AURORA Topline Data

Bitopertin in EPP

April 1, 2024

disc medicine

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Bitopertin is an investigational agent and is not approved for use as a therapy in any jurisdiction worldwide

Agenda

01 **Introduction and Data Summary**
John Quisel, J.D., PhD, CEO

02 **Detailed Review of Topline AURORA Data**
Will Savage, M.D., PhD, CMO

03 **Closing Remarks**
John Quisel, J.D., PhD, CEO

04 **Q&A Session**

EPP Phase 2 Development Program

BEACON and AURORA Trials

BEACON

- **EPP and XLP**; N = >22 (fully enrolled for adults and adolescents)
- **Australia** (study opened July ’22)
- **Open-label, randomized, 24-week study**

Today’s Focus

AURORA

- **EPP**; N = 75 (fully enrolled)
- **US** (study opened October ’22)
- **Double-blind, placebo-controlled, 17-week study**

Key Takeaways from Topline AURORA Data

- Met primary endpoint demonstrating dose-dependent, statistically significant reductions in PPIX compared to placebo in both dose groups
- On the key secondary endpoint of cumulative time in sunlight, bitopertin patients had a positive response consistent with BEACON results, but the endpoint did not meet statistical significance due to strong placebo performance
- Dose-dependent reductions in the rate of phototoxic reactions with pain and improvements in PGIC, with statistical significance for the 60 mg dose group
- Generally well-tolerated with stable hemoglobin levels

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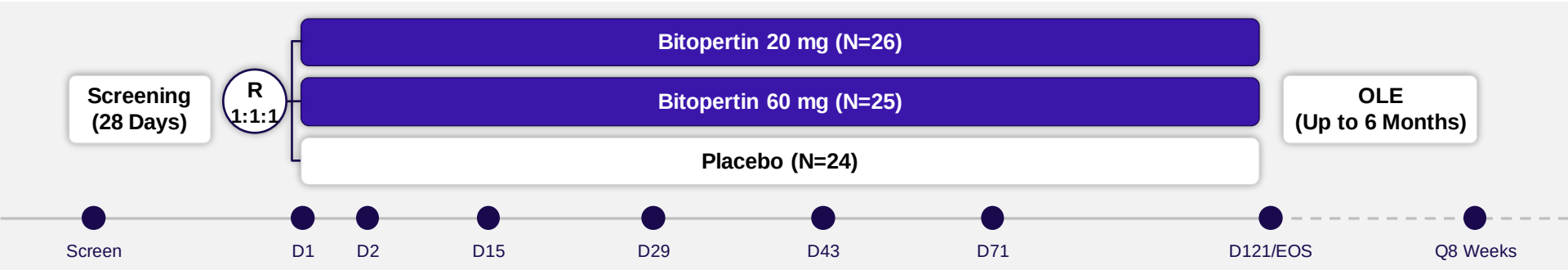
AURORA Trial Overview



Key Endpoints

- **Primary: percent change in PPIX**
- **Key Secondary: total time in sunlight on days with no pain from 10:00 am to 6:00 pm**
- **Secondary: time to prodromal symptom, pain intensity of phototoxic reactions**
- **Exploratory: patient-reported outcome measures, rate of phototoxic reactions**

Key Eligibility

- **Diagnosis of EPP**
- **≥ 18 years of age**
- **≥ 2-month washout of afamelanotide or dersimelagon**
- **Hgb ≥ 10 g/dL**
- **ALT/AST < 2x ULN**

Time to prodromal symptom = the time until a participant experiences an early warning signal of a phototoxic attack measured through a weekly sunlight challenge. If a participant is unable to elicit a prodrome during a sunlight challenge, the amount of time the participant chose to remain in light is recorded. R = randomization; D = day; EOS = end of study; OLE = open-label extension; PPIX = protoporphyrin IX; Hgb = hemoglobin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

