Bitopertin in EPP:

Initial Data from Phase 2 Open-label BEACON Trial – EHA 2023

Investor Webcast | June 9, 2023

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 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

Data to-date[1] provides evidence of proof of concept and potential functional benefit for EPP patients

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**

[1]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

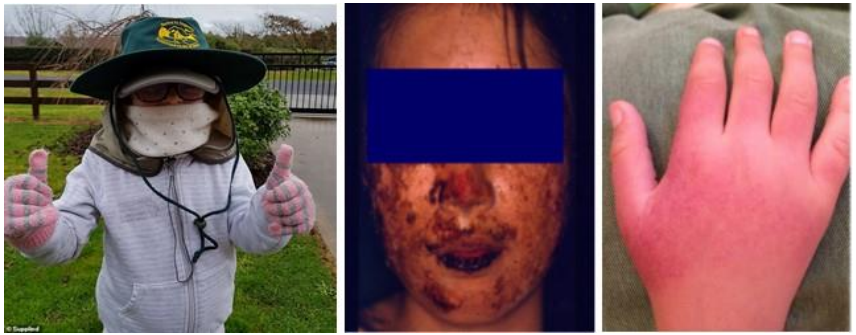


Image sources: *Daily Mail Australia* (2019); FDA Scientific Workshop on EPP (2016); Buonuomo et al. (2014) *Arch Dis Child*

Sources: Deybach et al (2009) *Orphanet Journal of Rare Diseases; American Porphyria Foundation;* Dickey et al (2021) *Genet. Med*
XLP = X-linked protoporpyria.

PPIX is a Driver of Disease in EPP / XLP Patients

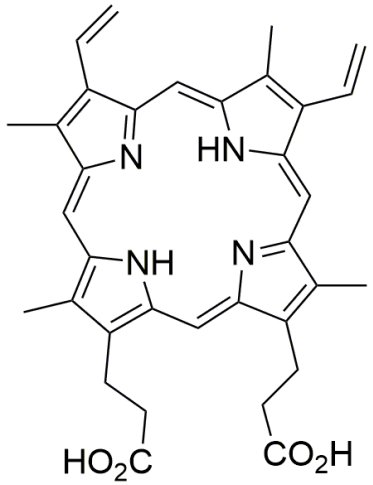
Accumulation of toxic and photo-active metabolite results in a variety of complications

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



Protoporphyrin IX

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

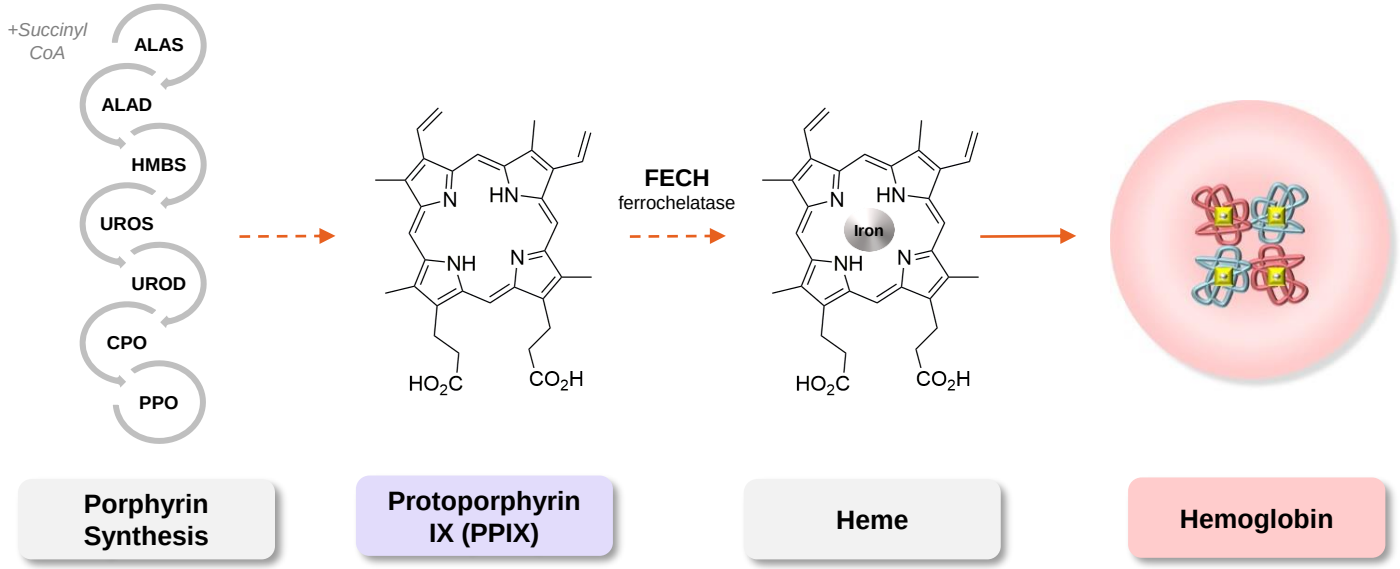
Designed to reduce disease-causing PPIX by limiting uptake of glycine into developing erythrocytes

