Interim analysis from ongoing Phase 3 FORTIFY study of BBP-418 for patients with limb girdle muscular dystrophy 2I/R9 meets efficacy endpoints

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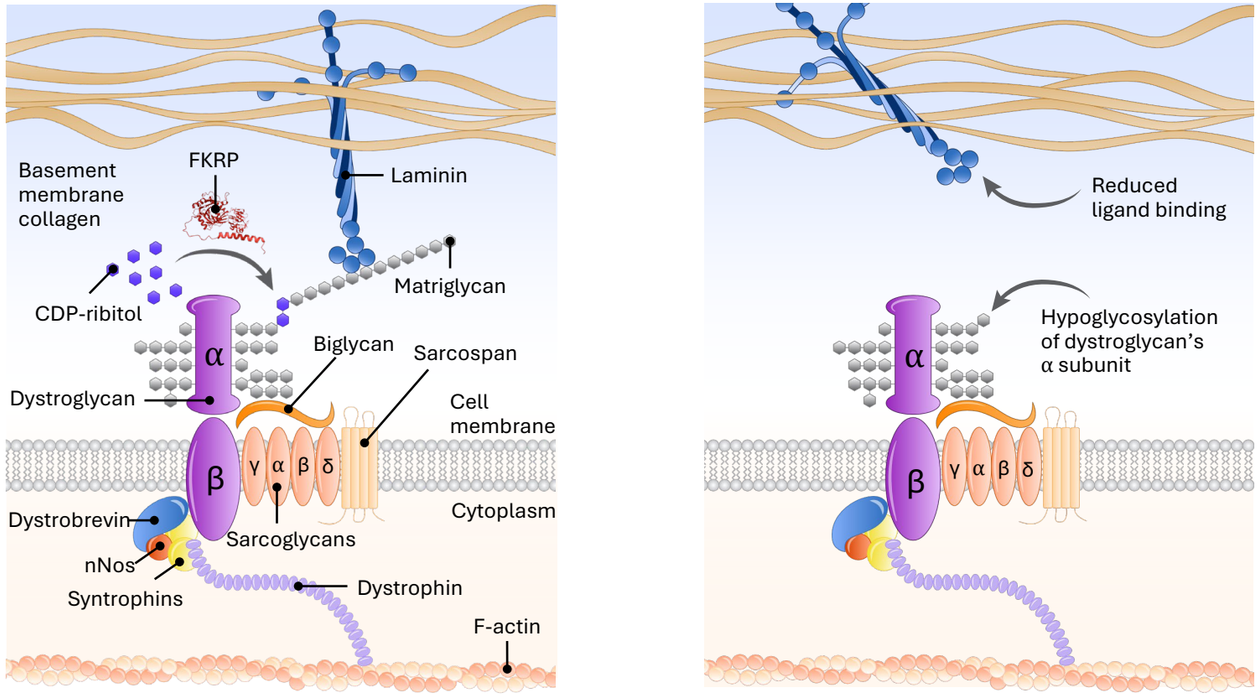
Douglas Sproule, Ada Lee, Amy Rainey, David Paul, Uma Sinha, Thulashitha Rajasingham: Employees of ML Bio Solutions, Inc. and BridgeBio Pharma, Inc. at the time of this analysis and may hold stock in the company

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LGMD2I/R9 is caused by mutations in *FKRP* that result in reduced glycosylation of alpha-dystroglycan (αDG), leading to progressive muscle damage[1]

Molecular pathogenesis of LGMD2I/R9[2-4]



Images adapted from Nickolls AR, Bönnemann CG. *Dis Model Mech*. 2018; 11(12):dmm035931. FKRP structure adapted from Jumper J, *et al*. *Nature*. 2021 Aug;596(7873):583-589 and Fleming J, et al. *J Mol Biol*. 2025 Aug 1;437(15):168967.[2-4]

In **healthy muscle cells**, glycosylated αDG links the muscle cell membrane to the extracellular matrix[2]

In **affected muscle cells**, hypoglycosylation of αDG results in loss of αDG-laminin binding[2]

- In healthy muscle cells, **αDG plays an important role** in linking the muscle cell membrane (sarcolemma) to the extracellular matrix[2]
  - **Glycosylation of αDG is required** to form a glycopeptide chain that binds to laminin in the extracellular matrix
- LGMD2I/R9 is caused by **mutations in *FKRP*** that lead to **reduced function of the FKRP enzyme**, resulting in **decreased glycosylation of αDG[1]**
- **Reduced glycosylation of αDG** leads to the progressive muscle damage seen in LGMD2I/R9[1]

There are NO approved disease-modifying therapies for LGMD2I/R9[5]

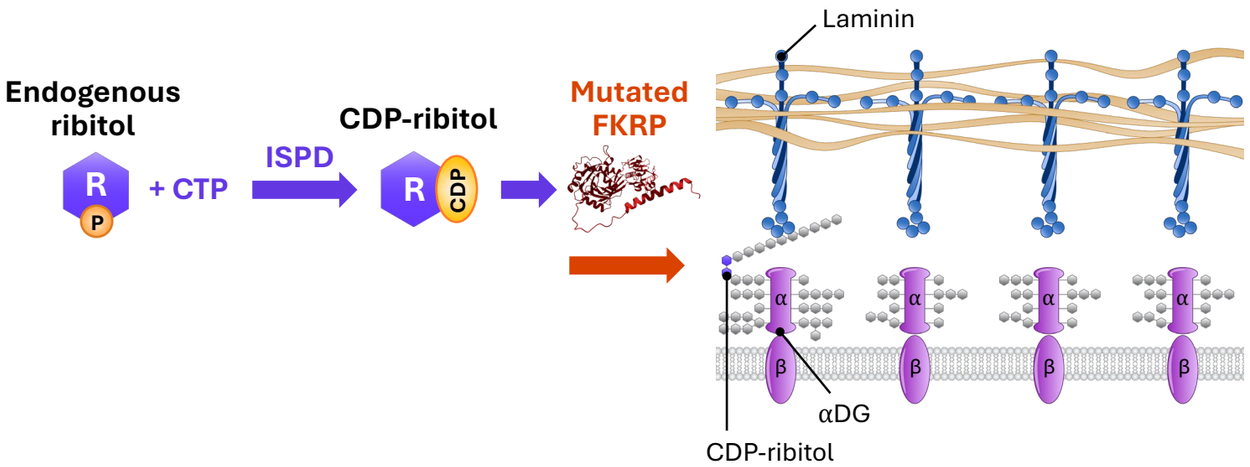
CDP=cytidine diphosphate; FKRP=fukutin-related protein; LGMD2I/R9=limb-girdle muscular dystrophy type 2I/R9; nNos=neuronal nitric oxide synthase.