Disposition and Baseline Characteristics

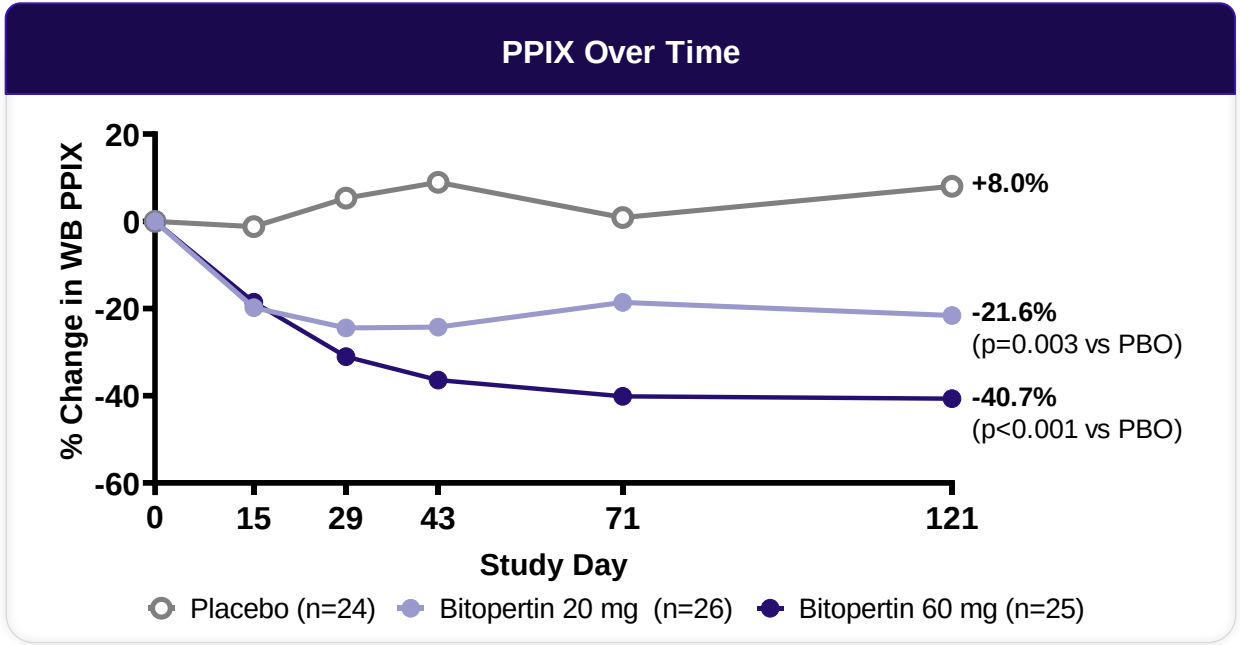
	Placebo (n=24)	Bitopertin 20 mg (n=26)	Bitopertin 60 mg (n=25)
Randomized	24	26	25
Completed Study	24	26	22
Discontinued Prior to Day 121	0	0	3
Characteristic			
Mean Age, years	42.3	45.0	47.8
Female, n (%)	12 (50%)	14 (54%)	12 (48%)
White, n (%)	24 (100%)	24 (92%)	24 (96%)
Baseline PPIX, Mean ± SE (ng/mL)	8,691 ± 903	8,155 ± 1337	10,597 ± 983
Time to Prodrome, n (%)			
< 30 min	9 (38%)	9 (35%)	8 (32%)
≥ 30 min	15 (63%)	17 (65%)	17 (68%)
Geography, n (%)			
Midwest or Northeast	17 (71%)	15 (58%)	15 (60%)
South or West	7 (29%)	11 (42%)	10 (40%)
Seasonality, n (%)[a]			
Fall/Winter	10 (42%)	12 (46%)	11 (44%)
Spring/Summer	14 (58%)	14 (54%)	14 (56%)

[a] Season that encompasses majority of participant's double-blind treatment period

AURORA Met Primary Endpoint

Statistically Significant Reductions in Whole-Blood (WB) Metal-Free PPIX

- Bitopertin reduced PPIX levels consistent with BEACON
- Significant reductions observed in both 20 mg and 60 mg doses

