

Interim Analysis From the Ongoing Phase 3 FORTIFY Study of
BBP-418 for Patients With Limb-Girdle Muscular Dystrophy 2I/R9
Meets Efficacy Endpoints

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Katherine D. Mathews, M.D.,¹ Tahseen Mozaffar, M.D.,² Volker Straub, M.D., Ph.D.,³ Robert D. Henderson, M.B.B.S., Ph.D.,⁴ Douglas Sproule, M.D., M.Sc.,⁵ Ada Lee, M.D.,⁵ Amy Rainey,⁵ David Paul,⁵ Tricia Blankenbiller, M.S.,⁵ Uma Sinha, Ph.D.,⁵ John Vissing, M.D.,⁶ for the FORTIFY study group.

¹University of Iowa, Iowa City, IA, United States; ²University of California, Irvine, Orange, CA, United States; ³Newcastle University, Newcastle Upon Tyne, United Kingdom; ⁴University of Queensland, Brisbane, Australia; ⁵ML Bio Solutions Inc., a BridgeBio company, Palo Alto, CA, United States; ⁶University of Copenhagen, Copenhagen, Denmark

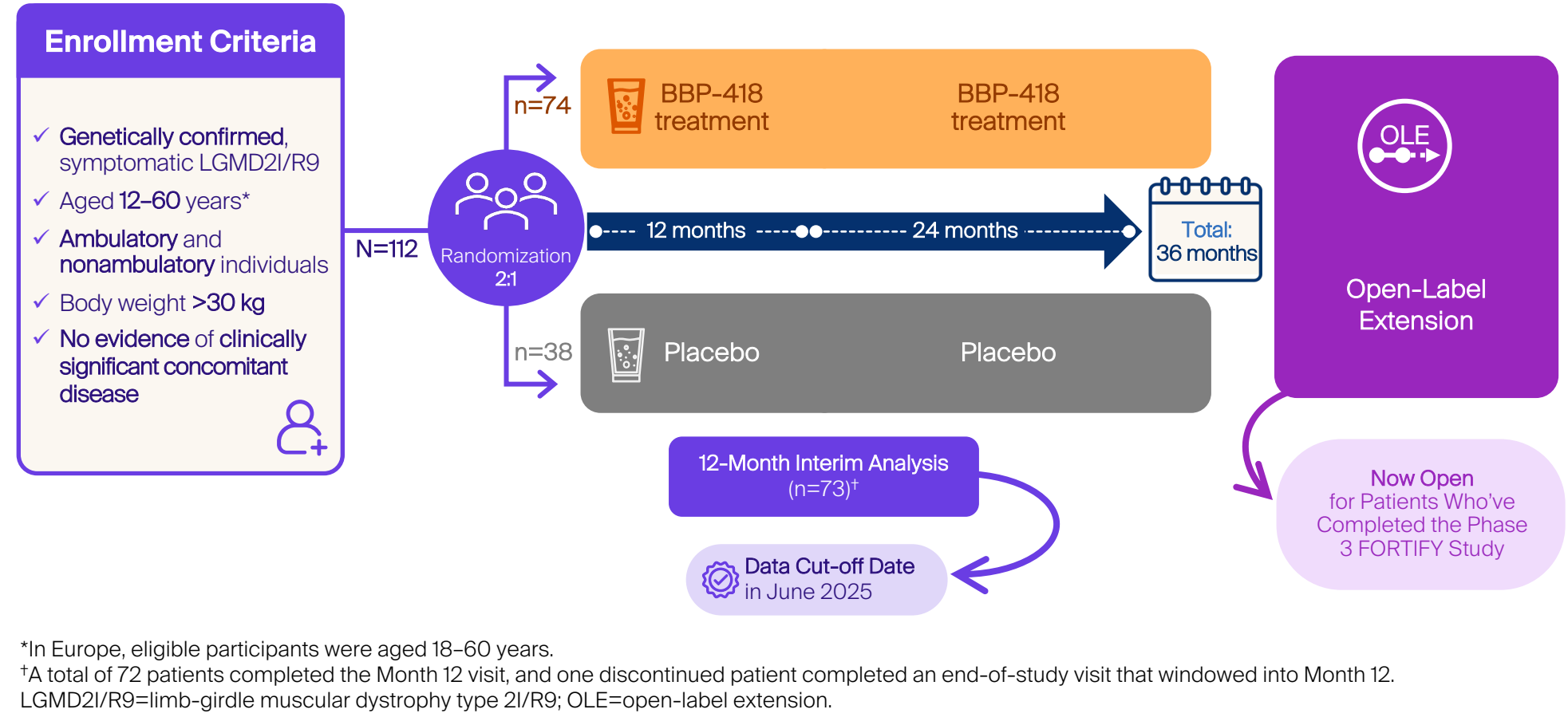
BACKGROUND

- Limb-girdle muscular dystrophy type 2I/R9 (LGMD2I/R9; fukutin-related protein [FKRP]-related) is an autosomal recessive disorder characterized by progressive, irreversible muscle damage and cardiopulmonary decline^{1,2}
- LGMD2I/R9 is caused by pathogenic variants in *FKRP* that impair glycosylation of alpha-dystroglycan (αDG)^{1,2}
- No approved therapies exist for LGMD2I/R9²
- BBP-418 is an investigational, oral small molecule designed to restore αDG glycosylation and stabilize muscle integrity during contraction^{3,4}

METHODS

- FORTIFY (NCT05775848) is an ongoing, randomized, double-blind, placebo-controlled, phase 3 study evaluating the efficacy and safety of BBP-418 in individuals with LGMD2I/R9 (**Figure 1**)⁵
- A prespecified 12-month interim analysis evaluated biochemical, functional, and safety outcomes
- Quality of life was assessed at baseline and Month 12 in adult and pediatric participants using Patient-Reported Outcomes Measurement Information System (PROMIS®)-57 and -37, respectively

Figure 1. Study Design⁵



RESULTS

- A total of 74 and 38 individuals were randomized to the BBP-418 and placebo arms, respectively
- All 74 patients randomized to the BBP-418 arm are still ongoing and no treatment discontinuation had occurred at the time of analysis
- Baseline demographic and disease characteristics were generally similar between arms (**Table 1**)