1. Kanagawa M. *Int J Mol Sci*. 2021;22:13162. doi:10.3390/ijms.222313162 2. Nickolls AR, Bönnemann CG. *Dis Model Mech*. 2018;11(12):dmm035931. doi:10.1242/dmm.035931 3. Jumper J, et al. *Nature*. 2021;596(7873):583-589. doi:10.1038/s41586-021-03819-2 4. Fleming J, et al. *J Mol Biol*. 2025 Aug 1;437(15):168967. doi: 10.1016/j.jmb.2025.168967. 5. Jensen SM, et al. *J Neuromuscul Dis*. 2024;11(1):59-74. doi:10.3233/JND-221629

BBP-418 is being investigated as an upstream substrate to drive residual activity of the mutant FKRP enzyme

LGMD2I/R9 Disease Mechanism[1-3]

- FKRP glycosylates αDG, stabilizing muscle cells by binding extracellular ligands to act as a “shock absorber” for muscle fibers
- Partial loss-of-function mutation in FKRP results in dysfunctional, hypoglycosylated αDG in muscle cells, increasing cell susceptibility to damage

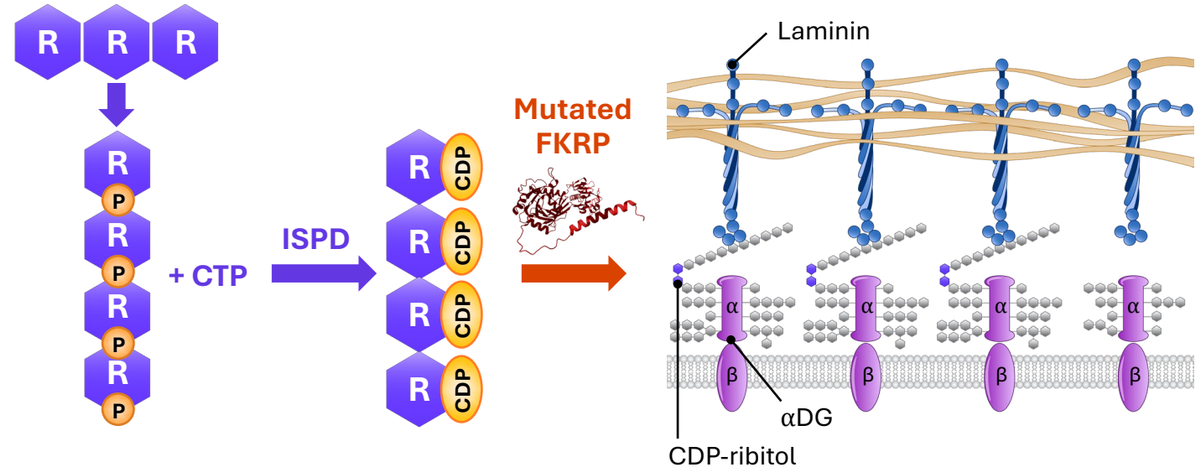


Mutations in *FKRP* prevent addition of CDP-ribitol to αDG, limiting αDG’s ability to function as a “shock absorber” for muscle fibers[1-3]

Proposed BBP-418 Therapeutic Approach

Supply supraphysiological levels of synthesized, pharmaceutical-grade ribitol upstream aiming to drive residual activity of mutant FKRP enzyme and increase αDG glycosylation levels[4]

Orally administered BBP-418 (synthesized, pharmaceutical-grade ribitol)[5]



Potential partial restoration of αDG glycosylation[4]

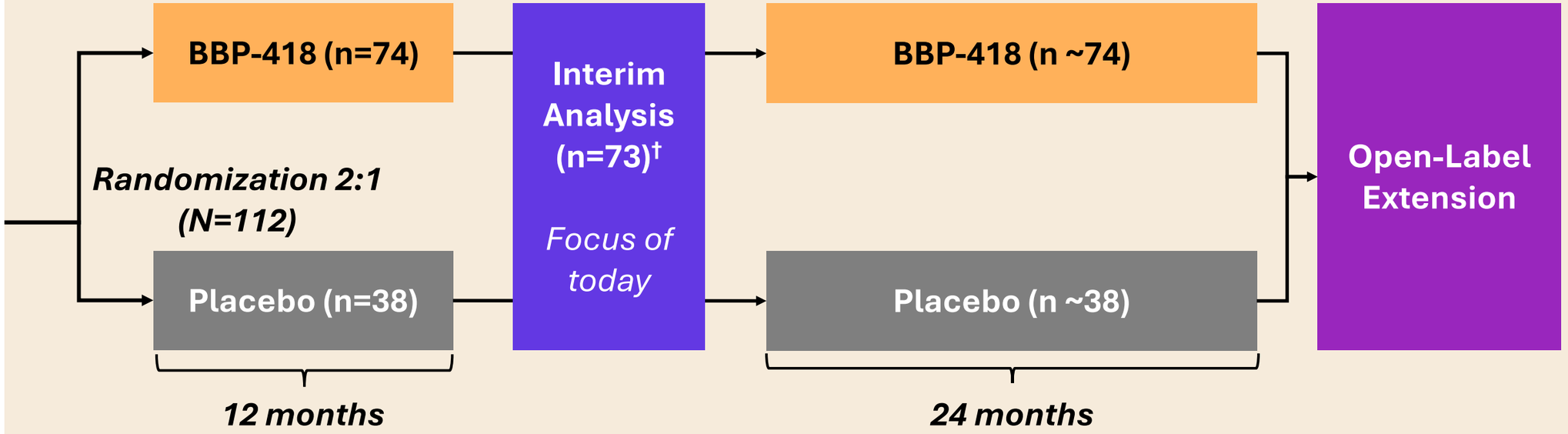
αDG=alpha dystroglycan; CDP=cytidine diphosphate; CTP=cytidine triphosphate; FKRP=fukutin-related protein; ISPD=isoprenoid synthase domain-containing protein; LGMD2I/R9=limb-girdle muscular dystrophy type 2I/R9; P=phosphate; R=ribitol.

