Preliminary Results from MLB-01-003: An Open Label Phase 2 Study of BBP-418 in Patients with Limb-girdle Muscular Dystrophy Type 2I/R9

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Disclosures

- I have the following conflict/s of interest to declare:
  - I receive VCU contracted funds from several sponsors for clinical research studies (PI or Co-I), including NSPharma, Italafarmaco, Santhera (ReveraGen), Dyne, Novartis (Avexis), Astellas, Fulcrum and ML Bio.
  - Additionally, I receive Co-I funding for clinical research in cerebral palsy and muscular dystrophy from the NIH and CDC, respectively.
  - I am Co-I in several other studies, but do not receive funding for them.

- BBP-418 has not been approved to treat patients by any regulatory authority in any country.

- Phase 2 study is ongoing and in a limited number of subjects. All results are preliminary and may be subject to change.

LGMD2I/R9 is caused by mutations in FKRP and characterized by an established genotype/phenotype association

	Birth	Early Childhood	Late Childhood	Adolescence to adulthood
L276I Homozygotes **Prevalence** *(L276I/L276I)* **68%**	Asymptomatic	Asymptomatic	▪ **Age of symptom onset 18 ± 3 years old** ▪ Lower limb & proximal weakness ▪ +/-calf hypertrophy, muscle pain, ↑ serum CK levels	**Loss of ambulation:** 25% by age 40 **Respiratory decline**: Non-invasive assistance required by 10% by age 40 and invasive assistance required by <1% **Cardiac dysfunction**: ~30%
Other FKRP genotypes **Prevalence** *(L276I/ non-L276I)* **29%** *(non-L276I/ non-L276I)* **2%**	Asymptomatic	▪ **Age of symptom onset 5 ± 1 years old** ▪ Lower limb & proximal weakness ▪ +/-calf hypertrophy, muscle pain, ↑ serum CK levels	▪ Lower limb & proximal weakness ▪ +/-calf hypertrophy, muscle pain, ↑ serum CK levels	**Loss of ambulation:** most by age 20 **Respiratory decline**: Invasive assistance required by 5% by age 30 **Cardiac dysfunction**: ~60%

Source: 1) Sveen et al, Annals of Neurology, 2006; 2) Richard et al, Neuromuscular Disorders, 2016 3) Gedlinske et al, Neurology, 2020 4) GnomAD database 5) Liu, et al, Genet Med., 2018 6) Libell et al, Muscle Nerve, 2020

Alpha Dystroglycan (αDG), disrupted in LGMD2I (LGMD R9 FKRP-related), is an integral part of the dystrophin-glycoprotein complex

