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

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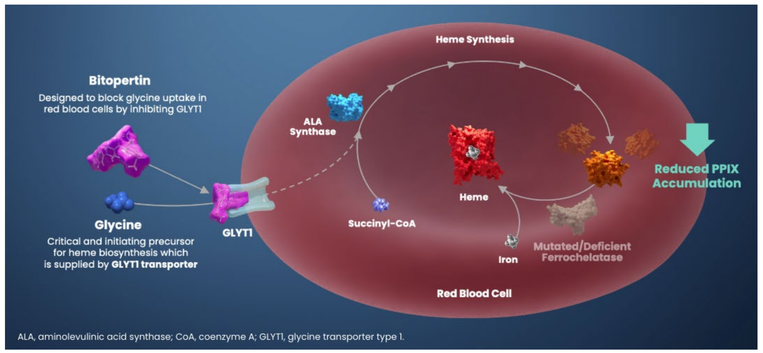
INTRODUCTION

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

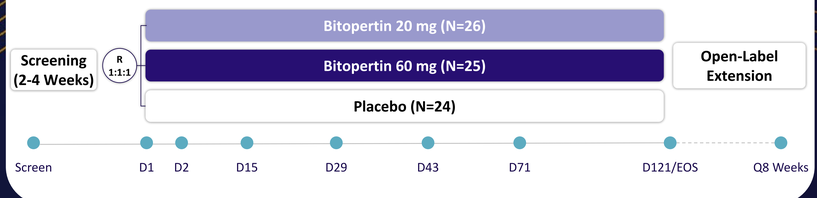
- Diagnosed by FECH/ALAS2 genotyping or biochemical porphyrin analysis
- 2-month washout of afamelanotide or dersimelagon

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)
- PGIC, patient-reported quality of life



RESULTS

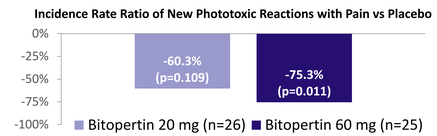
Disposition and Baseline Characteristics:

	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%)

Phototoxic Reactions with Pain

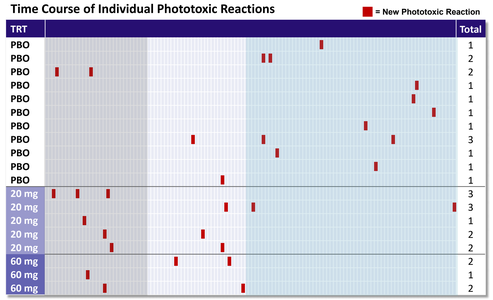
- Dose-dependent, significant reduction in rate of phototoxic reactions
- Greatest reduction in phototoxic reaction rate after Day 60
- Max pain score from phototoxic reaction reduced with bitopertin

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

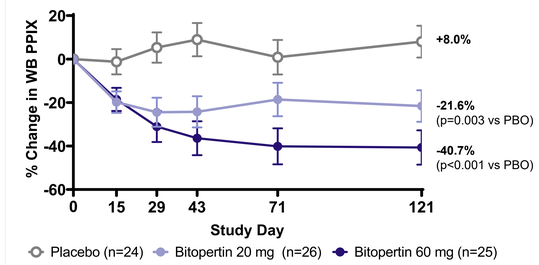
Time Course of Individual Phototoxic Reactions



Each row depicts a participant reporting new phototoxic reactions during the double-blind period and corresponding study day for new reaction (in red). Participants without a full phototoxic reaction throughout the entire study are not shown. PBO = placebo; 20 mg = bitopertin 20 mg; 60 mg = bitopertin 60 mg

Primary Endpoint: Percent Change in Whole Blood PPIX

- Dose-dependent, significant reductions in PPIX

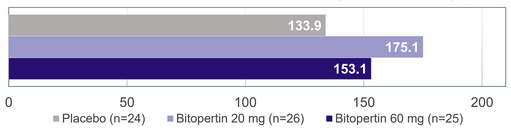


Least-squares means and p-values for percent changes in PPIX analyzed using a mixed model for repeated measures (MMRM) to compare 20 mg and 60 mg bitopertin dose groups to placebo.