1. Gerin I, et al. *Nat Commun.* 2016;7:11534. doi:10.1038/ncomms11534. 2. Nickolls AR, Bönnemann CG. *Dis Model Mech.* 2018;11(12):dmm035931. doi:10.1242/dmm.035931 3. Han R, et al. *Proc Natl Acad Sci USA*. 2009;106(31):12573–12579. 4. Wu B, et al. *PLoS One*. 2025;20(8):e0325239. doi:10.1371/journal.pone.0325239 5. Cataldi MP, et al. *Nat Commun*. 2018;9:3448. doi:10.1038/s41467-018-05990-z

FORTIFY (NCT05775848) is an ongoing randomized, placebo-controlled Phase 3 study with a pre-specified interim analysis

Enrollment Criteria:

- Genetically confirmed, symptomatic LGMD2I/R9
- 12–60 years of age*
- Ambulatory and non-ambulatory individuals
- Body weight >30 kg
- No evidence of clinically significant concomitant disease



Interim Endpoints:

- Glycosylated αDG‡ (*primary*)
- Serum creatine kinase (CK)
- Ambulatory measure: 100-meter timed test (100MTT)
- Pulmonary function: forced vital capacity (FVC)

Final Analysis Endpoints:

- North Star Assessment for Limb Girdle-type Dystrophies (NSAD, *primary*)
- Ambulatory measures
  - 10-meter walk test (10MWT)
  - 100MTT
- Pulmonary function: FVC
- Upper limb function: Performance of Upper Limb Scale 2.0 (PUL 2.0)
- Quality of life (QoL) measures

Placebo and BBP-418 arms were stratified by age group (adult vs pediatric), ambulatory status, and genotype (L276I homozygous vs other *FKRP* genotype)

*Phase 3 trial population limited to 18-60 years in the European Union (EU) region. †72 patients completed the month 12 visit, and 1 patient that discontinued completed an end-of-study (EOS) visit that windowed into month 12. ‡% of control is glycosylated αDG levels relative to a control reference standard from a healthy donor.
αDG=alpha-dystroglycan; LGMD2I/R9= limb-girdle muscular dystrophy type 2I/R9.

ClinicalTrials.gov identifier: NCT05775848. Updated September 9, 2025. Accessed February 22, 2026. https://clinicaltrials.gov/study/NCT05775848/

Demographics and baseline characteristics in the FORTIFY Phase 3 study were mostly well balanced between BBP-418 and placebo arms

Full Analysis Set*	BBP-418 (n=74)	Placebo (n=38)
Age – mean (SD), yr	37.1 (14.2)	33.3 (14.0)
12 to <18 – no. (%)	10 (13.5)	5 (13.2)
18 to 60 – no. (%)	64 (86.5)	33 (86.8)
Sex – no. (%)		
Male	39 (52.7)	14 (36.8)
Female	35 (47.3)	24 (63.2)
Race – no. (%)		
White	73 (98.6)	35 (92.1)
Ethnicity – no. (%)		
Hispanic	3 (4.1)	2 (5.3)
Not Hispanic	71 (95.9)	36 (94.7)
Mutation status – no. (%)		
L276I homozygous	55 (74.3)	28 (73.7)
Other *FKRP* genotype	19 (25.7)	10 (26.3)

*The Full Analysis Set consists of randomized participants who had at least one efficacy assessment post-randomization.
SD=standard deviation.

BBP-418 and placebo groups' baselines were similar on key endpoints

Biomarker EPs

Glycosylated αDG as measured by Western blot

Muscle tissue physiology

Clinical EPs

Functional status

Endpoint (units)	BBP-418	Placebo
Glycosylated αDG (% of control)*		
Mean (SD)	22.71 (16.61)	20.66 (14.67)
Randomized patients (Full analysis set†)	n=73	n=38
Serum CK (U/L)		
Mean (SD)	2449.5 (3014.4)	2099.5 (1832.7)
NSAD ≥ 3 (Primary efficacy set‡)	n=67	n=36
100MTT (m/s)		
Mean (SD)	1.33 (0.82)	1.37 (0.80)
Ambulatory patients (Secondary efficacy set§)	n=62	n=32
FVC (% predicted, sitting position)		
Mean (SD)	77.95 (16.94)	77.17 (16.40)
Ambulatory patients (Secondary efficacy set§)	n=59	n=33

*% of control describes glycosylated αDG levels relative to a control reference standard from a healthy donor. †The full analysis set consists of randomized participants who had at least one efficacy assessment post-randomization. ‡The primary efficacy set consists of randomized participants who provided a total score of ≥3 on the NSAD at baseline. §The secondary efficacy set consisted of 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=creatine kinase; EP=endpoint; FVC=forced vital capacity; m/s=meter/second; n=number of participants in the set; 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.

Nickolls AR, Bönnemann CG. *Dis Model Mech.* 2018;11(12):dmm035931. doi:10.1242/dmm.035931

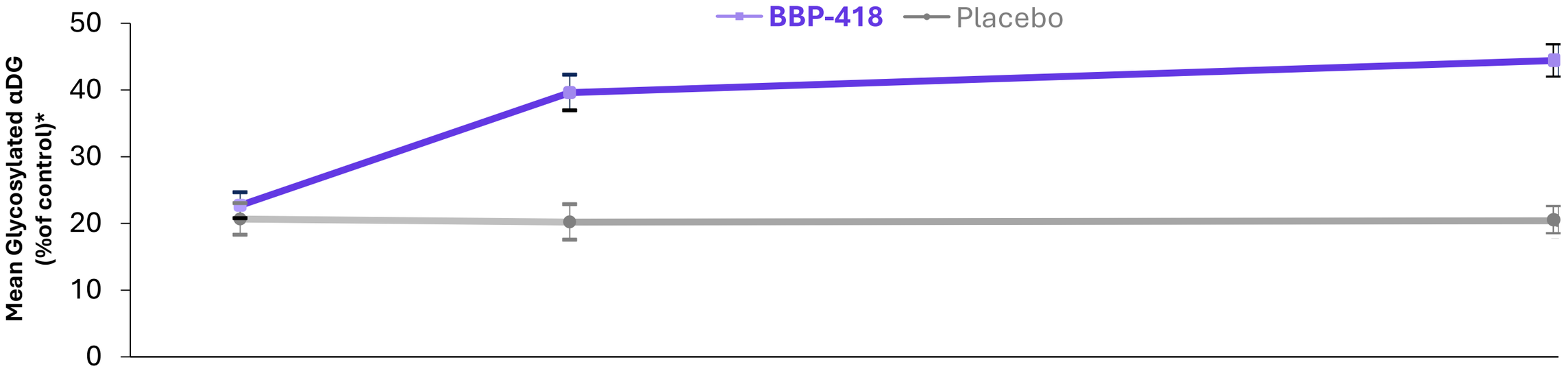
The Phase 3 interim analysis results show consistent and favorable effects of BBP-418 versus placebo on clinical and biomarker endpoints