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

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

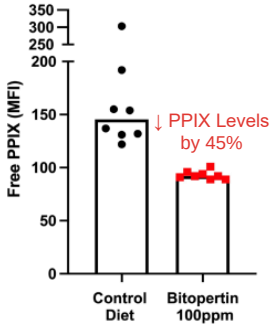
- Patients' blood was exposed to light outside their body then returned to the patient
- The procedure reduced PPIX levels by ~30%
- As a result, **daylight tolerance was increased by 14x** on average (e.g., from 30 minutes at baseline to 7 hours post-treatment)

Poh-Fitzpatrick, J Am Acad Dermatol 1997;36:40-3; Wulf et al. Photodiagnosis Photodyn Ther. 2020;29:101582

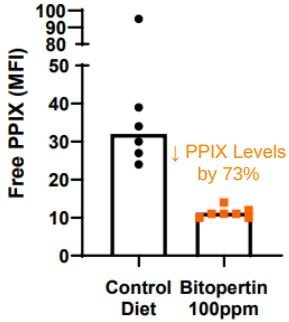
Bitopertin Reduced PPIX in Models of EPP / XLP

Effects on PPIX have the potential to be disease-modifying

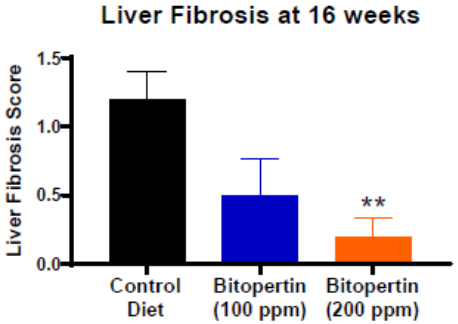
In vivo - EPP Model (Mouse)
FECH^{m1pas} Missense Mutation



In vivo - XLP Model (Mouse)
ALAS2^{Q548X} Gain-of-Function Mutation



In vivo – EPP Model (Mouse)
FECH^{m1pas} Missense Mutation



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

	Bitopertin 20 mg (n=8)	Bitopertin 60 mg (n=7)	Total (n=15)
Enrolled	8	7	15
Completed Day 43	5	4	9
Completed Treatment Period (Day 169)	0	1	1

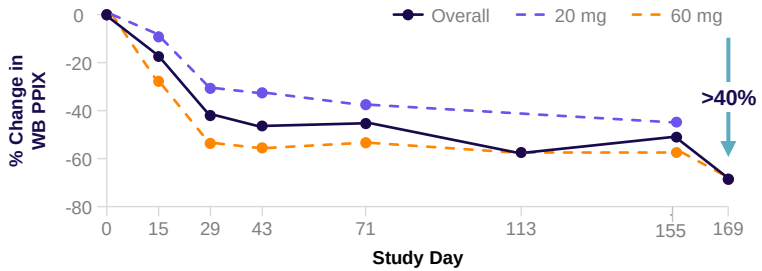
Trial Endpoints: Changes in blood PPIX levels, light tolerance, time to prodromal symptom (TTPS)*, safety, tolerability, and PK