Table 1. Baseline Demographic and Disease Characteristics

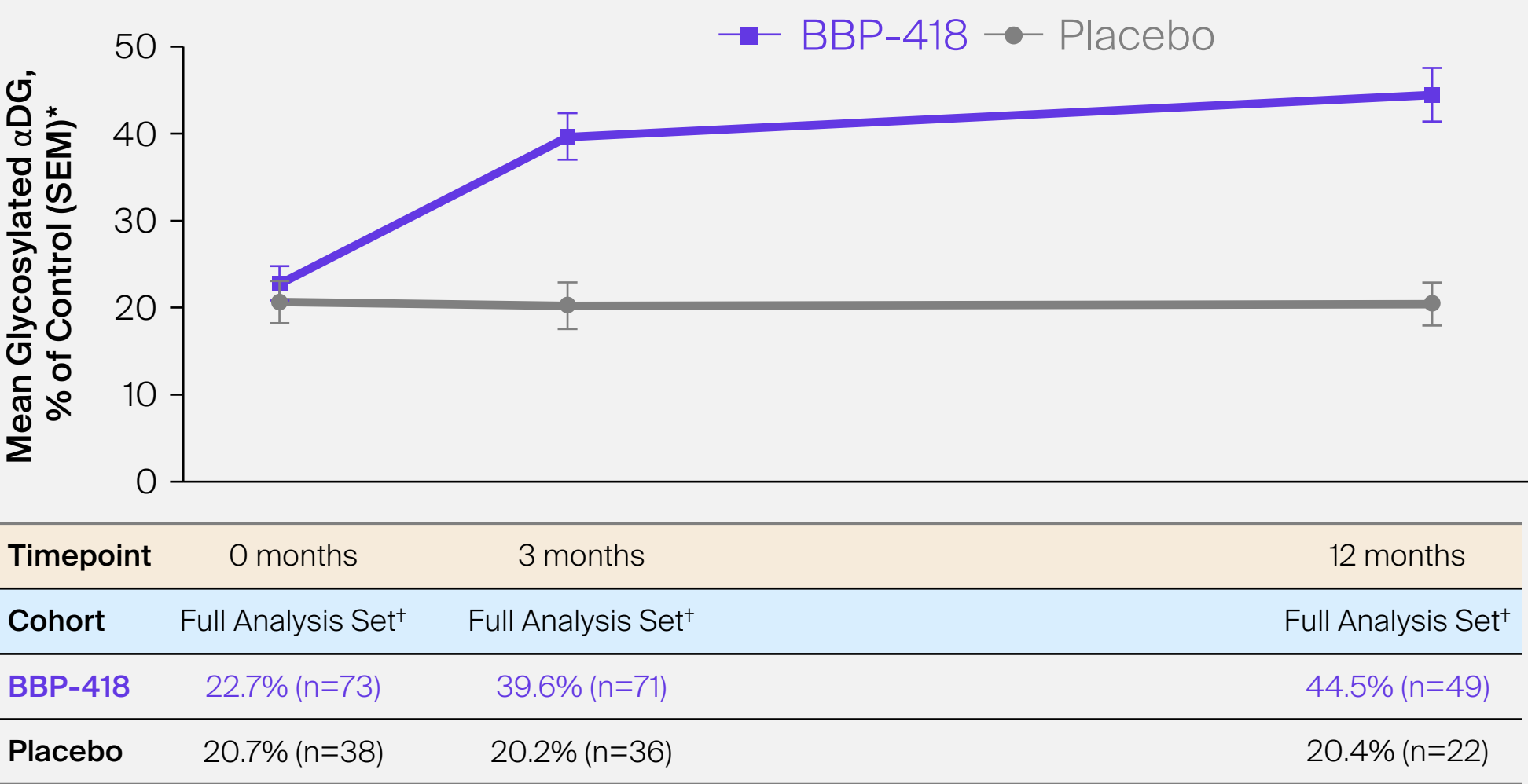
	BBP-418 (n=74*)	Placebo (n=38*)
Mean age, years (SD)	37.1 (14.2)	33.3 (14.0)
12 to <18, n (%)	10 (13.5)	5 (13.2)
≥18 to 60, n (%)	64 (86.5)	33 (86.8)
Male sex, n (%)	39 (52.7)	14 (36.8)
White race, n (%)	73 (98.6)	35 (92.1)
Not Hispanic, n (%)	71 (95.9)	36 (94.7)
Mutation status, n (%)		
L276I homozygous	55 (74.3)	28 (73.7)
Other <i>FKRP</i> genotype	19 (25.7)	10 (26.3)
Mean glycosylated αDG, % of control (SD) [†]	n=73* 22.71 (16.61)	n=38* 20.66 (14.67)
Mean serum CK, U/L (SD)	n=67 [‡] 2449.5 (3014.4)	n=36 [‡] 2099.5 (1832.7)
Mean 100MTT, m/s (SD)	n=62§ 1.33 (0.82)	n=32§ 1.37 (0.80)
Mean FVC in the sitting position, % predicted (SD)	n=59§ 77.95 (16.94)	n=33§ 77.17 (16.40)

*Data derived from the Full Analysis Set, which comprised randomized participants who had ≥1 efficacy assessment post-randomization.
†Glycosylated αDG level relative to a control reference standard from a healthy donor.
‡Data derived from the Primary Efficacy Set, which comprised randomized participants with a total baseline NSAD score of ≤3.
§Data derived from the Secondary Efficacy Set, which comprised randomized participants with nonzero scores at screening (or if a score was not available at screening, then it was nonzero at baseline) for all of the following: 10MWT (or if 10MWT was not available, then NSAD item #29a [velocity]), PUL 2.0, and FVC (% predicted, sitting) (or if FVC was not available, then the investigator reported that spirometry was performed).
¶10MWT=10-meter walk test; 100MTT=100-meter timed test; αDG=alpha-dystroglycan; CK=creatinine kinase; FVC=forced vital capacity; m/s=meter/second; NSAD=North Star Assessment for Limb-Girdle-type Dystrophies; PUL 2.0=Performance of Upper Limb Scale 2.0; SD=standard deviation; U/L=units/liter.

