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ORAL ABSTRACTS

102.IRON HOMEOSTASIS AND BIOLOGY

Interim Analyses from the Beacon Trial: A Phase 2, Randomized, Open-Label Trial of Bitopertin in Erythropoietic Protoporphyria

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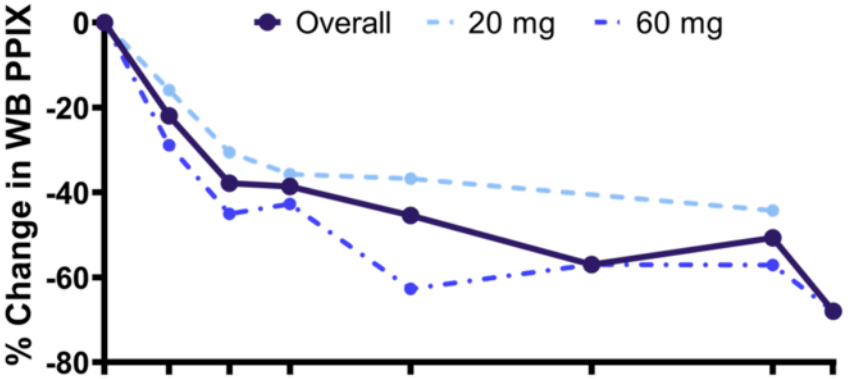
Introduction: Erythropoietic protoporphyria (EPP) is associated with accumulation of photoreactive protoporphyrin IX (PPIX) in the skin and other organs, causing debilitating phototoxic skin reactions following exposure to sunlight, and potentially life-threatening protoporphyric hepatopathy in some patients. Reduction of PPIX is associated with amelioration of disease in the settings of hematopoietic stem cell transplant, pregnancy, and extracorporeal photoinactivation.
Glycine transporter 1 (GlyT1) supplies extracellular glycine for the initial step of heme biosynthesis in erythroid cells. Bitopertin is an investigational, orally-administered inhibitor of GlyT1. It is hypothesized that GlyT1 inhibition leads to a decrease in heme pathway intermediates, including PPIX, and can improve light tolerance.
Methods: BEACON is a Phase 2, randomized, open-label, parallel-arm trial (ACTRN12622000799752) of 22 participants who will receive oral, once-daily administration of 20 mg or 60 mg of bitopertin for 24 weeks. The trial is being conducted at 2 sites in Australia and includes participants ≥18 years of age with a confirmed diagnosis of EPP. The primary efficacy endpoint is percent change in whole-blood metal-free PPIX. Additional endpoints include daily patient-reported outcomes (PRO) of light tolerance and quality of life, as well as safety and tolerability.
Results: As of data cutoff (05 July 2023), a total of 17 subjects had been enrolled. Treatment with bitopertin resulted in mean (SD) decreases in PPIX of -39% ± 17% by Day 43 (n=12), with more pronounced decreases observed with 60 mg compared to 20 mg (Figure 1). Bitopertin also improved multiple measures of light tolerance. A participant randomized to 20 mg bitopertin reported a >80-fold increase in sunlight tolerance on Day 88 of treatment, increasing from 4.5 minutes at baseline to over 6 hours; no prodromes were reported during any sunlight challenge after Day 20. A participant randomized to 60 mg bitopertin reported a >200-fold increase in sunlight tolerance on Day 74 of treatment, increasing from 1.3 minutes at baseline to over 4 hours, and did not report a prodrome during any sunlight challenge after Day 120. Aggregate measures of light tolerance also improved over time, including time to prodrome averaged over a 2-week period and weekly averages of total time in sunlight. The proportion of prodrome-free sunlight challenges increased from 2% during screening to 49% while receiving bitopertin (n=17), and the proportion of days without symptoms (with sun exposure) increased from 26% during screening to 74% while receiving bitopertin (n=17). Improvements in weekly averages of total time in sunlight were consistent and observed in 15/15 participants with post-baseline PPIX values. The greatest increases in weekly averages of total time in sunlight were observed in participants who experienced reductions in PPIX of at least 30% (Figure 2), for whichtotal time in sunlight increased from a weekly average of 339 minutes at baseline to a maximum of 999 minutes with bitopertin (n=11; mean duration of treatment: 133 days [range: 76 to ≥169 days]). Patient-reported phototoxic reactions decreased by 93% while on treatment compared to baseline (n=17). By Day 43, 15/16 participants reported in the Patient Global Impression of Change (PGIC) their EPP was much better or a little better, and 15/16 reported in the Patient Global Impression of Severity (PGIS) their EPP was mild or not at all severe. A majority (13/16) of participants responded in a novel PRO, the EPP Impact Questionnaire (EPIQ), that EPP had little or no impact on their quality of life while receiving bitopertin.
No serious adverse events, discontinuations due to adverse events, or dose reductions have been reported. A total of 12 (71%) participants reported treatment-emergent adverse events; only dizziness and headache were reported in more than one subject. No meaningful changes in hemoglobin have been observed.
Conclusion: By reducing whole-blood PPIX levels, bitopertin targets the underlying pathophysiology of EPP, resulting in consistent improvements in multiple measures of light tolerance and quality of life. Bitopertin has been well tolerated to date