Endpoints	LS Mean Change from Baseline BBP-418	LS Mean Change from Baseline Placebo	*P*-value
Interim analysis key endpoints (α-controlled)			
Glycosylated αDG at 3 months (% of control)*	+17.12	-0.04	<0.0001
Glycosylated αDG at 12 months (% of control)*	+23.60	+0.82	<0.0001
Serum CK at 12 months (U/L)	-1869	+186	<0.0001
100MTT at 12 months (m/s)	+0.14	-0.12	<0.0001
FVC at 12 months (% predicted, sitting position)	+3.0	-1.9	0.0071
Final analysis key endpoints at 12 months (non-α-controlled)			
NSAD (points)	+1.3	-1.3	0.0001†
10MWT (m/s)	+0.13	-0.1	<0.0001†
PUL 2.0 (points)	+0.8	+1.1	0.6779

*% of control describes glycosylated αDG levels relative to a control reference standard from a healthy donor. †Nominally statistically significant based on exploratory analysis; analysis not part of α-controlled hierarchy at interim analysis.
10MWT=10-meter walk test; 100MTT=100-meter timed test; αDG=alpha-dystroglycan; CK=creatine 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; U/L=units/liter.

Patients treated with BBP-418 experienced an increase in glycosylated αDG at 3 months which was sustained at 12 months

Mean glycosylated αDG (% of control)* (± standard error of the mean, SEM)

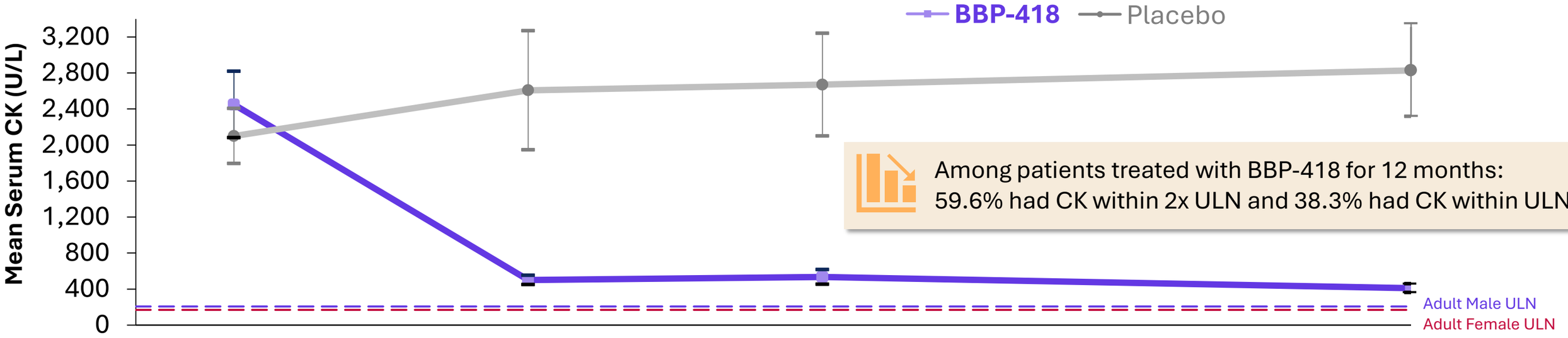


Timepoint	0 months	3 months	12 months
Cohort	Full analysis set†	Full analysis set†	Full analysis set†
BBP-418	22.7% (n=73)	39.6% (n=71)	44.5% (n=49)
Placebo	20.7% (n=38)	20.2% (n=36)	20.4% (n=22)

*% of control describes glycosylated αDG levels relative to a control reference standard from a healthy donor. †The Full Analysis Set consists of randomized participants who had at least one efficacy assessment postrandomization.
αDG=alpha-dystroglycan; SEM=standard error of the mean.

Patients treated with BBP-418 experienced a rapid reduction in serum CK from baseline at 3 months that was sustained through 12 months

Mean CK (U/L) (±SEM)*

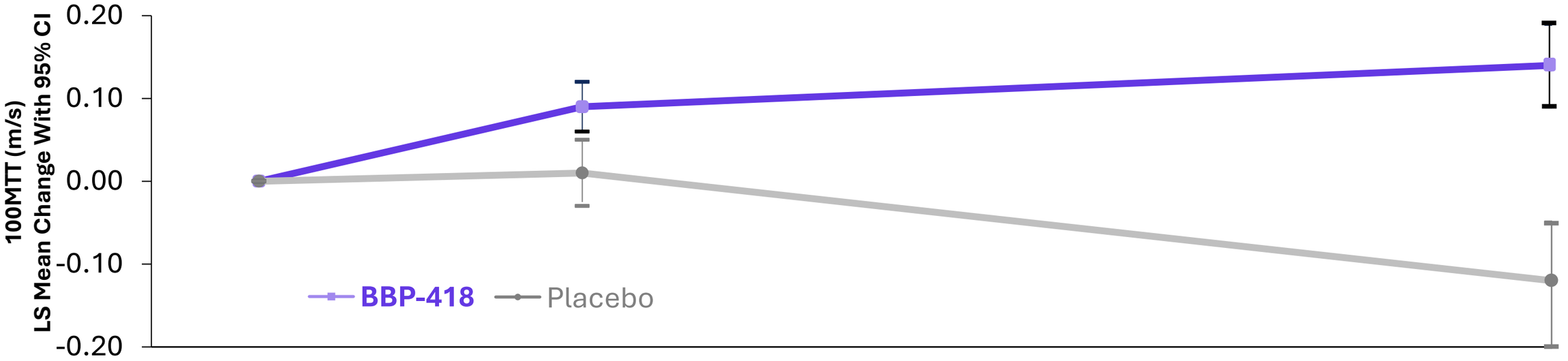


Timepoint	0 months	3 months	6 months	12 months
Cohort	Primary efficacy set†	Primary efficacy set†	Primary efficacy set†	Primary efficacy set†
BBP-418	2449.5 (n=67)	500.7 (n=45)	534.1 (n=67)	410.1 (n=47)
Placebo	2099.5 (n=36)	2607.4 (n=23)	2670.9 (n=35)	2828.5 (n=22)

*Mean ±SEM from Baseline to 12-month timepoint; †The Primary Efficacy Set consists of randomized participants who provided a total score of ≥3 on the NSAD at baseline.
CK=creatine kinase; SEM=standard error of the mean; U/L=units/liter; ULN=upper limit of normal.