*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

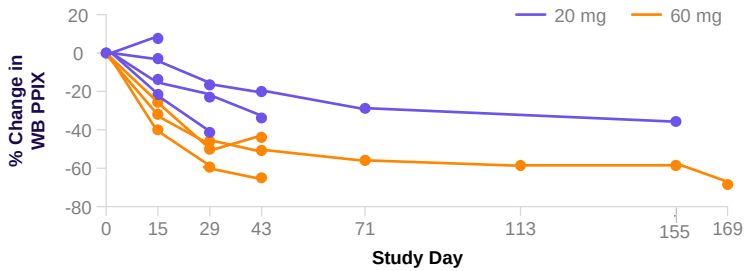
- Whole-blood (WB) metal-free PPIX reduction was observed in trial participants
- Dose-dependent reductions were observed across broad range of baseline WB PPIX levels (140-3,410 µg/dL)

PPIX Changes Over Time



Overall N	15	9	6	5	2	1	2	1
20mg	8	5	3	2	1	0	1	0
60mg	7	4	3	3	1	1	1	1

Individual PPIX Data



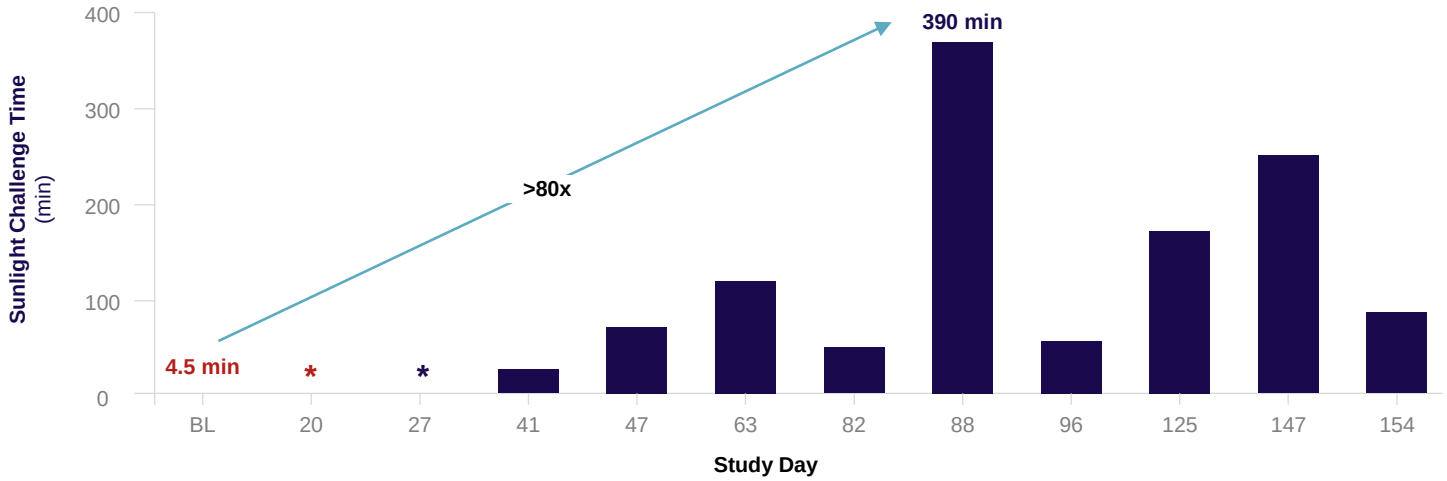
20 mg	8	5	3	2	1	0	1	0
60 mg	7	4	3	3	1	1	1	1