with no changes in hemoglobin, and its safety profile in EPP is consistent with prior studies that enrolled more than 4000 participants. Updated results will be presented at the meeting.

Disclosures Mensing: *Disc Medicine:* Current Employment, Current equity holder in publicly-traded company. **Chin:** *Disc Medicine:* Current Employment, Current equity holder in publicly-traded company. **Howell:** *Disc Medicine:* Current Employment, Current equity holder in publicly-traded company. **Mangus:** *Agios:* Current equity holder in publicly-traded company; *Disc Medicine:* Current Employment, Current equity holder in publicly-traded company; *Bristol-Myers Squibb:* Current equity holder in publicly-traded company. **Savage:** *Disc Medicine:* Current Employment, Current equity holder in publicly-traded company, Divested equity in a private or publicly-traded company in the past 24 months.

Figure 1. Percent Changes in Whole-Blood (WB) Protoporphyrin IX (PPIX) with Bitopertin



Overall N	17	15	14	12	6	1	2	1
20 mg	8	8	7	7	4	0	1	0
60 mg	9	7	7	5	2	1	1	1

Data as of 29 May 2023

Figure 2. Maximum Changes from Baseline in Weekly Total Time in Sunlight and Corresponding Changes in PPIX with Bitopertin

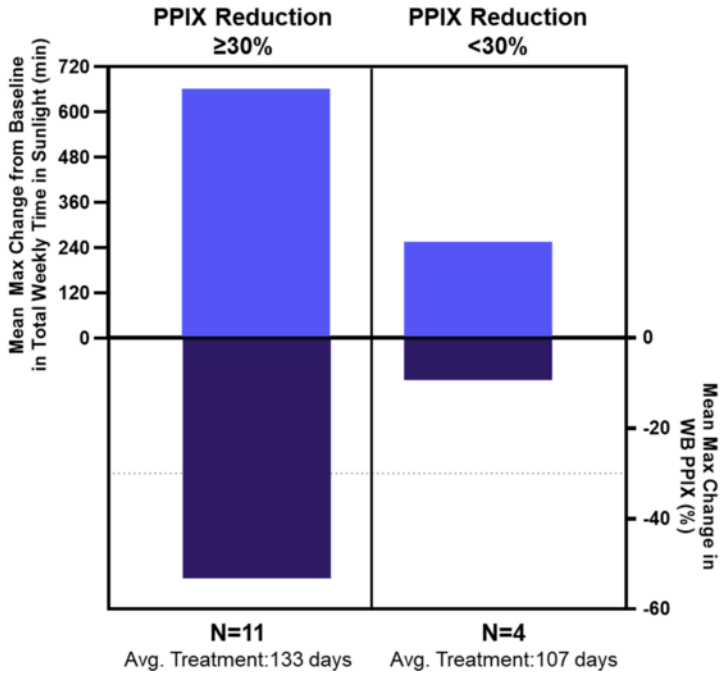


Figure 1

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