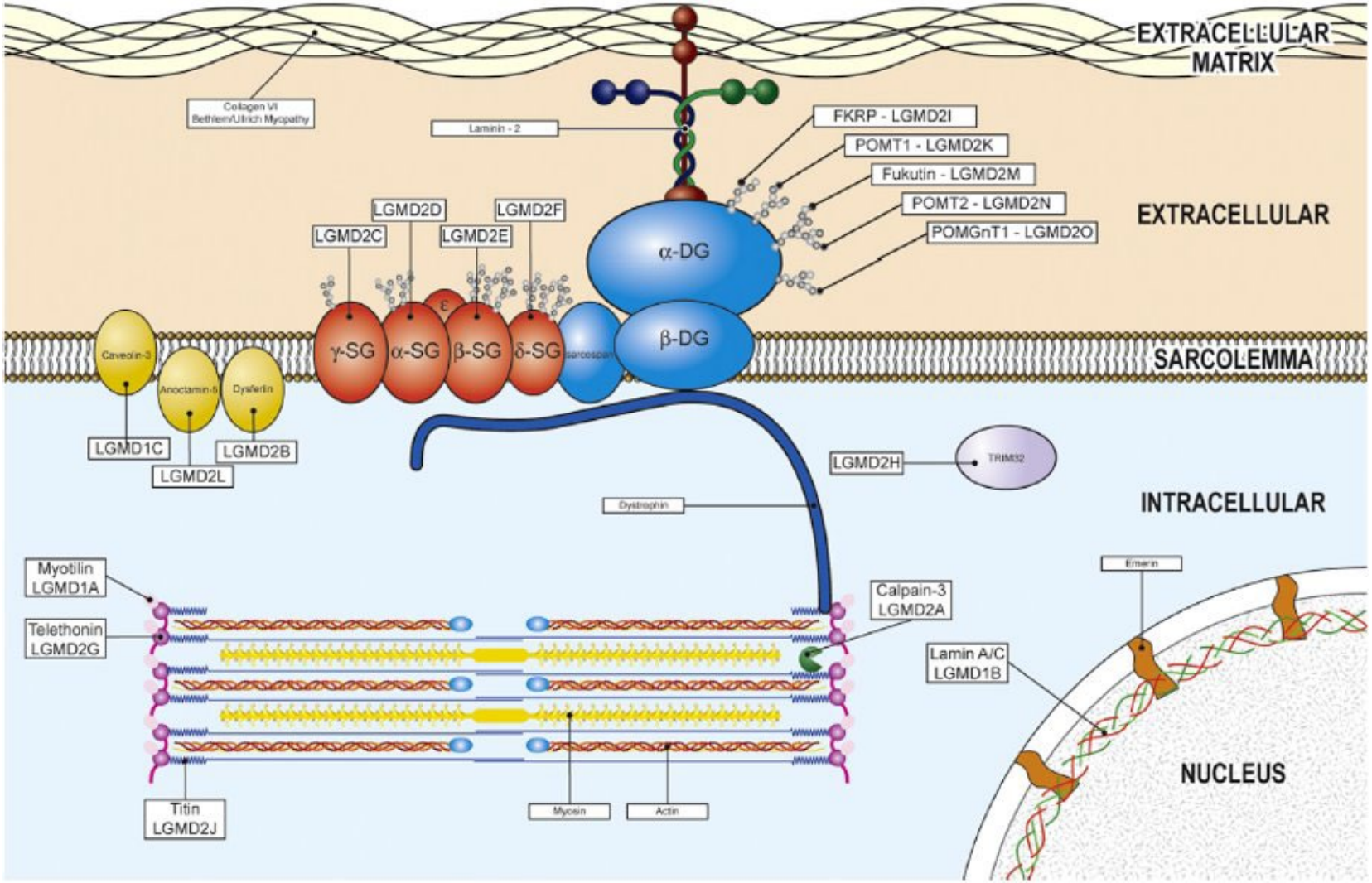


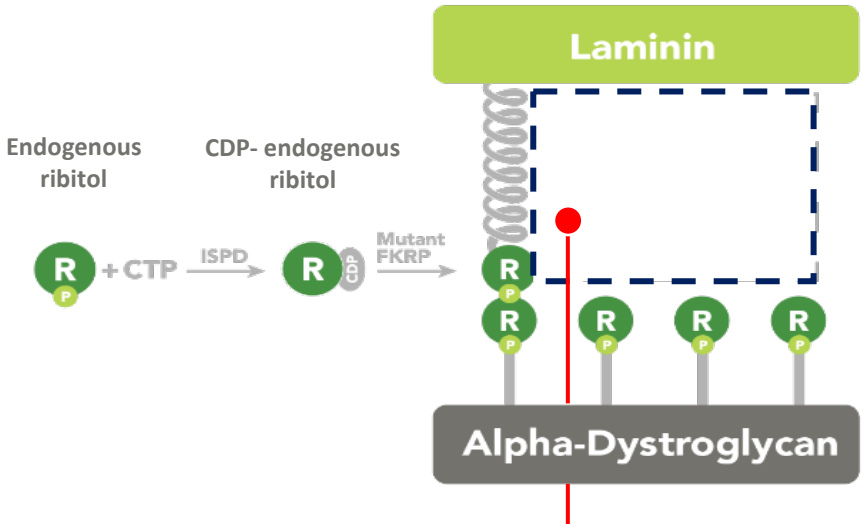
Figure from Wicklund et al., The limb-girdle muscular dystrophies. Neurologic Clinics, 2014.