Efficacy

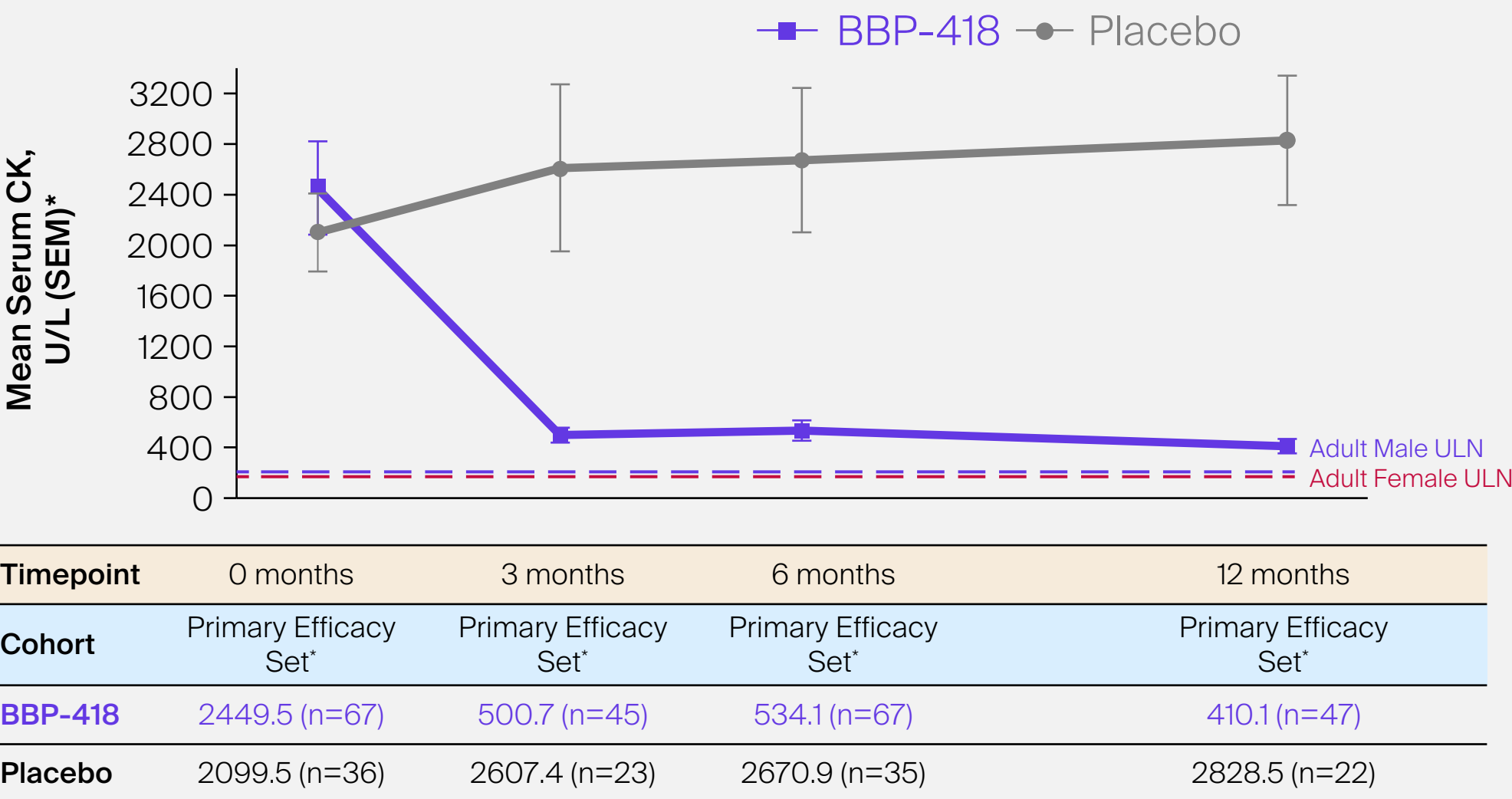
- At the prespecified interim analysis, BBP-418 showed a 1.8-fold increase in mean glycosylated αDG from baseline at Month 3 ($P<0.0001$), which was sustained through Month 12 ($P<0.0001$ vs placebo) (**Figure 2**)