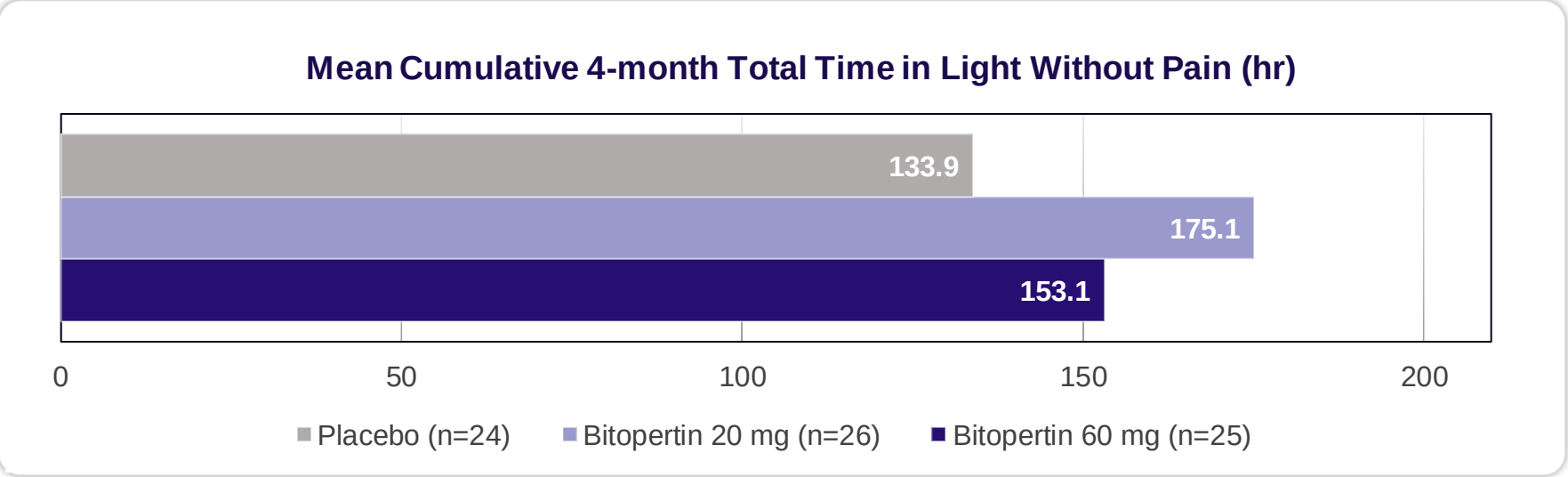


Least-squares means and p-values for percent changes in PPIX analyzed using a mixed model for repeated measures (MMRM) to compare 20 mg 60 mg bitopertin dose groups versus placebo.

AURORA Topline Data: Key Secondary Endpoint

Cumulative Time in Light without Pain

- Bitopertin treatment effect similar to BEACON results
- Did not meet statistical significance due to strong performance of placebo arm

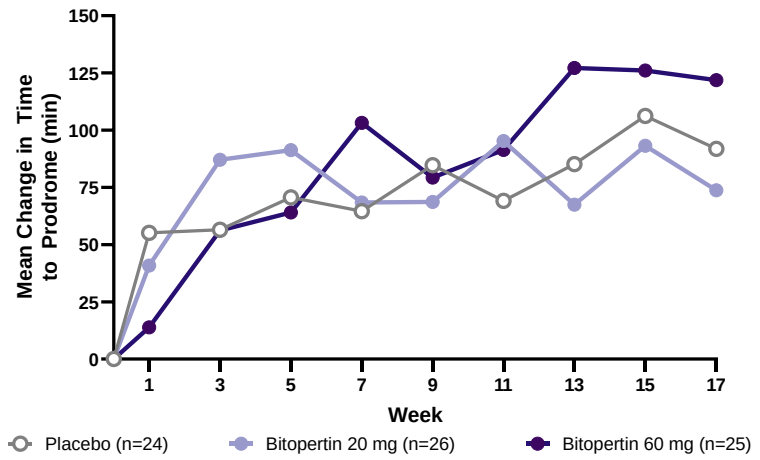


Least-squares means for cumulative time in light measured via daily diary, adding all time in light between the hours of 10:00 am and 6:00 pm on days without any pain, and analyzed using an analysis of variance model to compare 20 mg 60 mg bitopertin dose groups versus placebo.

