo-controlled, double-blind study
- Enrolled 75 adults with EPP

Key Eligibility Criteria

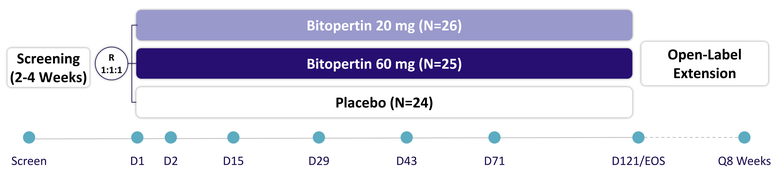
- Diagnosed by FECH/ALAS2 genotyping or biochemical porphyrin analysis
- 2-month washout of afamelanotide or dersimelagon

Endpoints

- Primary: Percent change in whole blood (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)
- Patient Global Impression of Change (PGIC), patient-reported quality of life



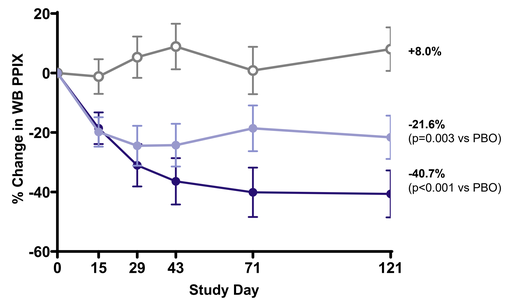
RESULTS

Disposition and Baseline Characteristics:

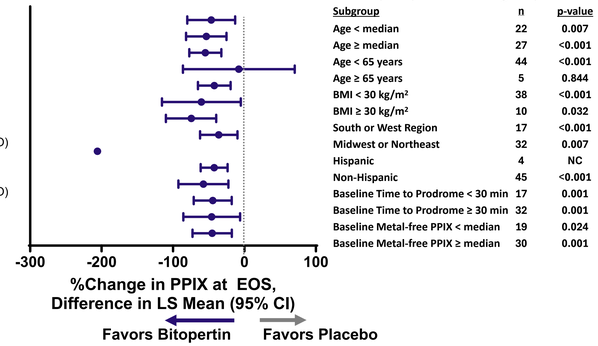
	Placebo (n=24)	Bitopertin 20 mg (n=26)	Bitopertin 60 mg (n=25)
Randomized	24	26	25
Completed Study	24	26	22
Discontinued Prior to Day 121	0	0	3
Characteristic			
Age (years), Mean	42.3	45.0	47.8
Female, n (%)	12 (50%)	14 (54%)	12 (48%)
White, n (%)	24 (100%)	24 (92%)	24 (96%)
WB PPIX (ng/mL), Mean ± SE	8,691 ± 903	8,155 ± 1337	10,597 ± 983
Daily Sunlight Exposure (hr), Mean (range)	1.29 (0.18, 3.31)	1.17 (0.26, 4.03)	1.07 (0.04, 2.78)
Time to Prodrome, n (%)			
< 30 min	9 (38%)	9 (35%)	8 (32%)
≥ 30 min	15 (63%)	17 (65%)	17 (68%)

Primary Endpoint: Percent Change in Whole Blood PPIX

- Dose-dependent, significant reductions in PPIX
- PPIX reductions observed across all prespecified subgroups



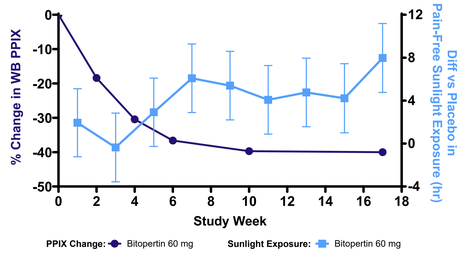
Least-squares means and p-values for percent changes in PPIX analyzed using a mixed model for repeated measures (MMRM) to compare 20-mg and 60-mg bitopertin dose groups to placebo.