Figure 2. Mean Glycosylated αDG Levels ± SEM



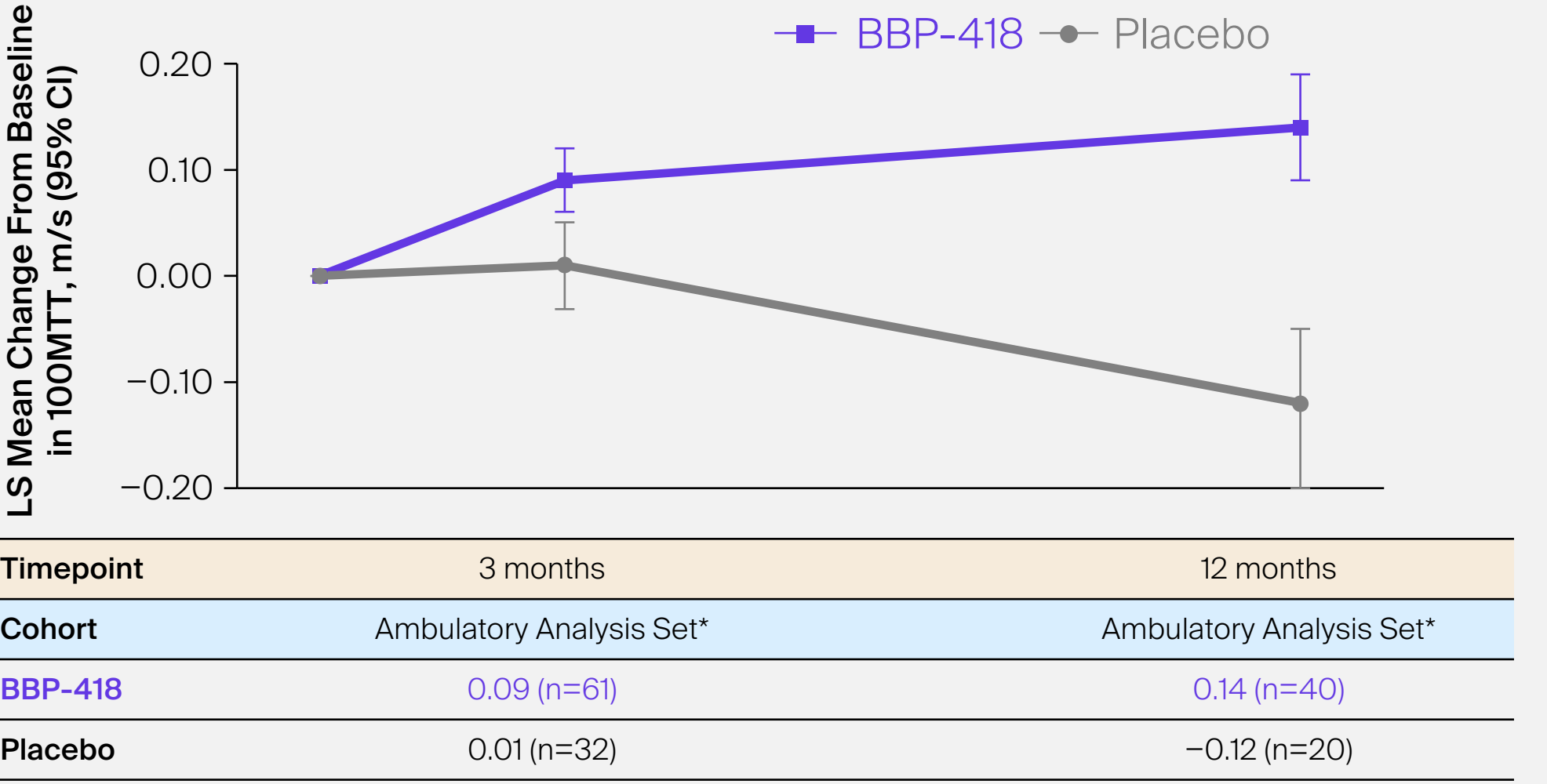
- Between baseline and Month 12, serum creatine kinase (CK) levels decreased by 82% among BBP-418–treated participants ($P<0.0001$ vs placebo) (**Figure 3**)
 - Among participants treated with BBP-418 for 12 months, 59.6% had serum CK levels within 2 times the upper limit of normal (ULN) and 38.3% had serum CK levels within the ULN