AURORA Topline Data: Light Tolerance

- Large improvements in light tolerance in all treatment groups, as measured by the time to prodrome assessed in weekly sunlight challenges

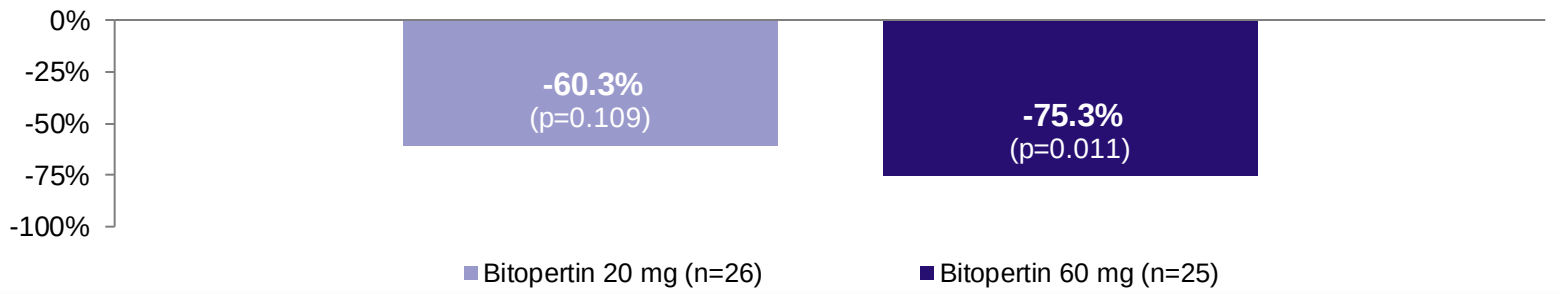
Time to Prodrome Averaged Over 2-Week Intervals



AURORA Topline Data: Phototoxic Reactions with Pain

- Dose-dependent reduction in rate of phototoxic reactions with pain, reaching statistical significance in the 60 mg dose group

Incidence Rate Ratio of New Phototoxic Reactions with Pain vs. Placebo

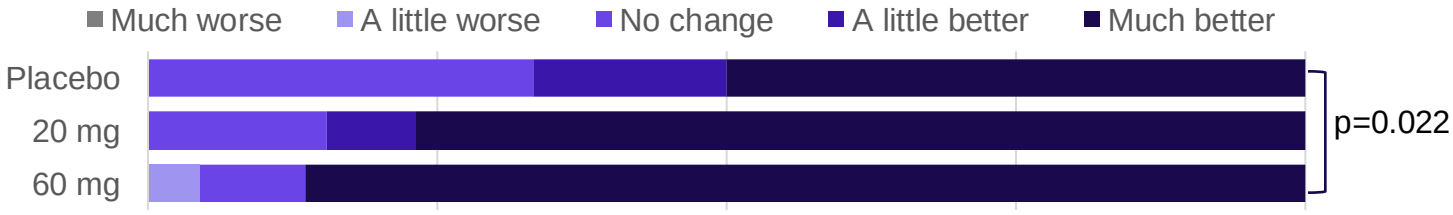


	Screening (2-4 weeks)		Double-Blind Period (17 weeks)	
	# of New Reactions	# of Subjects	# of New Reactions	# of Subjects
Placebo (n=24)	4	2 (8%)	15	11 (46%)
Bitopertin 20 mg (n=26)	11	8 (31%)	11	5 (19%)
Bitopertin 60 mg (n=25)	8	6 (24%)	5	3 (12%)

