Bitopertin in EPP: Initial Data from Phase 2 Open-label BEACON Trial – EHA 2023

Investor Webcast | June 9, 2023
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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 Initial BEACON Data
Will Savage, M.D., PhD, CMO

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

04 Q&A Session
Key Takeaways from Initial BEACON Data

Initial data demonstrated:

- Dose-dependent reductions in PPIX levels >30% at low and high doses
- Significant effects on sunlight tolerance
- Improved patients’ reported quality of life
- No meaningful changes in hemoglobin levels observed

Data to-date provides evidence of proof of concept and potential functional benefit for EPP patients

Data reflect initial results from 15 subjects enrolled as of the data cutoff of May 8, 2023, with a range of treatment durations from 18 days to 6 months. The data cutoff for PPIX data was April 7, 2023.
Erythropoietic Protoporphyria (EPP)
Rare, debilitating and lifelong condition characterized by extreme pain and damage to skin caused by light

Genetic condition caused by defective heme biosynthesis – deficient enzyme ferrochelatase
- Lifelong and presents in early childhood
- Caused by accumulation of toxic metabolite PPIX
- XLP, mechanistically similar disease, also PPIX-related

Debilitating and potentially life-threatening
- Skin: severe phototoxicity, disabling pain attacks (days), edema
- Hepatobiliary disease: gallstones, liver dysfunction or failure
- Psychosocial well-being (fear, anxiety) and development

No cure or disease-modifying treatment
- Avoid sun / light, protective clothing, window tinting, Zn/Ti Oxide
- One FDA-approved agent, afamelanotide, a surgically-implanted tanning agent

EPP and XLP Prevalence:
Approximately 7-8k+ addressable patients in US and Europe; recent genetic studies suggest number may be higher

Image sources: Daily Mail Australia (2019); FDA Scientific Workshop on EPP (2016); Buonuomo et al. (2014) Arch Dis Child
PPIX is a Driver of Disease in EPP / XLP Patients
Accumulation of toxic and photo-active metabolite results in a variety of complications

**Skin**
- Porphyrin ring absorbs light and **emits energy and heat**
- Oxidative damage to endothelial capillaries and surrounding tissue, perivascular edema, complement activation
- Pain, burning sensation, swelling, inflammation, chronic skin lesions

**Psychosocial**
- Issues with focus and concentration
- Lack of sleep, physical and social isolation
- Significant lifestyle modification, fear and anxiety

**Hepatobiliary**
- PPIX accumulation in bile canaliculi, causing oxidative damage
- Cholelithiasis requiring surgery or impaired liver function (~25%) and end-stage liver disease requiring transplant (2-5%)
- Clinical and biochemical surveillance

**Other Complications**
Nutritional deficiency resulting in osteoporosis and propensity for fractures, chronic alterations to skin (e.g., fragile), mild anemia
Bitopertin: Investigational, Oral, Selective GlyT1 Inhibitor
Designed to reduce disease-causing PPIX by limiting uptake of glycine into developing erythrocytes

Glycine
Critical and initiating precursor for heme biosynthesis and is supplied by GlyT1 transporter

Bitopertin
Designed to block glycine uptake in RBCs by inhibiting GlyT1

Heme Biosynthesis Pathway

Heme
Porphyrin Synthesis
Protoporphyrin IX (PPIX)
Hemoglobin
A >30% reduction in PPIX levels has been shown to significantly impact photosensitivity.

### Pregnant EPP Patients

- During pregnancy, EPP patients experience a **30-50% reduction in PPIX levels**
- This reduction is accompanied by a **marked improvement in light tolerance**

### PPIX Photoinactivation Study

- Patients' blood was exposed to light outside their body then returned to the patient
- The procedure reduced PPIX levels by ~30%
- As a result, **daylight tolerance was increased by 14x** on average (e.g., from 30 minutes at baseline to 7 hours post-treatment)

Bitopertin Reduced PPIX in Models of EPP / XLP

Effects on PPIX have the potential to be disease-modifying

In these models, bitopertin reduced PPIX, the driver of disease pathophysiology, and, based on the data, is expected to be disease-modifying.