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



Dose:
20 mg

Baseline PPIX
2,740 µg/dL

Day 71 Change in PPIX:
-30%

Day 155 Change in PPIX:
-38%

Prodrome-Free
Prodrome

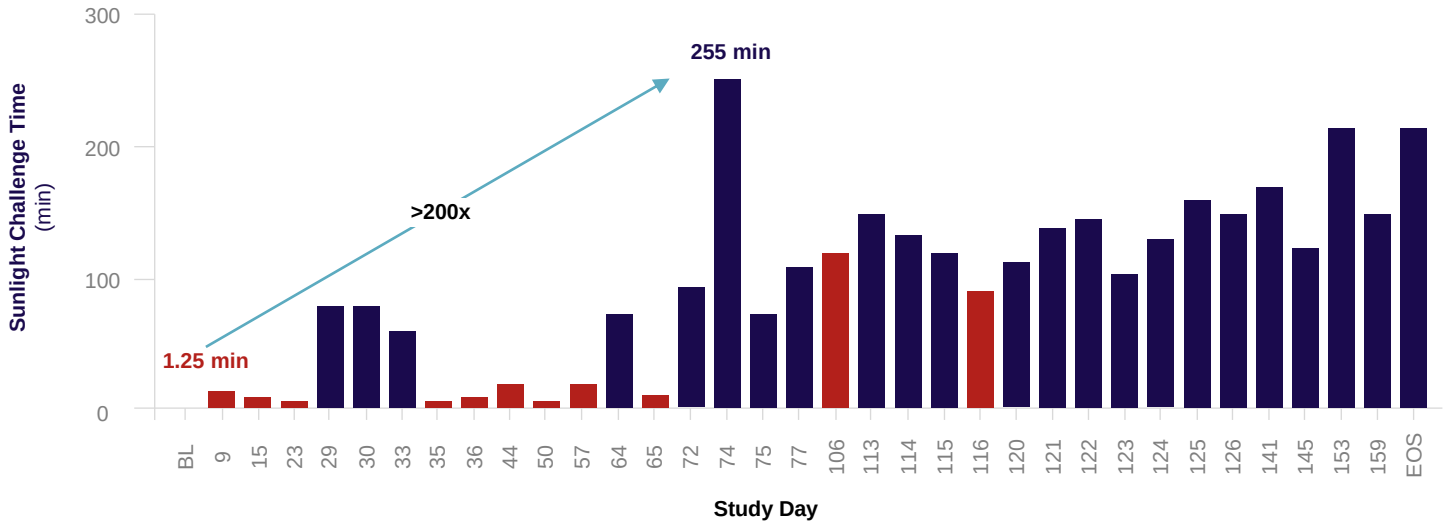
Additional data not visible due to y-axis scale include prodrome (*) after 2 minutes of sunlight and prodrome-free (*) challenge with 4 minutes of sunlight