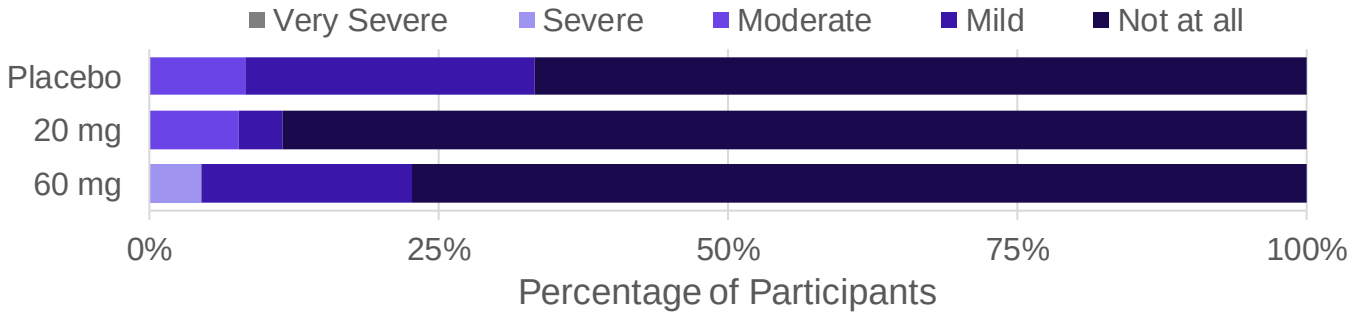
AURORA Topline Data: Patient-Reported Outcomes

- Dose-dependent improvements in Patient Global Impression of Change (PGIC), reaching statistical significance in the 60 mg dose group at end of study

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



PGIS: *"Overall, how severe was your EPP in the past 7 days?"*



Percentages calculated using data for PGIC and PGIS from participants who completed the study (D121): n=26 for 20 mg bitopertin, n=22 for 60 mg bitopertin; n=25 for placebo; PGIS = patient global impression of severity

Safety and Tolerability

- No serious adverse events with bitopertin
- Stable hemoglobin levels
- Favorable safety profile consistent with prior studies enrolling >4,000 participants

	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%)
SAEs	1 (4%)	0	0
Common TEAEs			
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%)

TEAEs leading to discontinuation: rash and dizziness; common TEAEs include those reported in >5 participants during study regardless of treatment assignment.
AE = adverse event; Hgb = hemoglobin; TEAE = treatment-emergent adverse event

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Key Takeaways and Next Steps

- **Met primary endpoint, demonstrating dose-dependent, statistically significant reductions in protoporphyrin IX (PPIX) compared to placebo in both 20 mg and 60 mg dose groups**
- **Improved measures of light tolerance, including the key secondary endpoint, in both 20 mg and 60 mg dose groups, but did not meet statistical significance compared to placebo**
- **Dose-dependent reductions in the rate of phototoxic reactions with pain and improvements in PGIC, with statistical significance at the 60 mg dose group compared to placebo**
- **Generally well-tolerated with stable hemoglobin levels**

Next Steps for Bitopertin in EPP

- We plan to further evaluate the data internally and with KOLs, regulators, and patient advocacy groups to determine the optimal registrational endpoints moving forward

Projected Upcoming Milestones and Events

Multiple additional data catalysts anticipated in 2024 across portfolio

Program	Indication	H1 2024	H2 2024	2025
Bitopertin Heme Synthesis Modulator	**Erythropoietic Porphyrias (EPP and XLP)**	• Phase 2 AURORA Data (March-April)	• End of Ph 2 Meeting / Other Regulatory Interaction	• Development Activities Pending Regulatory Feedback
	Diamond-Blackfan Anemia (DBA)		• Initial Phase 2 Data	
DISC-0974 Hepcidin Suppression	**Anemia of Myelofibrosis (MF)**	• Updated Phase 1b Data	• Final Phase 1b Data • Initiate Phase 2 Study	• Phase 2 Topline Data
	Anemia of Chronic Kidney Disease (CKD)		• Phase 1b Data (hemoglobin)	• Phase 2a Topline Data
DISC-3405 Hepcidin Induction	**Polycythemia Vera and Diseases of Iron Overload / Ineffective Erythropoiesis**	• Phase 1 SAD Data	• Phase 1 SAD/MAD Data	• Phase 2 in PV Initiation

Supported by a strong financial position with $360M in cash[1], which funds all catalysts well into 2026

SAD = single ascending dose; MAD = multiple ascending dose; PV = polycythemia vera

[1]As of December 2023

Thank You

We would like to extend our gratitude to the patients and families that participated in AURORA, investigators, advocacy groups, and our team

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