Difference of 0.27 m/s observed between BBP-418 and placebo arms in 100MTT at 12-month interim analysis

LS Mean Change from Baseline in 100MTT (±95% CI)



Timepoint	3 months	12 months
Cohort	Ambulatory Analysis Set*	Ambulatory Analysis Set*
BBP-418	0.09 (n=61)	0.14 (n=40)
Placebo	0.01 (n=32)	-0.12 (n=20)

*This analysis is based on the secondary efficacy set which consisted of 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: (1) 10MWT (or if 10MWT was not available, then NSAD Item #29a [velocity]), (2) PUL 2.0 (3) FVC (% predicted, sitting) (or if FVC was not available, then the investigator reported that spirometry was performed).
LS mean change from baseline at 3- and 12-month timepoints; comparison of BBP-418 change from baseline to Placebo change from baseline is based on a linear mixed model for repeated measures.
n = number of participants with observed values.
10WT=10-meter walk test; 100MTT=100-meter timed test; CI=confidence interval; FVC=forced vital capacity; LS=least-squares; m/s=meter/second; NSAD=North Star Assessment for Limb Girdle-type Dystrophies; PUL 2.0=Performance of Upper Limb Scale 2.0.

LS mean time to complete 100MTT was significantly different between the treatment and placebo arms

Endpoint	LS mean time to complete 100MTT at 12 months (s)	LS mean (99% CI) change from baseline to 12 months (s)
BBP-418	85.1	-12.4 (-26.9, 2.0)
Placebo	116.1	+18.6 (-1.1, 38.2)
Treatment difference		-31.0 (-55.4, -6.6; p=0.0011)*



A time to complete the 100 MTT of <83 seconds (>1.2 m/s) reflects the ability to ambulate in the community, while completion in >125 seconds (<0.8 m/s) reflects ambulation largely limited to household settings[1,2]



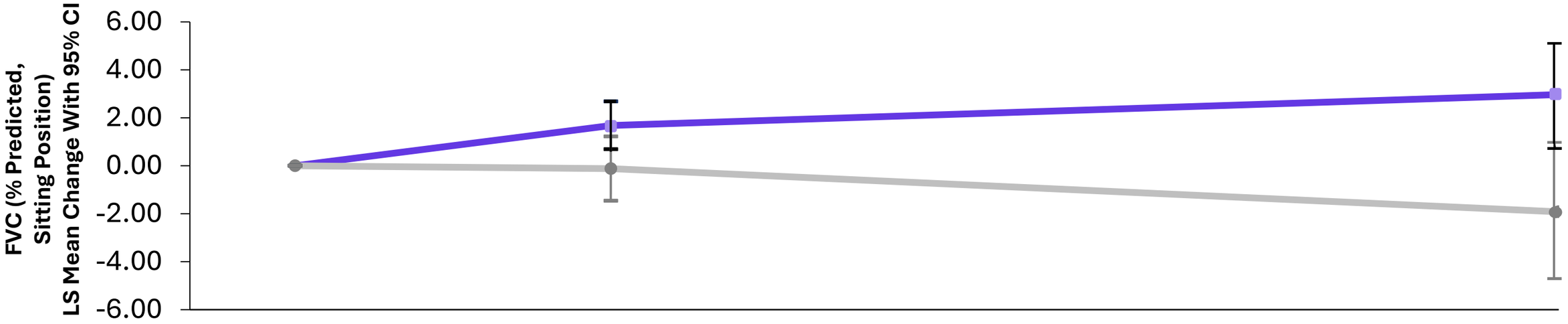
BBP-418-treated patients completed ~31 seconds faster than placebo-treated

*Nominally statistically significant based on exploratory analysis; analysis not part of α-controlled hierarchy at interim analysis.
Least-squares mean change from baseline at 12-month timepoint; Comparison of BBP-418 change from baseline to Placebo change from baseline is based on a linear mixed model for repeated measures. Test conducted in secondary efficacy set
100MTT=100-meter timed test; CI=confidence interval; LS=least-squares; m/s=meter/second; s=second.

1. Alfano LN, et al. 2025;12(7):1324-1333. doi: 10.1002/acn3.70064. 2. James MK, et al. *Neurol Genet.* 2025;11:e200323. doi:10.1212/NXG.0000000000200323.

Patients treated with BBP-418 registered ~3% increase in predicted volume from baseline FVC, resulting in a difference of ~5% predicted volume versus placebo

LS Mean Change from Baseline in FVC (% predicted) (±95% CI)



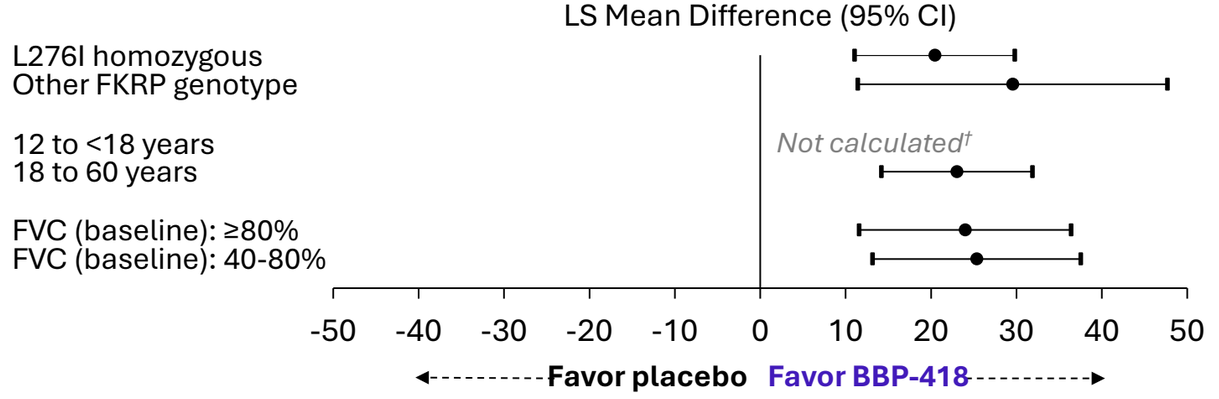
Timepoint	3 months	12 months
Cohort	Ambulatory Analysis Set*	Ambulatory Analysis Set*
BBP-418	1.68 (n=58)	2.97 (n=35)
Placebo	-0.12 (n=32)	-1.92 (n=21)

*This analysis is based on the secondary efficacy set which consisted of 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: (1) 10MWT (or if 10MWT was not available, then NSAD Item #29a [velocity]), (2) PUL 2.0 (3) FVC (% predicted, sitting) (or if FVC was not available, then the investigator reported that spirometry was performed). LS mean change from baseline at 3- and 12-month timepoints; comparison of BBP-418 change from baseline to Placebo change from baseline is based on a linear mixed model for repeated measures.
Reported n's are observed n's.
10MWT=10-meter walk test; CI=confidence interval; FVC=forced vital capacity; LS=least-squares; NSAD=North Star Assessment for Limb Girdle-type Dystrophies; PUL 2.0=Performance of Upper Limb Scale 2.0.

