

INTRODUCTION

ERYTHROPOIETIC PROTOPORPHYRIA (EPP) AND X-LINKED PROTOPORPHYRIA (XLP)

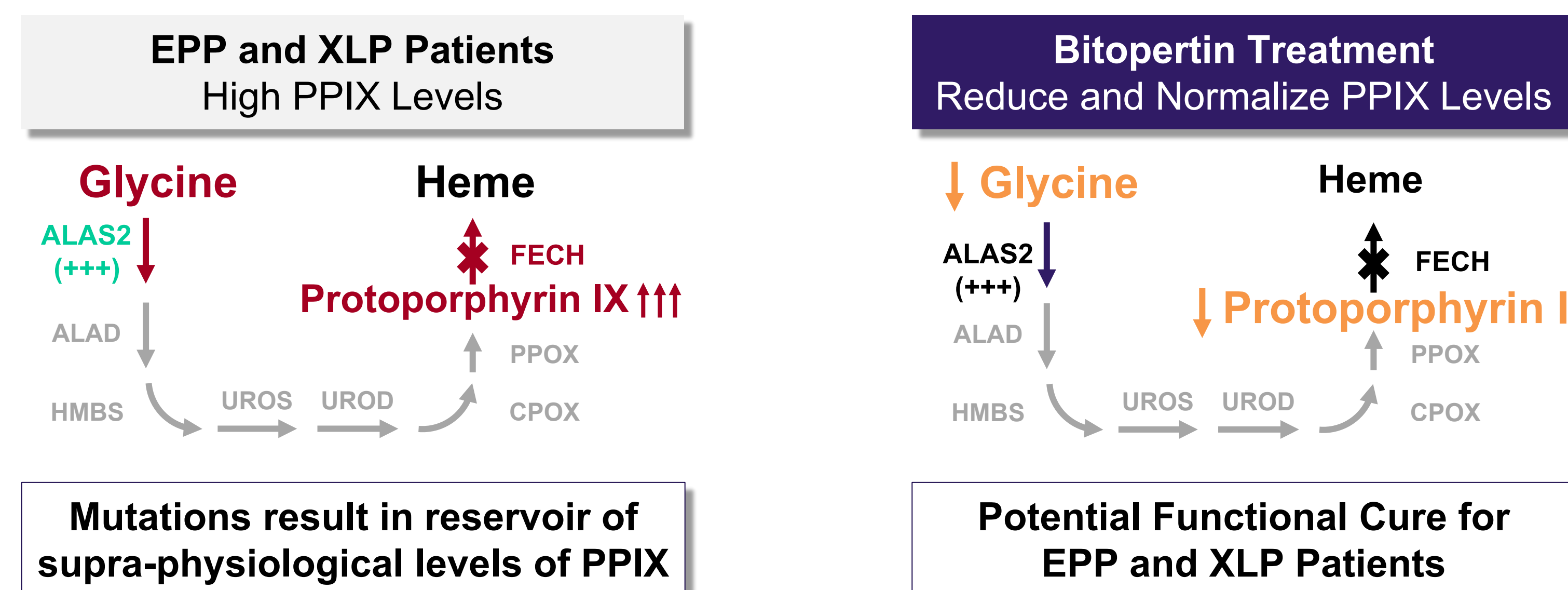
EPP and XLP are rare disorders caused by pathogenic variants in the ferrochelatase (*FECH*) or 5-aminolevulinic acid synthase 2 (*ALAS2*) genes, which result in accumulation of photoreactive protoporphyrin IX (PPIX). PPIX elevations cause debilitating phototoxic skin reactions following exposure to sunlight and can cause potentially life-threatening hepatopathy in some patients. Higher PPIX reductions are associated with amelioration of disease in the settings of hematopoietic stem cell transplant, pregnancy, and extracorporeal photoinactivation.¹⁻³

MECHANISM OF DISEASE AND BITOPERTIN TREATMENT

Bitopertin is an investigational small molecule inhibitor of glycine transporter 1 (GlyT1). GlyT1 supplies extracellular glycine for the initial step of heme biosynthesis in erythroid cells.⁴ It is hypothesized that GlyT1 inhibition can decrease PPIX accumulation and improve light tolerance.⁵ Bitopertin has exhibited a favorable safety profile in prior clinical studies in other indications with cumulative enrollment of >4,000 subjects.