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

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



Dose:
60 mg

Baseline PPIX
1,100 µg/dL

Day 71 Change in PPIX:
-59%

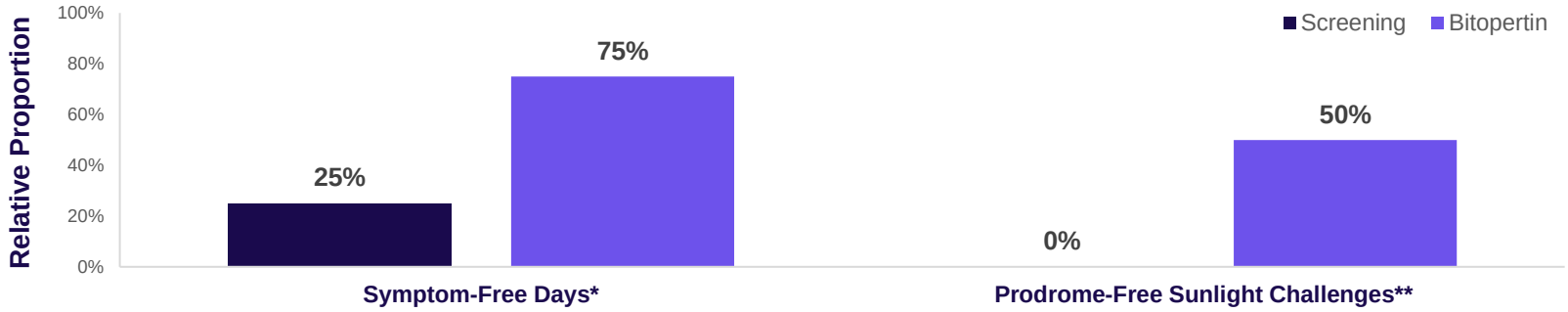
Day 169 Change in PPIX:
-72%

Prodrome-Free
Prodrome

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

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***



	Days w/ Sun Exposure	Sunlight Challenges
Screening	163	42
On-Treatment	679	135

*as assessed with a daily diary; **as assessed with a weekly sunlight challenge; ***summed across all patients

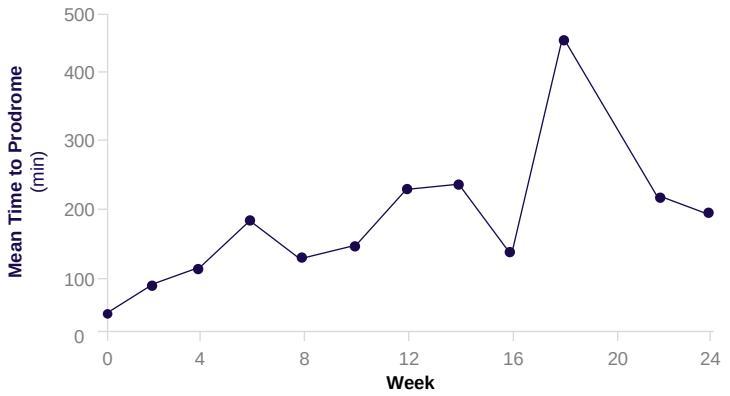
Percentages calculated relative to total number of days with sunlight exposure (left) or total number of weekly sunlight exposure challenges (right) from all study participants (n=15) during screening or while receiving bitopertin (20 mg and 60 mg dose groups combined).

Light Tolerance: Aggregated Data

Time to Prodrome and Weekly Total Time in Sunlight

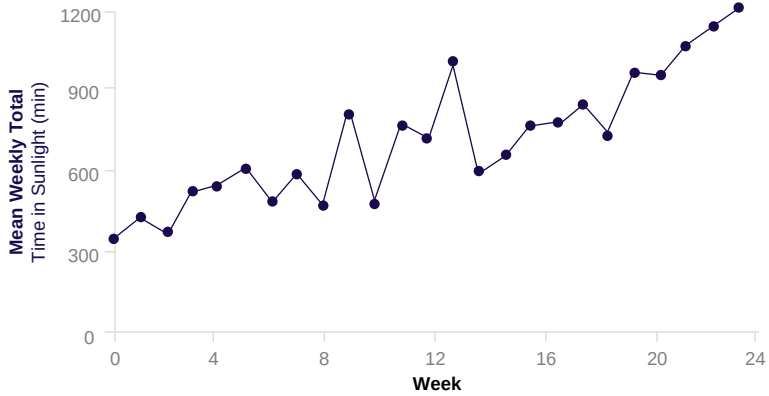
Patients reported an increase in average time to prodrome, and average total time patients were able to spend in the sun over a one-week period, for both 20 mg and 60 mg groups

Time to Prodrome



No. of Subjects	15	13	14	11	8	4	5	1	1	2		2	1
No. of Challenges	42	27	30	25	13	8	10	2	1	12		5	2

Weekly Total Time in Sunlight



No. of Subjects	15	14	13	11	8	5	4	3	2	2	2	2	1
No. of Diary Entries	163	55	64	39	28	20	21	13	12	13	11	11	7

Time to prodrome during weekly sun exposure challenges averaged over a two-week period, including cumulative time in sunlight challenges where the patient did not report a prodrome (left); 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. Data are averaged for 20 mg and 60 mg bitopertin dose groups combined.

