BEACON: A PHASE 2, RANDOMIZED, OPEN LABEL STUDY OF BITOPERTIN TO EVALUATE THE SAFETY, TOLERABILITY, EFFICACY, AND PROTOPORPHYRIN IX CONCENTRATIONS IN PARTICIPANTS WITH ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

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INTRODUCTION

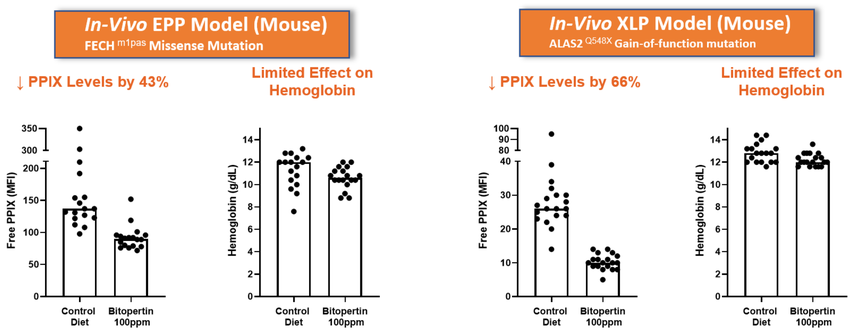
Erythropoietic protoporphyria (EPP) is caused by mutations in the Ferrochelatase (FECH) or 5′-aminolevulinate synthase 2 (ALAS2) genes, resulting in toxic accumulation of photoreactive protoporphyrin IX (PPIX). High levels of PPIX can result in debilitating phototoxic skin reactions, as well as hepatopathy caused by biliary stasis. Reduction of PPIX is associated with amelioration of disease in the settings of hematopoietic stem cell transplant, pregnancy and extracorporeal photoinactivation.[1-3]

Bitopertin is a small molecule inhibitor of glycine transporter 1 (GlyT1), which imports extracellular glycine into erythropoietic precursors. GlyT1 is needed to supply adequate amounts of glycine for the heme synthesis pathway to enable the large amounts of hemoglobin needed for normal red blood cell production.[4]

Figure 1: Mechanism of Disease and Bitopertin Treatment[4]

In EPP mouse models with *FECH* or *ALAS2* mutations, treatment with bitopertin resulted in 43-66% reduction in blood PPIX levels, as compared to controls.[5] These data, combined with a favorable safety profile of bitopertin that has previously been established in clinical trials with over 4,000 participants and healthy volunteers, motivates the current study to evaluate this potentially disease-modifying treatment.

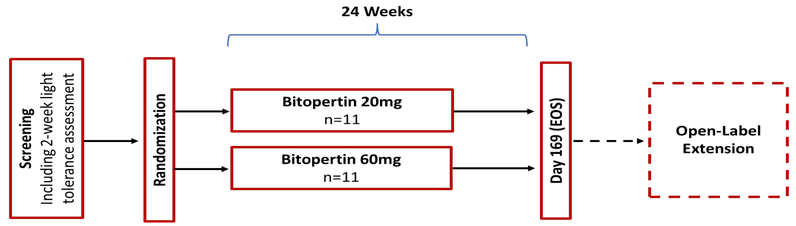
Figure 2: Effects of Bitopertin on PPIX and Hemoglobin Levels in Mouse Models of EPP and XLP[5]



METHODS

- Phase 2, randomized, open-label, parallel arm trial of 20 and 60 mg oral bitopertin once daily for 24 weeks in patients with EPP
- Randomized dose assignment is stratified by <30 or ≥30 minutes time to prodrome
- The trial is being conducted at the Royal Melbourne Hospital, Melbourne, Australia and Royal Prince Alfred Hospital, Sydney, Australia (ACTRN12622000799752)
- Patients who complete the 24-week regimen of 20 mg or 60 mg may continue treatment in the open-label extension portion of the study on 60 mg bitopertin

Figure 3: Phase 2 Study Design



- Participants are assessed on Days 1, 2, 15, 29, 43, 71, 113, 155, and 169
- Open-label extension visits are to occur every 8 weeks for up to 6 months

ENROLLMENT CRITERIA

Inclusion Criteria:

- Been diagnosed with EPP or XLP by FECH or ALAS2 genotyping or by biochemical porphyrin analysis
- Have completed a 2-month washout of afamelanotide or dersimelagon, if applicable
- Aspartate aminotransferase (AST) and alanine transaminase (ALT) <2× upper limit of normal (ULN) and total bilirubin <ULN (unless documented Gilbert syndrome) at Screening. Albumin >lower limit of normal (LLN)

Exclusion Criteria:

- Major surgery within 8 weeks of screening
- Other than EPP, an inherited or acquired red cell disease associated with anemia
- History of liver transplant

PPIX

- LC-MS/MS methods were developed and validated following regulatory guidance for the quantitation of PPIX and ZnPPIX in human blood and plasma. Whole blood samples (for research purpose only) from EPP patients were tested for PPIX to assess the baseline levels in EPP patients when measured using this method
- The measured concentration of PPIX in whole blood ranges from 2.8 to 34.1 µM, with a mean value of 14.2 µM (n=8). These values are comparable with data reported in the literature (erythrocyte PPIX in EPP patients: men: mean of 56 µM (6-139 µM), women: mean of 38 µM (6-82 µM))[6]

Patient Reported Outcome Measures

- Total hours of pain-free sunlight exposure, time to prodrome, patient global impression of severity and change (PGIS, PGIC), and quality of life are assessed by patient reported outcome measures
- Measures were developed and their content validity established via a concept elicitation and cognitive debrief study

RESULTS

Table: Screening Average Light Tolerance
Average time to prodrome reported during screening period, responses ranged from 1 to >60 minutes

	<10 minutes	10-30 minutes	31-59 minutes	>60 minutes
N	2	2	1	1

- Prodrome is the first symptom experienced due to light exposure (e.g., itching, burning, tingling, etc.)
- Screening time to prodrome is an average of 1 or 2 participant directed sun exposures, or historical average (as feasible during screening)

ENDPOINTS

Primary:

- Percent change from baseline in metal-free PPIX levels

Key Secondary:

- Total hours of sunlight exposure to skin on days with no pain from 1000 to 1800 hours (10:00 AM to 6:00 PM)

Secondary:

- A two-week average daily sunlight exposure time (minutes) to first prodromal symptom (burning, tingling, itching or stinging) associated with sunlight exposure between 1-hour post-sunrise and 1 hour pre-sunset
- Pain intensity of phototoxic reactions according to a Likert scale (0-10)
- Safety and tolerability of bitopertin, as assessed by the incidence of treatment-emergent adverse events, vital signs, physical examinations, and clinical laboratory parameters
- Erythrocyte total PPIX concentrations
- Plasma and blood total PPIX concentrations
- Plasma bitopertin concentrations

CONTACT INFORMATION

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