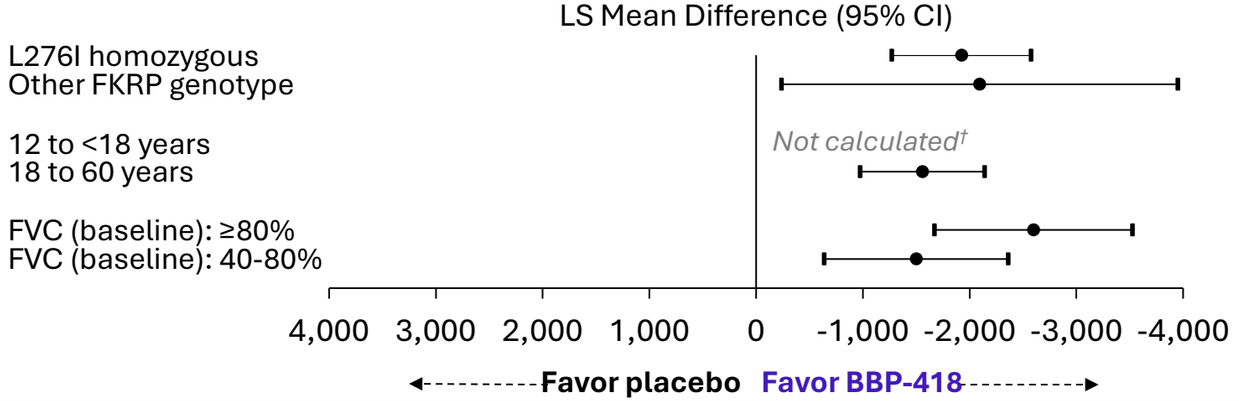
Planned subgroup analyses show consistent benefit of BBP-418 vs. placebo in all subgroups across α-controlled efficacy endpoints at 12 months

Biomarker

Glycosylated αDG (% of control)*

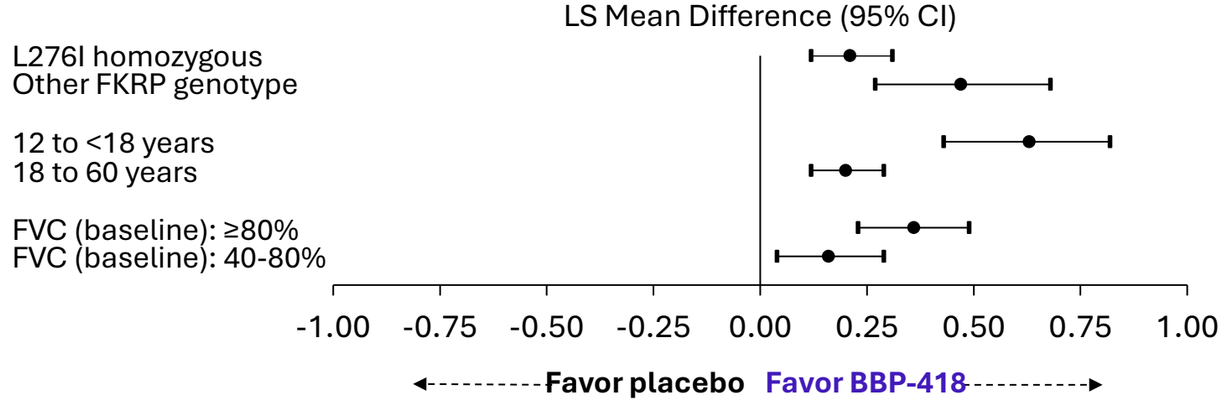


Serum CK (U/L)

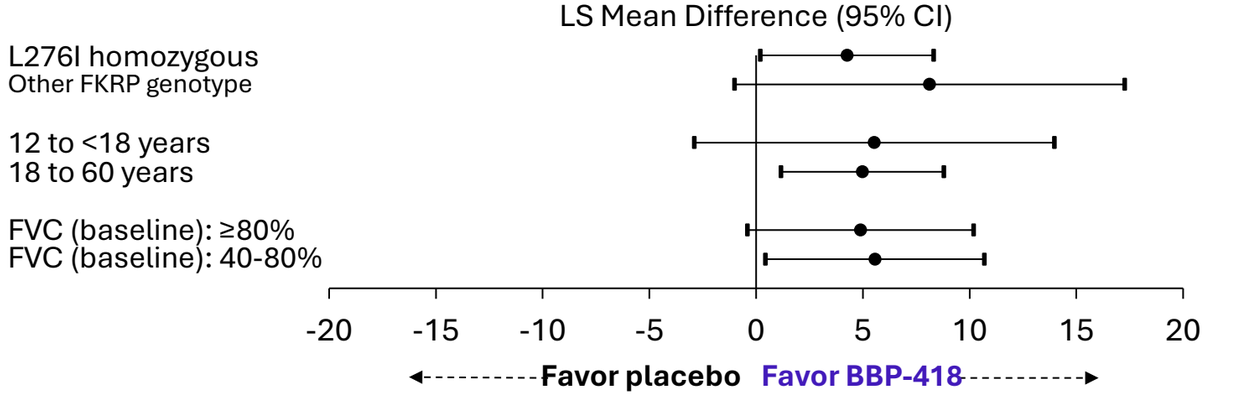


Clinical

100-meter timed test (m/s)



Forced vital capacity (% predicted)

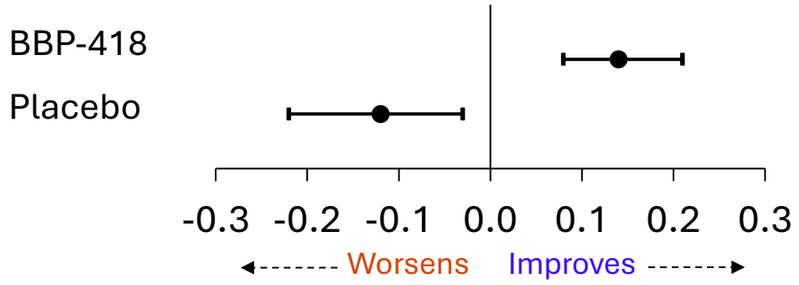


*Describes glycosylated αDG levels relative to a control reference standard from a healthy donor. †Pre-specified inferential statistics not performed for subgroups representing <15% of all participants in relevant analysis set.
αDG=alpha dystroglycan; CI=confidence interval; CK=creatine kinase; FKRP=fukutin-related protein; FVC=forced vital capacity; LS=least-squares; m/s=meter/second; U/L=units/liter.