Data presented at the 63rd ASH Annual Meeting (December 2021); Studies performed in collaboration with Boston Children’s Hospital (PI: Paul Schmidt, Advisor: Mark Fleming)
Two Ongoing Phase 2 Clinical Trials
BEACON, an open-label, parallel-dose trial in Australia, and AURORA, a US-based double-blind, placebo-controlled trial

Today’s Focus

BEACON

- EPP and XLP; N = ~22
- Australia (study open July ‘22)
- Open-Label, randomized, 24-week study

AURORA

- EPP; N = ~75
- US (study open October ‘22)
- Double-blind, placebo-controlled, 17-week study

Trial Endpoints:
Changes in blood PPIX levels, light tolerance, time to prodromal symptom (TTPS), safety, tolerability, and PK
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BEACON Trial Overview
Enrollment data as of 8 May 2023

<table>
<thead>
<tr>
<th></th>
<th>Bitopertin 20 mg (n=8)</th>
<th>Bitopertin 60 mg (n=7)</th>
<th>Total (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>8</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Completed Day 43</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Completed Treatment Period (Day 169)</td>
<td>0</td>
<td>1</td>
<td>1</td>
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</tbody>
</table>

Screening (28 Days)
Randomized, Treatment Period (6 months)
1:1 Bitopertin 20mg (N=11) and Bitopertin 60 mg (N=11)
OLE (Up to 6 Months)

Trial Endpoints: Changes in blood PPIX levels, light tolerance, time to prodromal symptom (TTPS)*, safety, tolerability, and PK

*Time to prodromal symptom = the time until a patient experiences an early warning signal of a phototoxic attack, measured through a weekly sunlight challenge; If a patient was unable to elicit a prodrome during a sunlight challenge, the patient would record the amount of time that the patient chose to remain in light
EOS = end of study; OLE = open label extension
Primary Endpoint: % Change in Whole-Blood PPIX

- Whole-blood (WB) metal-free PPIX reduction was observed in trial participants.
- Dose-dependent reductions were observed across broad range of baseline WB PPIX levels (140-3,410 µg/dL)

### PPIX Changes Over Time

#### Study Day

<table>
<thead>
<tr>
<th>% Change in WB PPIX</th>
<th>0</th>
<th>15</th>
<th>29</th>
<th>43</th>
<th>71</th>
<th>113</th>
<th>155</th>
<th>169</th>
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</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0</td>
<td>15</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>20 mg</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>60 mg</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

### Individual PPIX Data

#### Study Day

<table>
<thead>
<tr>
<th>% Change in WB PPIX</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>20 mg</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>60 mg</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

PPIX data as of 7 April 2023
Light Tolerance: Time to First Prodromal Symptom
Individual Patient Sunlight Challenges (20 mg QD)

>80x increase in sunlight challenge time
Patient did not report a prodrome with sunlight challenge after Day 20

Study Day
BL 20 27 41 47 63 82 88 96 125 147 154

Sunlight Challenge Time (min)

0 100 200 300 400

4.5 min

>80x

Dose:
20 mg

Baseline PPIX
2,740 µg/dL

Day 71 Change in PPIX:
-30%

Day 155 Change in PPIX:
-38%

Prodrome-Free
Prodrome

Additional data not visible due to y-axis scale include prodrome (*) after 2 minutes of sunlight and prodrome-free (•) challenge with 4 minutes of sunlight.
Sunlight challenge time for individual participant while receiving 20 mg of bitopertin. Participants could complete more than 1 sunlight exposure challenge per week and if a patient was unable to elicit a prodrome during a sunlight challenge (blue bars), the patient would record the amount of time that the patient chose to remain in sunlight.