EFFECTS OF BITOPERTIN IN MOUSE MODELS OF EPP AND XLP⁵

Bitopertin lowered blood PPIX levels by >40% vs controls, was associated with decreased liver PPIX levels, and reduced histopathological evidence of liver cholestasis and fibrosis vs controls.^{6,7}



BEACON (ACTRN12622000799752) was designed to evaluate the safety, tolerability, and efficacy of bitopertin in individuals with EPP

METHODS

STUDY DESIGN

- Phase 2, randomized, open-label, parallel-arm trial
- Enrolling 22 subjects with EPP or XLP

KEY ELIGIBILITY CRITERIA

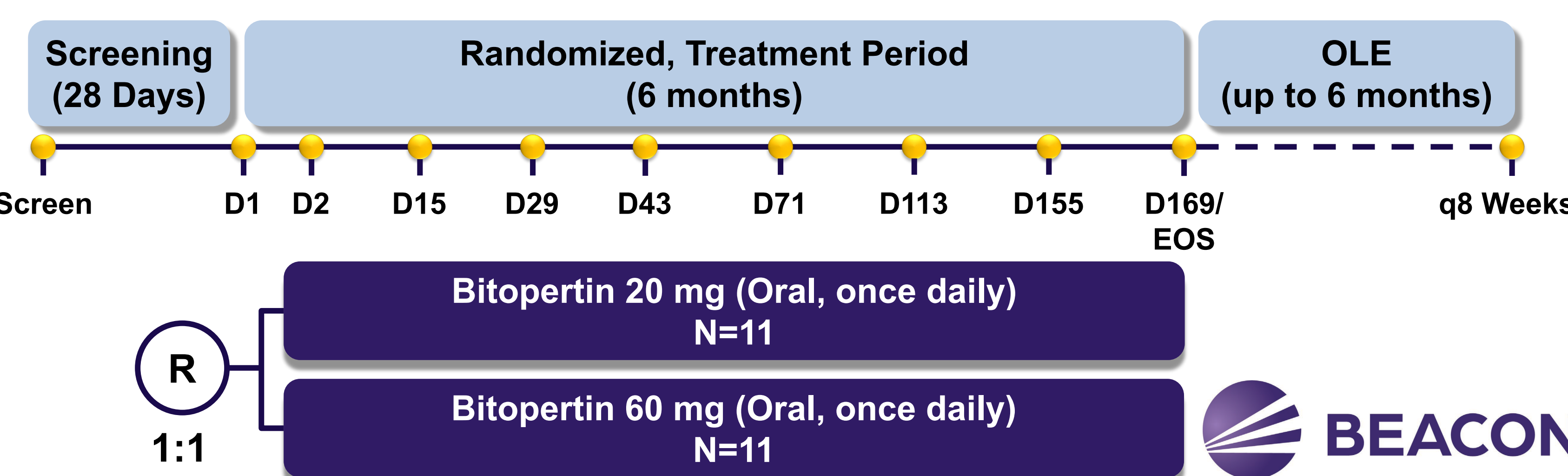
- ≥18 years of age
- Diagnosed by *FECH*/*ALAS2* genotyping or biochemical porphyrin analysis
- 2-month washout of afamelanotide or dersimelagon

ENDPOINTS

- Primary:** Percent change in whole blood (WB) metal-free PPIX
- Key secondary:** Total hours of sunlight exposure on days with no pain from 10:00 to 18:00 hours

STUDY ASSESSMENTS

- Daily** sun exposure diary
- Weekly** sun exposure challenge (time to prodrome)
- PGIC/PGIS; patient-reported quality of life (QOL)
- Liver fibrosis (FibroScan® or ARFI)



Bitopertin is an investigational drug and is not approved for use by any regulatory agency.