Figure 3. Mean Serum CK Levels ± SEM



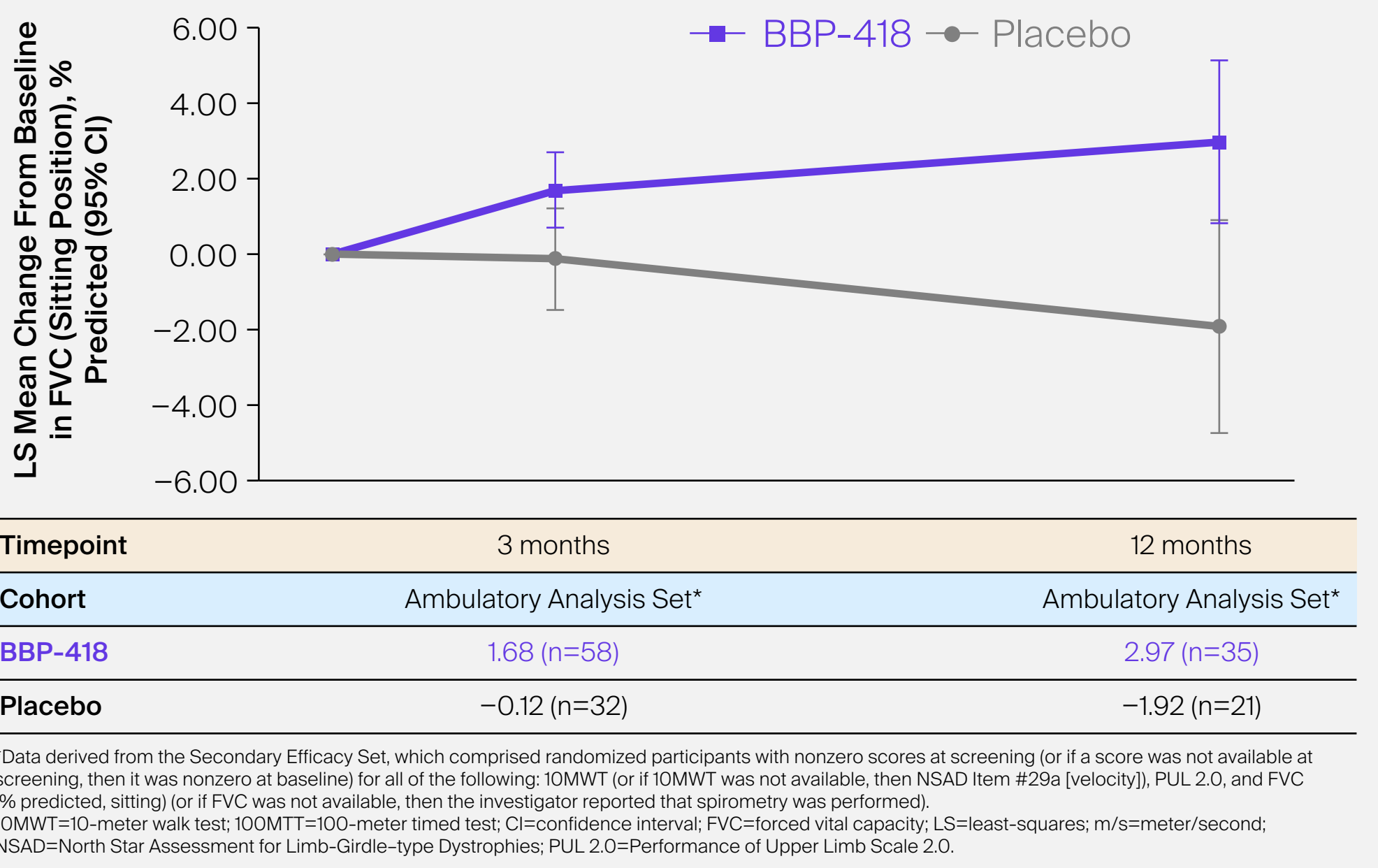
- Statistically significant and clinically meaningful improvements in 100-meter timed test (100MTT) velocity were observed among BBP-418–treated participants (**Figure 4**)
 - Between baseline and Month 12, BBP-418–treated participants experienced an increase in 100MTT velocity of 0.14 m/s
 - At the interim analysis, there was a difference of 0.27 m/s in 100MTT velocity between the BBP-418 and placebo arms ($P<0.0001$)