Average total time in sun recorded in daily sun exposure diaries over a one-week period for 20 mg and 60 mg bitopertin dose groups combined. Incomplete diary entries counted as zero minutes; The data for weeks 23 and 24 represents the available diary data for completed weeks at the time of the data cut-off and represents 1 subject

Measures of Quality of Life

Patient Global Impression of Change at Day 43

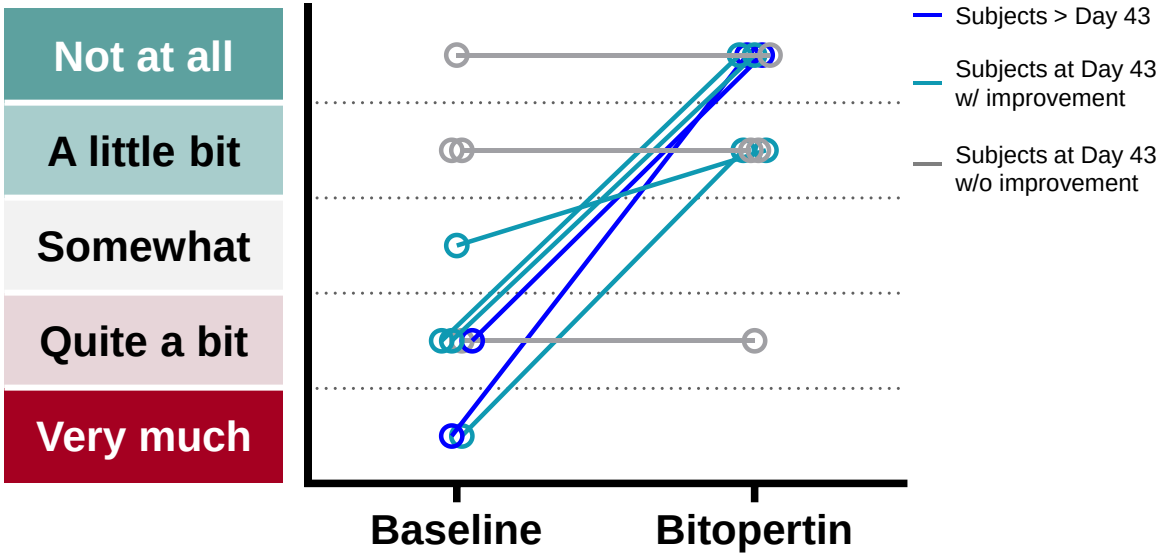
10/10 participants reported their EPP was **much better** (n=8) or a **little better** (n=2)

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)

EPP Questionnaire

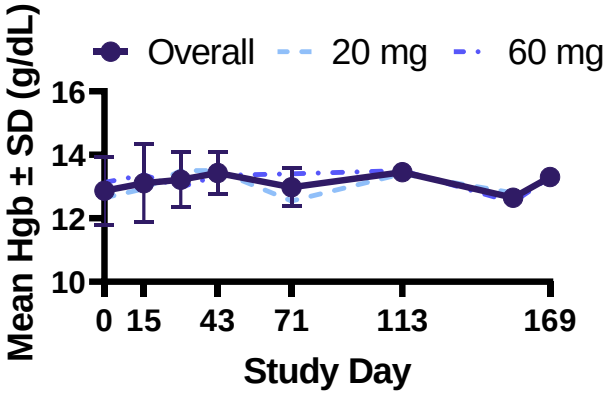
"In the past 7 days, how much did having EPP impact your overall quality of life?"



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)



	Bitopertin 20 mg (n=8)	Bitopertin 60 mg (n=7)	Total (n=15)
Total Number of TEAEs (all Grade 1)	8	8	16
Subjects with any TEAE (all Grade 1)	6 (75%)	6 (86%)	12 (80%)
TEAEs reported in >1 subject			
Dizziness	4 (50%)	5 (71%)	9 (60%)
Headache	2 (25%)	1 (14%)	3 (20%)

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

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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

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Thank You

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