RESULTS - EFFICACY

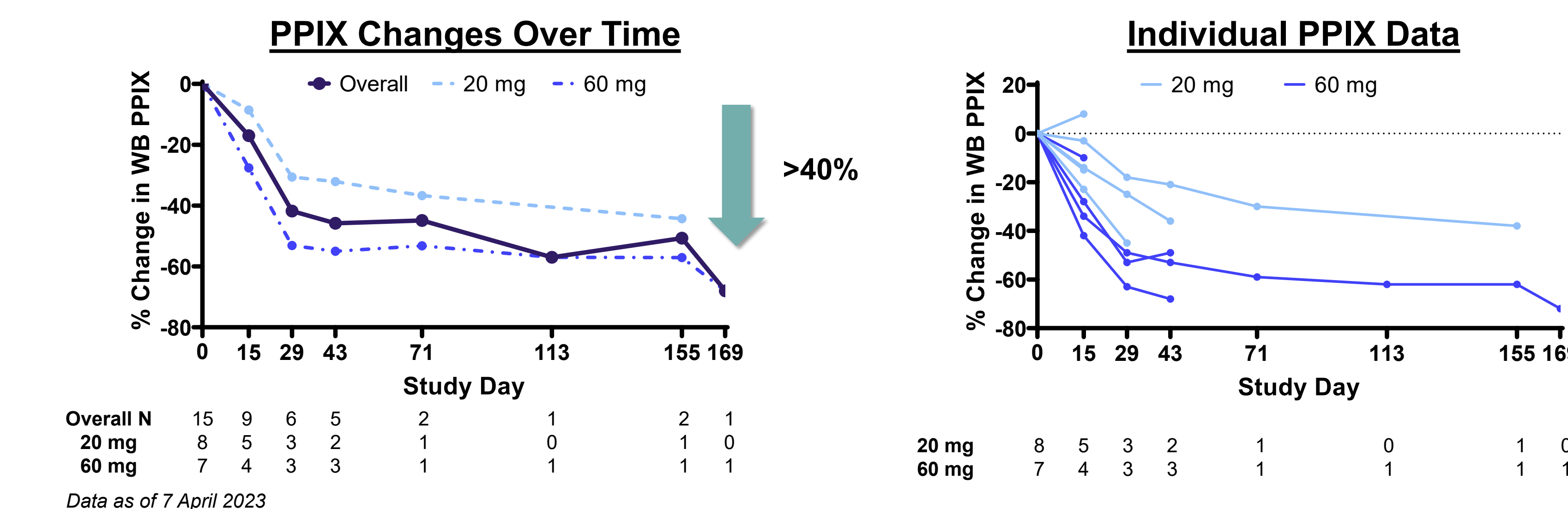
DISPOSITION

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

Data as of 8 May 2023.