Figure 4. LS Mean Change From Baseline in 100MTT



- BBP-418–treated participants also experienced statistically significant and clinically meaningful improvements in FVC (forced vital capacity; sitting position) (**Figure 5**)
 - Between baseline and Month 12, BBP-418–treated participants registered a 3% increase in percent predicted volume
 - At Month 12, a difference of 5% was observed between the BBP-418 and placebo arms ($P=0.0071$)

Figure 5. LS Mean Change From Baseline in FVC



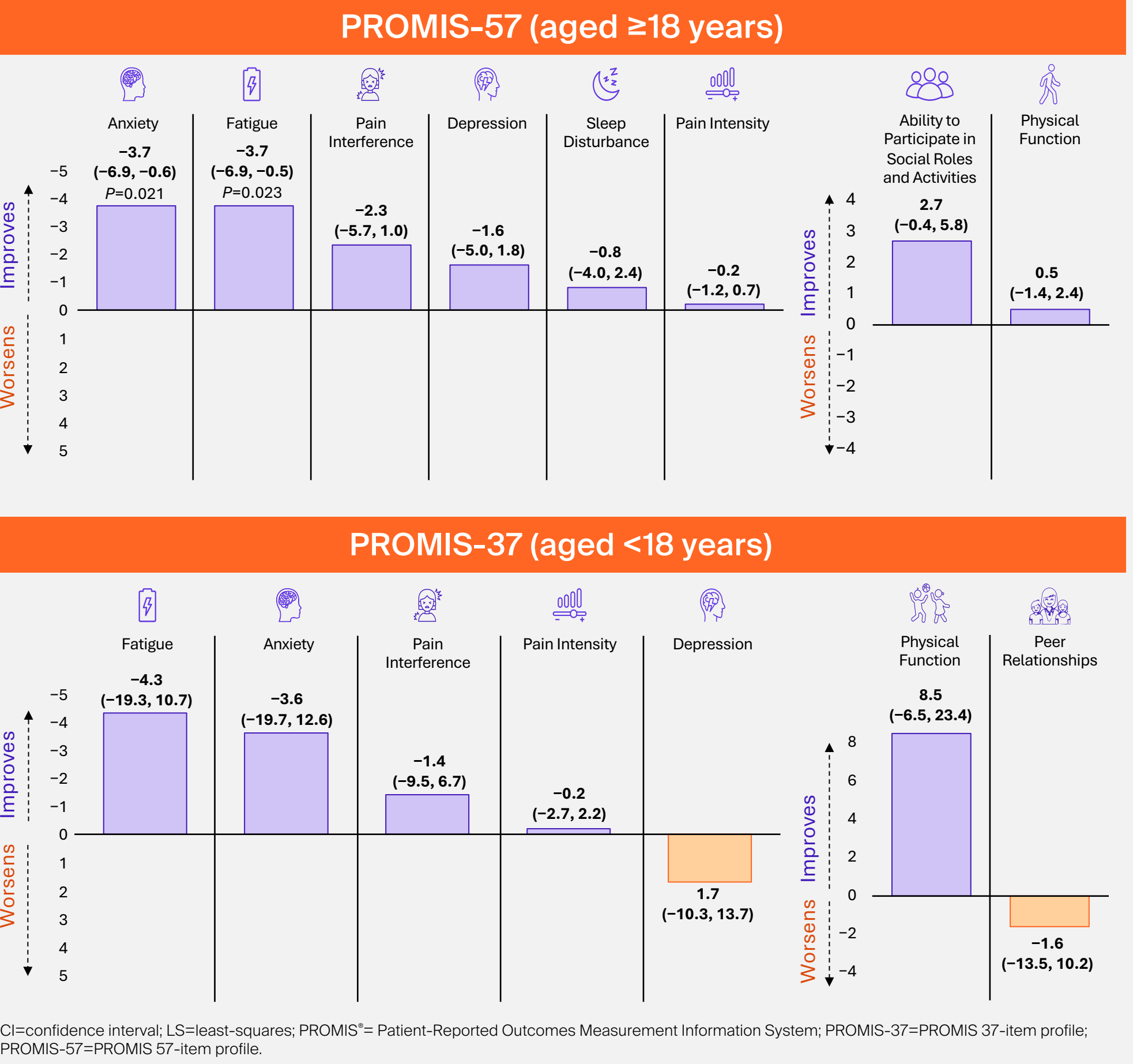
Safety

- BBP-418 was generally well tolerated
 - Diarrhea was the most common treatment-emergent adverse event (TEAE) (BBP-418, 39.2%; placebo, 52.6%), all reports of which were grade 1–2
 - Most TEAEs were Grade 1–2; Grade 3–4 TEAEs occurred at similar rates in participants treated with BBP-418 (5.4%) and placebo (5.3%)
 - No participant treated with BBP-418 discontinued treatment due to a TEAE
 - There were no deaths or treatment-related serious TEAEs

Patient-Reported Outcomes

- Among participants aged ≥18 years, least-squares (LS) mean changes from baseline to Month 12 in PROMIS-57 T-scores favored BBP-418 versus placebo across all domains (**Figure 6**)
 - LS mean difference (95% confidence interval [CI]) was clinically meaningful and nominally statistically significant for **anxiety** ($P=0.021$) and **fatigue** ($P=0.023$)
- Among those aged <18 years, LS mean change from baseline to Month 12 in PROMIS-37 T-scores for fatigue, anxiety, and physical function favored BBP-418 versus placebo, but statistical significance was not achieved (likely owing to the small sample size) (**Figure 6**)

Figure 6. Difference in LS Mean in PROMIS® Domains (non-α-controlled, 95% CI)



CONCLUSIONS

- Interim data from the ongoing, 3-year FORTIFY phase 3 trial in individuals living with LGMD2I/R9 demonstrated that BBP-418 provides improvements in ambulation and pulmonary function, with supportive effects on motor function and patient-reported outcomes along with significant improvements in biomarkers, including αDG glycosylation and serum CK
- The BBP-418 safety profile was characterized by predominantly mild-to-moderate TEAEs, no deaths, no treatment-related serious TEAEs, and no discontinuation of BBP-418 treatment due to TEAEs
- These data support BBP-418 as the first potential therapy for LGMD2I/R9 and the New Drug Application submitted to the United States Food and Drug Administration

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