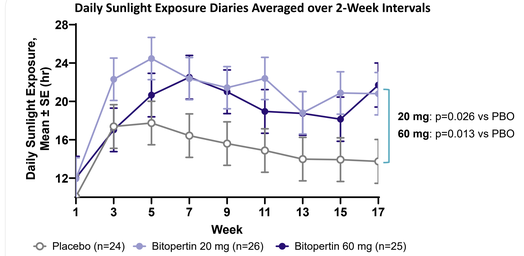
Key Secondary Endpoint: Cumulative Total Time in Light

- Bitopertin treatment effect similar to BEACON
- Not statistically significant compared to placebo
- Longitudinal analysis of daily sunlight exposure showed nominally significant improvements over time with bitopertin

Mean Cumulative 4-month Total Time in Light Without Pain (hr)



Daily Sunlight Exposure Diaries Averaged over 2-Weekly Intervals



Total daily sunlight exposure from 10:00 to 18:00 on days without pain averaged over 2-week periods and analyzed using MMRM to compare 20 mg and 60 mg bitopertin dose groups to placebo.

Association between PPIX Change and Light Tolerance

- Greater PPIX reductions in bitopertin participants reporting no phototoxic reactions (-36.5%) vs phototoxic reactions (-4.0%)
- PPIX reductions associated with improvements in multiple measures of light tolerance

Tertiles of PPIX Change

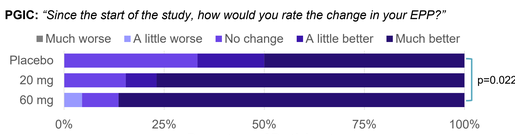
PPIX Decreased ← → PPIX Increased

Light Tolerance Measure (Mean ± SD)	Tertile 1 (-88% to -38%)	Tertile 2 (-38% to -7%)	Tertile 3 (-7% to 190%)
Cumulative total time in sunlight without pain (hr)	161.1 ± 142.6	124.5 ± 68.3	117.5 ± 83.2
Average time in sunlight without pain (hr)	1.61 ± 1.32	1.20 ± 0.72	1.16 ± 0.83
Change from baseline in time to prodrome (min)	117.4 ± 148.6	109.4 ± 121.1	64.1 ± 123.8

Quality of Life Measures

- Dose-dependent improvements in PGIC, reaching statistical significance in the 60 mg dose group at end of study
- Improvements in PGIC associated with reductions in PPIX

PGIC: *"Since the start of the study, how would you rate the change in your EPP?"*



Percentages calculated using data for PGIC from participants who completed the study (D121): n=26 for 20 mg bitopertin, n=22 for 60 mg bitopertin; n=24 for placebo

% PPIX Change	PGIC Response				
	Much worse	A little worse	No change	A little better	Much better
N	0	1	14	6	48
Mean (SD)	-	43.8	6.7 (64.9)	-0.4 (15.2)	-25.9 (31.7)

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 at both 20 mg and 60 mg doses
- Functional benefit observed with improvements in the key secondary endpoint at both 20 mg and 60 mg doses
- Dose-dependent reductions in the rate of phototoxic reactions and improvements in PGIC, with statistical significance at the 60 mg dose compared to placebo
- Consistent with profile for PPIX reductions, time course of phototoxic reactions and longitudinal analysis of daily sunlight exposure showed greater bitopertin treatment effect during the last 60 days of study
- Greater PPIX reductions associated with improvements in multiple light tolerance 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 individuals

REFERENCES

1. Heerfordt IM, Wulf HC. Br J Dermatol. 2016;175(6):1284-1289.
2. Wulf HC, Nissen CV, Philipsen PA. Photodiagnosis Photodyn Ther. 2020; 29:101582.
3. Poh-Fitzpatrick MB. J Am Acad Dermatol. 1997;36(1):40-43.
4. Garcia-Santos D, Schranzhofer M, Bergeron R, et al. Haematologica. 2017; 102(8):1314-1323.
5. Halloy F, Iyer P, Ghidini A, et al. Cell Chem Biol. 2021;28(8):1221-1234.

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