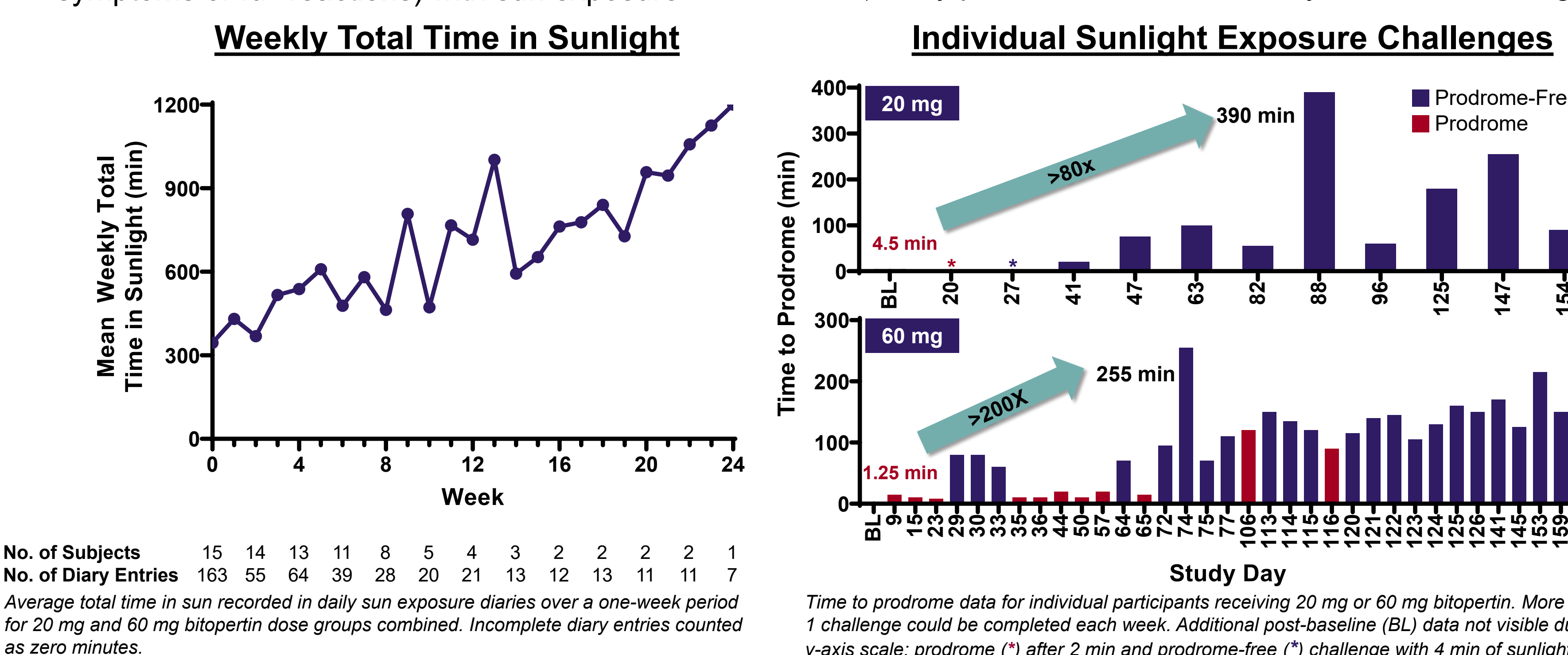
PRIMARY EFFICACY: CHANGES IN PPIX

- ↓ WB metal-free PPIX across broad range of baseline PPIX levels (420-3410 µg/dL)
- Dose-dependent reductions