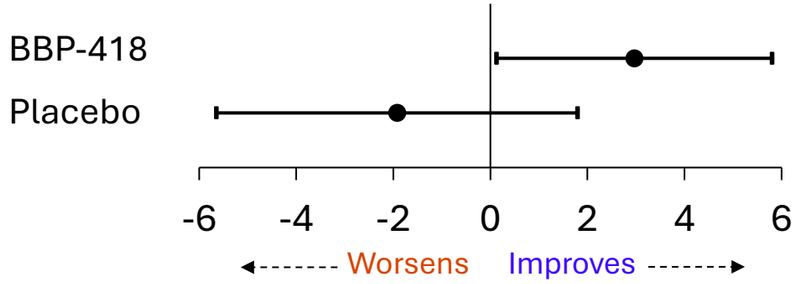
At 12 months, BBP-418 was associated with improvements in multiple functional assessments, contrasting with decline seen in placebo cohort

α-controlled at 0.01, 99% CI

100MTT velocity (m/s)*

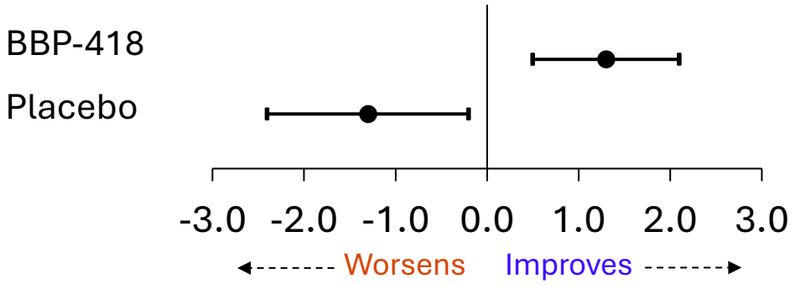


FVC (% predicted) *

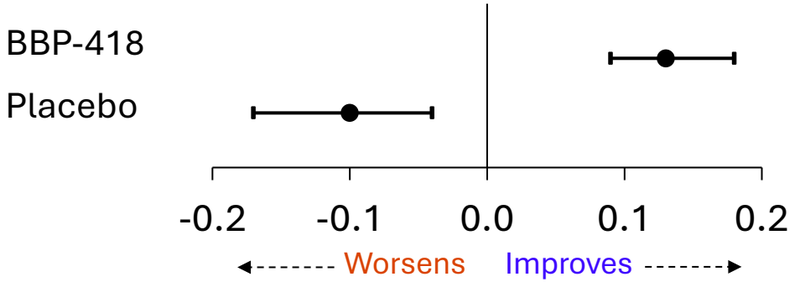


Non-α-controlled, 95% CI

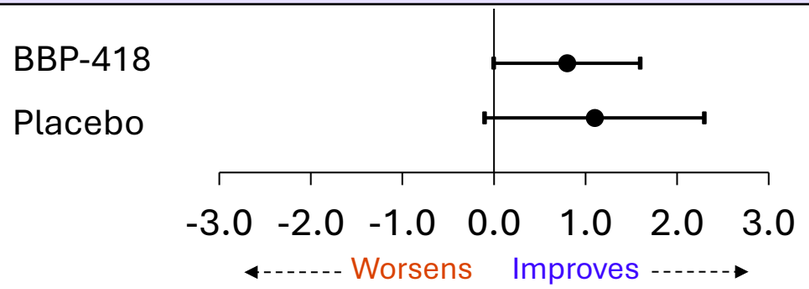
NSAD Total Score (points)†



10MWT velocity (m/s)†



PUL 2.0 Total Score (points)



Values represent LS mean change from baseline.
*P-values < 0.01. †Nominal P-values < 0.05.
10MWT=10-meter walk test; 100MTT=100-meter timed test; CI=confidence interval; 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.

α-controlled Endpoints

- **100MTT:** BBP-418-treated participants improved from baseline by 0.14 m/s whereas placebo participants deteriorated by 0.12 m/s*
- **FVC:** BBP-418-treated participants improved from baseline by 3.0% predicted whereas placebo participants deteriorated by 1.9%*

Non-α-controlled Endpoints

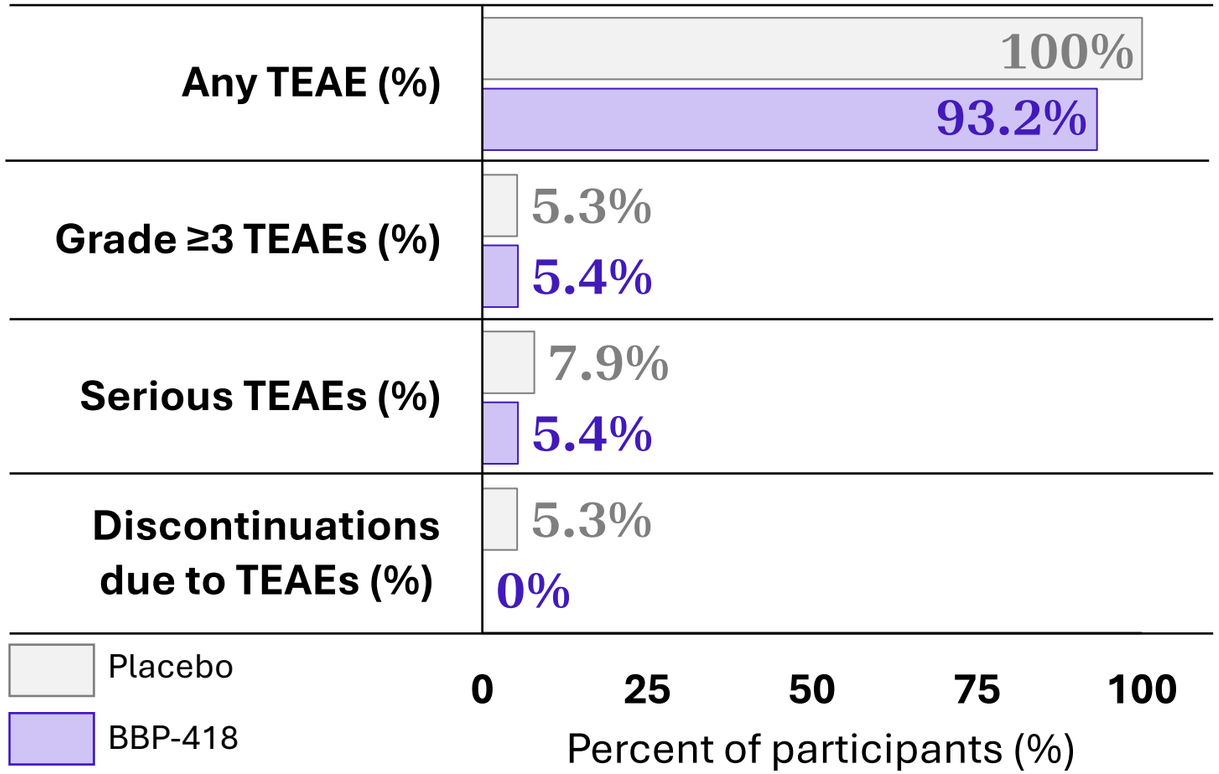
- **NSAD:** BBP-418-treated participants had a 1.3-point improvement from baseline whereas placebo participants had a 1.3-point deterioration†
- **10MWT:** BBP-418-treated participants improved from baseline 0.13 m/s whereas placebo participants had a 0.10 m/s deterioration†
- **PUL:** There was no difference between the BBP-418 treated participants and the placebo participants in the change from baseline PUL 2.0 score