Day 71 Change in PPIX:
-30%

Day 155 Change in PPIX:
-38%
Light Tolerance: Time to First Prodromal Symptom
Individual Patient Sunlight Challenges (60 mg QD)

>200x increase in sunlight challenge time
Patient did not report a prodrome with most sunlight challenges after Day 57

Sunlight challenge time for individual participant while receiving 60 mg of bitopertin. Participants could complete more than 1 sunlight exposure challenge per week and if a patient was unable to elicit a prodrome during a sunlight challenge (blue bars), the patient would record the amount of time that the patient chose to remain in sunlight.

**Dose:**
- 60 mg

**Baseline PPIX**
- 1,100 µg/dL

**Day 71 Change in PPIX:**
- -59%

**Day 169 Change in PPIX:**
- -72%

**Prodrome-Free**
- Prodrome-Free

**Prodrome**
- Prodrome
Light Tolerance: Days without Symptoms or Prodromes

- 96% reduction in patient-reported full phototoxic reactions*
- An increase in the proportion of total symptom-free days (no prodrome / early warning symptoms or full phototoxic reactions) with sun exposure was observed***

<table>
<thead>
<tr>
<th>Days w/ Sun Exposure</th>
<th>Symptom-Free Days*</th>
<th>Prodrome-Free Sunlight Challenges**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>25%</td>
<td>0%</td>
</tr>
<tr>
<td>On-Treatment</td>
<td>75%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Percentages calculated relative to total number of days with sunlight exposure (left) or total number of weekly sunlight exposure challenges (right) from all study participants (n=15) during screening or while receiving bitopertin (20 mg and 60 mg dose groups combined).
Patients reported an increase in average time to prodrome, and average total time patients were able to spend in the sun over a one-week period, for both 20 mg and 60 mg groups.
Measures of Quality of Life

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

Patient Global Impression of Change at Day 43
10/10 participants reported their EPP was much better (n=8) or a little better (n=2)

Patient Global Impression of Severity at Day 43
9/10 participants reported their EPP was mild (n=3) or not at all severe (n=6)

QOL data may be entered at Day 43 ± 3 days and includes data from 1 participant who had not completed Day 43 visit; Responses at baseline or most recent visit while receiving bitopertin (combined 20/60 mg doses, n=10), subjects with data beyond Day 43 shown in blue; for subjects at Day 43, relative improvements noted in green and no change in grey; Responses based on replies to EPP Questionnaire
Safety and Tolerability

- No reported serious adverse events
- No observed meaningful changes in mean hgb levels
- No reported discontinuations or dose reductions
- All reported TEAEs were Grade 1 in severity and transient (median / mean time to resolution, 0.5 / 2 days)

### Table: Total Number of TEAEs

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Number of TEAEs</strong> (all Grade 1)</td>
<td>8</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td><strong>Subjects with any TEAE</strong> (all Grade 1)</td>
<td>6 (75%)</td>
<td>6 (86%)</td>
<td>12 (80%)</td>
</tr>
<tr>
<td><strong>TEAEs reported in &gt;1 subject</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (50%)</td>
<td>5 (71%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (25%)</td>
<td>1 (14%)</td>
<td>3 (20%)</td>
</tr>
</tbody>
</table>

Data as of 8 May 2023. Summaries include uncoded TEAEs categorized by verbatim terms; hgb = hemoglobin.
Summary of Initial Data from BEACON

**Proof of Concept**
- Consistent reduction in PPIX at low and high doses

**Functional Outcomes**
- Significant effect on sunlight tolerance compared to baseline

**QoL Impact**
- Patients reported an improved quality of life

**Safety**
- No meaningful change in hemoglobin observed in patients treated with bitopertin
## Bitopertin Development Status and Upcoming Milestones

### Next EPP Milestones

- **BEACON trial data** – data from all subjects to be presented **YE 2023**

- **AURORA trial data** – data expected **YE 2023**, to be presented **early 2024**

### Additional Bitopertin Milestones

- Phase 2 NIH-led trial in Diamond-Blackfan Anemia—IND accepted; startup expected mid-year **2023**

- Planning underway for clinical and preclinical studies in additional indications
Q&A
Thank You