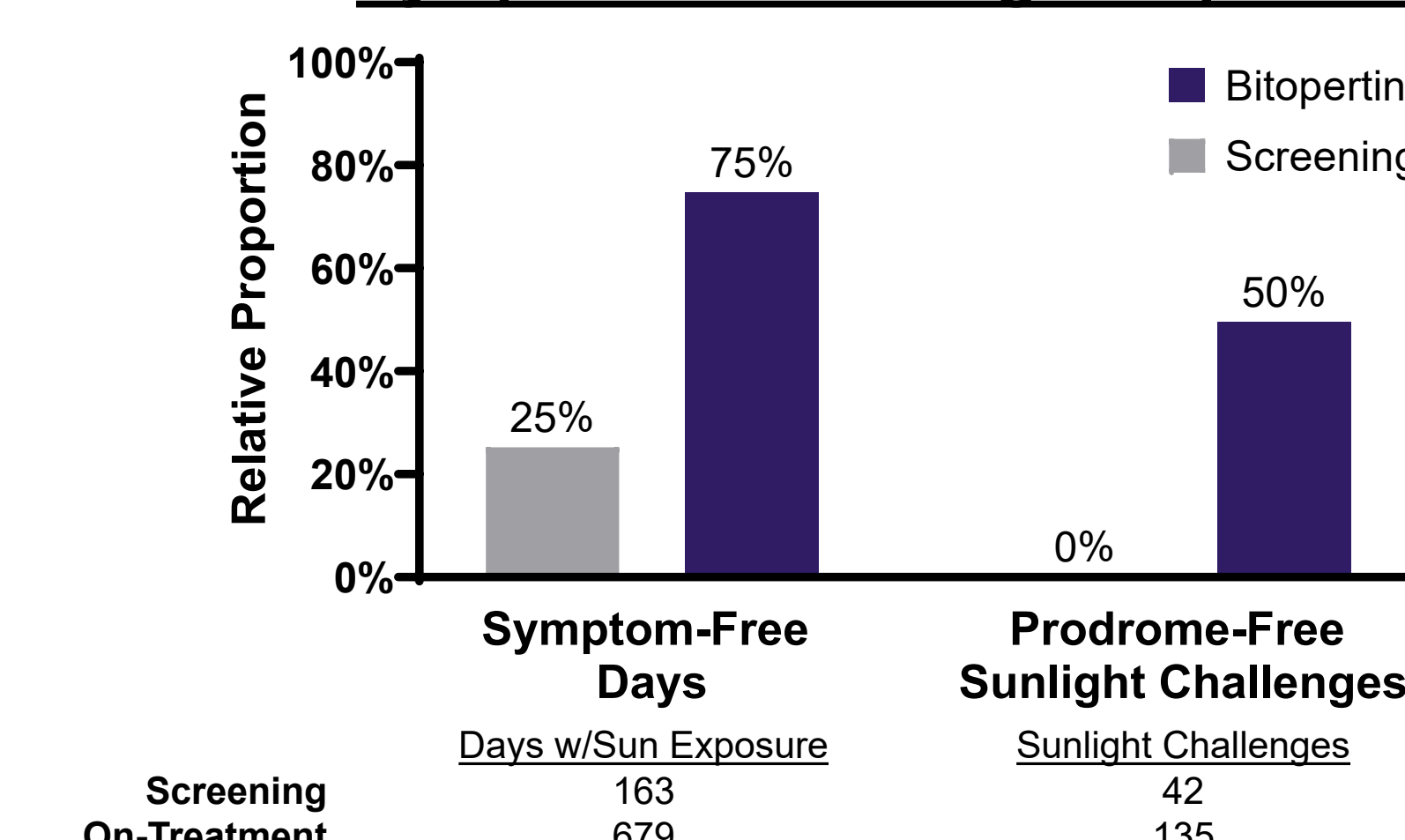


SECONDARY EFFICACY: LIGHT TOLERANCE

- ↑ Average weekly total time in sunlight
- ↑ Proportion of symptom-free days (no early warning symptoms or full reactions) with sun exposure
- ↑ Average time to prodrome and proportion of prodrome-free weekly sunlight exposure challenges
- ↓ Daily phototoxic reaction rate by 96% vs screening



Symptom-Free Sunlight Exposure



Time to first prodromal symptom during weekly sun exposure challenges averaged over a two-week period, including cumulative time in sunlight from challenges that did not elicit a prodrome. Data are averaged for 20 mg and 60 mg bitopertin dose groups combined.