Subgroup	n	p-value
Age < median	22	0.007
Age ≥ median	27	<0.001
Age < 65 years	44	<0.001
Age ≥ 65 years	5	0.844
BMI < 30 kg/m²	38	<0.001
BMI ≥ 30 kg/m²	10	0.032
South or West Region	17	<0.001
Midwest or Northeast	32	0.007
Hispanic	4	NC
Non-Hispanic	45	<0.001
Baseline Time to Prodrome < 30 min	17	0.001
Baseline Time to Prodrome ≥ 30 min	32	0.001
Baseline Metal-free PPIX < median	19	0.024
Baseline Metal-free PPIX ≥ median	30	0.001

Association between PPIX Change and Clinical Measures with Bitopertin

- Timing of PPIX reductions coincide with improvements in light tolerance
- Greater PPIX reductions in bitopertin participants reporting no phototoxic reactions (-36.5%) vs phototoxic reactions (-4.0%)
- Tertile analyses show PPIX reductions associated with improvements in multiple measures of light tolerance and how patients feel (PGIC)



Data for participants randomized to the bitopertin 60-mg group. Least-squares means results for percent change in WB metal-free PPIX levels and placebo-corrected total pain-free time in sunlight averaged over 2-week intervals are obtained from MMRM analyses.

Tertiles of PPIX Change: PPIX Increased ← → PPIX Decreased

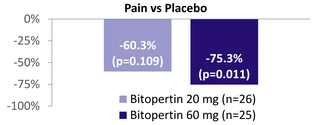
Clinical Measure	Tertile 3 (-7% to 191%) n=25	Tertile 2 (-38% to -7%) n=24	Tertile 1 (-89% to -38%) n=24
	Placebo, n=17; Bitopertin 20 mg, n=7; Bitopertin 60 mg, n=1	*Placebo, n=5; Bitopertin 20 mg, n=13; Bitopertin 60 mg, n=6*	*Placebo, n=2; Bitopertin 20 mg, n=6; Bitopertin 60 mg, n=16*
Cumulative total time in light without pain (mean ± SE, hr)	117.5 ± 16.6	124.5 ± 13.9	**161.1 ± 19.1**
Average daily time in light without pain (mean ± SE, hr)	1.16 ± 0.17	1.20 ± 0.15	**1.61 ± 0.27**
Change from baseline in time to prodrome (mean ± SE, min)	64.1 ± 8.4	109.4 ± 28.5	**117.4 ± 33.2**
Occurrence of phototoxic reaction (n,%)	8 (32%)	9 (38%)	**2 (8%)**
Occurrence of phototoxic reaction in last 60 days (n,%)	4 (16%)	5 (21%)	**1 (4%)**
PGIC Response of 'Much Better' (n,%)	12 (48%)	18 (75%)	**21 (91%)**

Only 57 patients completed sun exposure challenges at baseline and during the study period to calculate change from baseline in time to prodrome (n=20 in tertile 1, n=18 in tertile 2, n=19 in tertile 3).

Phototoxic Reactions with Pain

- Dose-dependent, significant reduction in rate of phototoxic reactions
- Max pain score from phototoxic reaction reduced with bitopertin

Incidence Rate Ratio of New Phototoxic Reactions with Pain vs Placebo



	Screening (2-4 weeks)		Double-Blind Period (17 weeks)		
	# of New Reactions	# of Subjects	# of New Reactions	# of Subjects	Median Max Pain Score
Placebo (n=24)	4	2 (8%)	15	11 (46%)	5.0
Bitopertin 20 mg (n=26)	11	8 (31%)	11	5 (19%)	4.0
Bitopertin 60 mg (n=25)	8	6 (24%)	5	3 (12%)	3.5

Safety

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

	Placebo (n=24)	Bitopertin 20 mg (n=26)	Bitopertin 60 mg (n=25)
Subjects with any TEAE	18 (75%)	20 (77%)	22 (88%)
TEAEs leading to discontinuation	0	0	2 (8%)
Serious adverse events	1 (4%)	0	0
TEAEs reported in >5 subjects			
Dizziness	4 (17%)	4 (15%)	11 (44%)
Median duration (days)	2.0	4.5	5.0
Nausea	2 (8%)	1 (4%)	4 (16%)
Alanine aminotransferase increased	3 (13%)	1 (4%)	2 (8%)

CONCLUSIONS

- AURORA met primary endpoint, with dose-dependent, statistically significant reductions in PPIX vs placebo
- PPIX reductions relative to placebo observed across all prespecified subgroups
- Reductions in PPIX were associated with improvements in multiple clinical outcomes, including measures of sunlight tolerance, reductions in phototoxic reactions, and how patients reported feeling (PGIC)
- Dose-dependent reductions in the rate of phototoxic reactions and associated pain from phototoxic events
- Bitopertin was well tolerated and safety profile in EPP consistent with prior studies in other indications enrolling >4,000 participants

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