Data support a tolerable and well-characterized safety profile for BBP-418 in LGMD2I/R9

Safety Population

- 112 randomized participants
  - **BBP-418: n=74**
  - **Placebo: n=38**
- Median exposure ≈13 months
- There were no deaths or treatment-related SAEs
- Phase 3 study remains ongoing with double-blind maintained

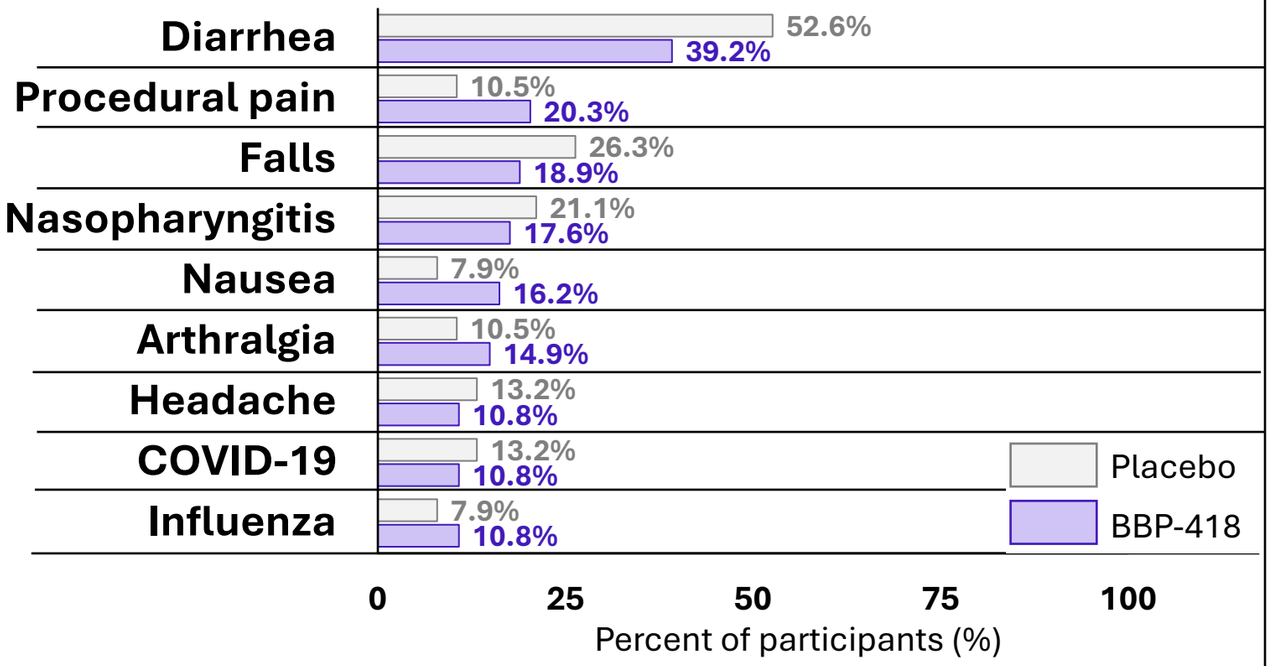
Treatment-Emergent Adverse Events*



*Percentages reflect participant-level incidence percentages.
LGMD2I/R9=limb-girdle muscular dystrophy type 2I/R9; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Most common TEAE associated with BBP-418 was diarrhea; no new or unexpected safety findings were observed

Most Common TEAEs (>10%)*



- All diarrhea events were Grade 1-2
- No diarrhea related Serious TEAEs

Laboratory and Cardiac Assessments

- No laboratory pattern suggestive of hepatic, renal, cardiac, hematologic, or metabolic toxicity
- No clinically meaningful changes in ECG parameters
  - QTcF >60 msec increase: 0% in both BBP-418 treated and placebo treated participants

*Percentages reflect participant-level incidence percentages
ECG=electrocardiogram; msec=millisecond; QTcF=QT interval corrected for heart rate using Fridericia's formula; TEAE=treatment-emergent adverse event.

Summary

MOA and Study Design

- Orally administered BBP-418 targets the biochemical defect of LGMD2I/R9
- FORTIFY (NCT05775848) is an ongoing, randomized, placebo-controlled Phase 3 study with a pre-specified interim analysis

Efficacy

- 12-month data from the Phase 3 FORTIFY study suggest consistent and favorable effects of BBP-418 versus placebo on all key endpoints and subgroups

Safety

- BBP-418 was generally well tolerated, with predominantly mild to moderate adverse events and no clinically meaningful organ-specific safety concerns identified

Overall, the FORTIFY interim analysis supports a favorable benefit–risk profile of BBP-418.

LGMD2I/R9=limb-girdle muscular dystrophy type 2I/R9; MOA=mechanism of action; NDA=new drug application.

Thank You

To the patients and families, advocates, physicians, clinical research staff, and collaborating research partners that are part of the FORTIFY trial.