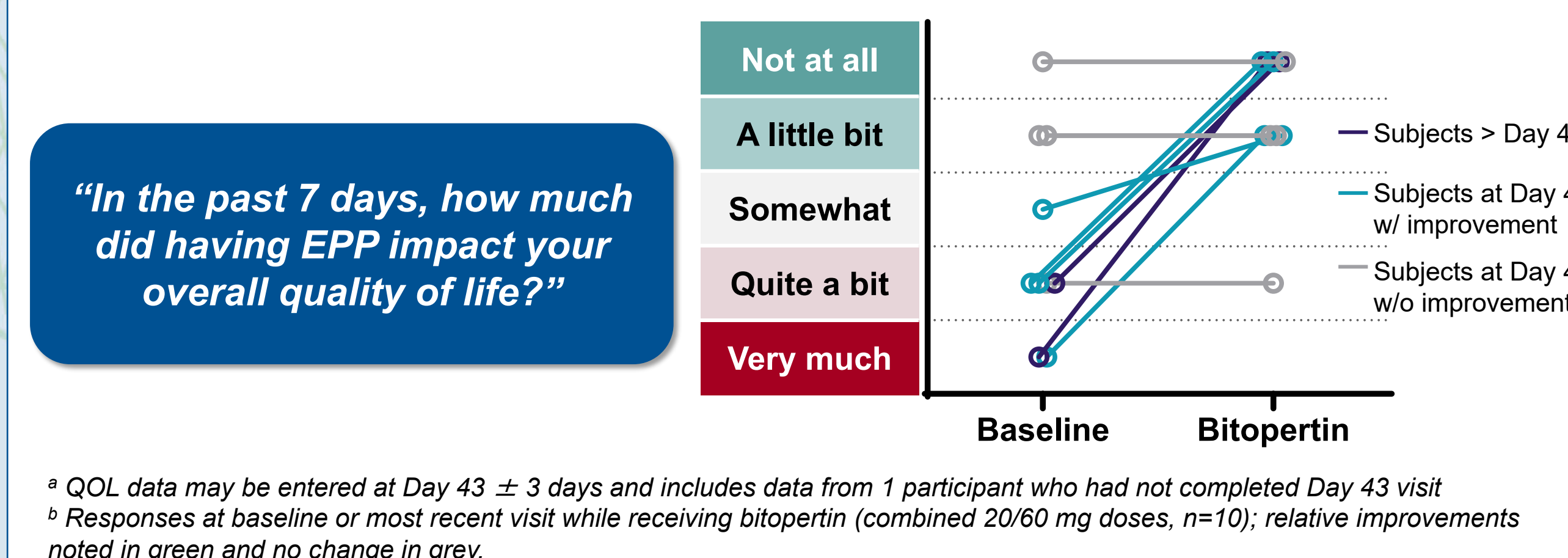
RESULTS - QUALITY OF LIFE

PATIENT GLOBAL IMPRESSION OF CHANGE/SEVERITY^a

- PGIC: 10/10 participants reported their EPP was **much better** (n=8) or a **little better** (n=2) in the last 7 days at Day 43
- PGIS: 9/10 participants reported **severity** of their EPP was **mild** (n=3) or **not at all** (n=6) in the last 7 days at Day 43

EPP IMPACT QUESTIONNAIRE (EPIQ)

- Improvements in novel EPP-specific PRO assessing QOL^{a,b}



RESULTS - SAFETY

- No serious adverse events
- No discontinuations or dose reductions
- All TEAEs Grade 1 in severity and transient^a
- No changes in mean hemoglobin levels

	Bitopertin 20 mg (n=8)	Bitopertin 60 mg (n=7)	Total (n=15)
Total number of TEAEs	8	8	16
Subjects with any TEAE	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. ^a Mean time to resolution: 2 days.

CONCLUSIONS

- Initial data establishes proof of concept that bitopertin targets underlying EPP pathophysiology by reducing whole-blood PPIX levels
- Functional benefit observed with bitopertin, including prolonged symptom-free periods of sun exposure and prodrome-free sunlight challenges
- Consistent improvements in multiple measures of light tolerance also associated with quality-of-life improvements
- Bitopertin has been well tolerated to date with no changes in hemoglobin
- Safety profile in EPP consistent with prior studies in >4,000 individuals

REFERENCES

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