Oral BBP-418 is under investigation as an upstream substrate supplement to drive residual activity of mutant FKRP in LGMD2I/R9, targeting the disease at its source

LGMD2I/R9 Disease Mechanism

Functional FKRP fully glycosylates alpha-dystroglycan (αDG) which stabilizes myocytes by binding extracellular ligands to act as a "shock absorber" for muscle fibers

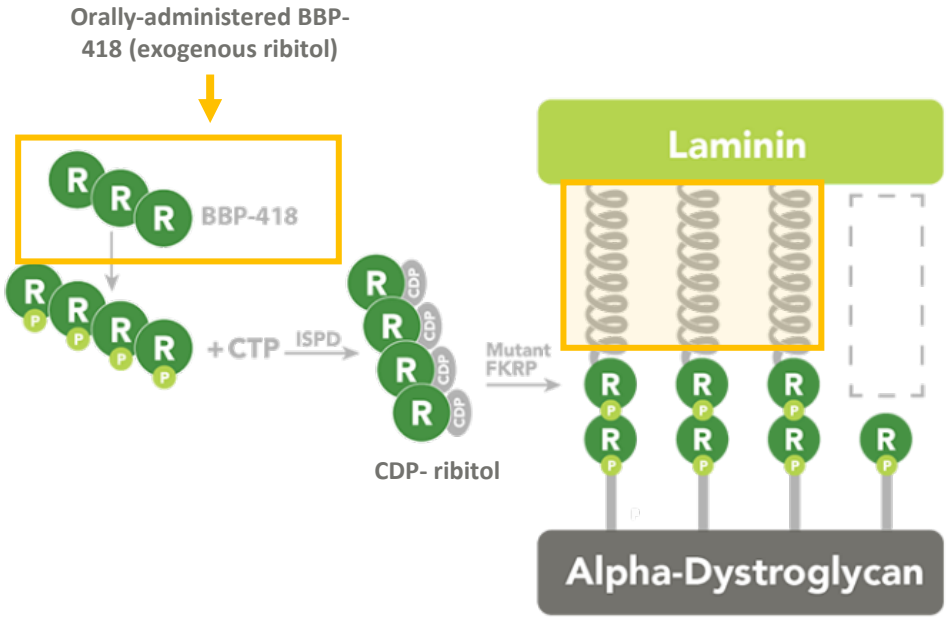
Partial loss of function mutation in FKRP results in dysfunctional, hypo-glycosylated αDG in myocytes which increases susceptibility to damage



Mutations in FKRP prevent addition of ribitol-5-P to alpha-dystroglycan (hypo-glycosylated αDG) limiting αDG's ability to function as a "shock absorber" for muscle fibers

Proposed BBP-418 Therapeutic Approach

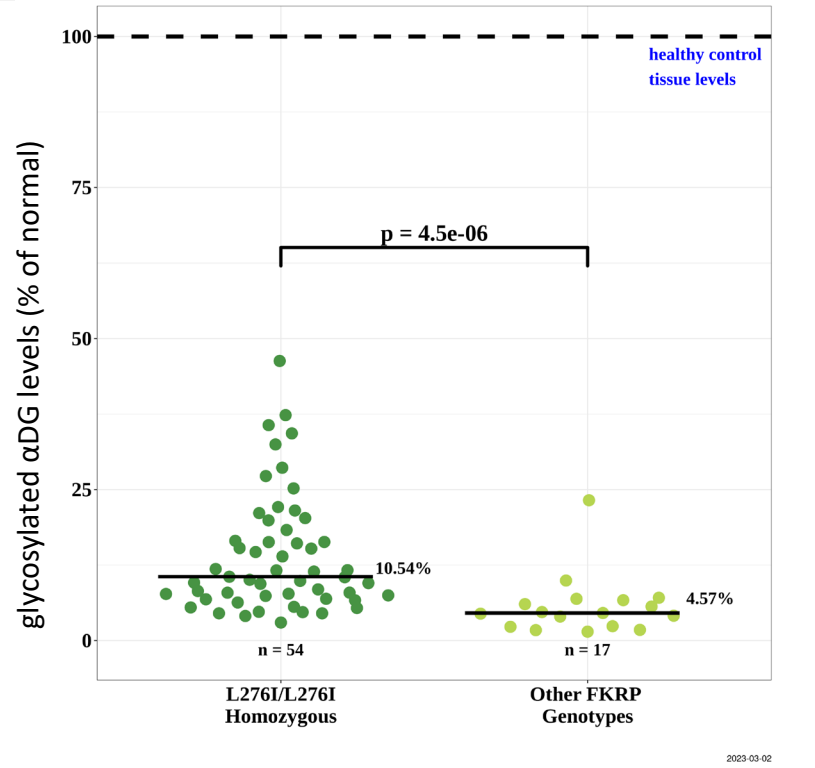
Supply supraphysiological levels of ribitol upstream aiming to drive residual activity of mutant FKRP enzyme and increase αDG glycosylation levels



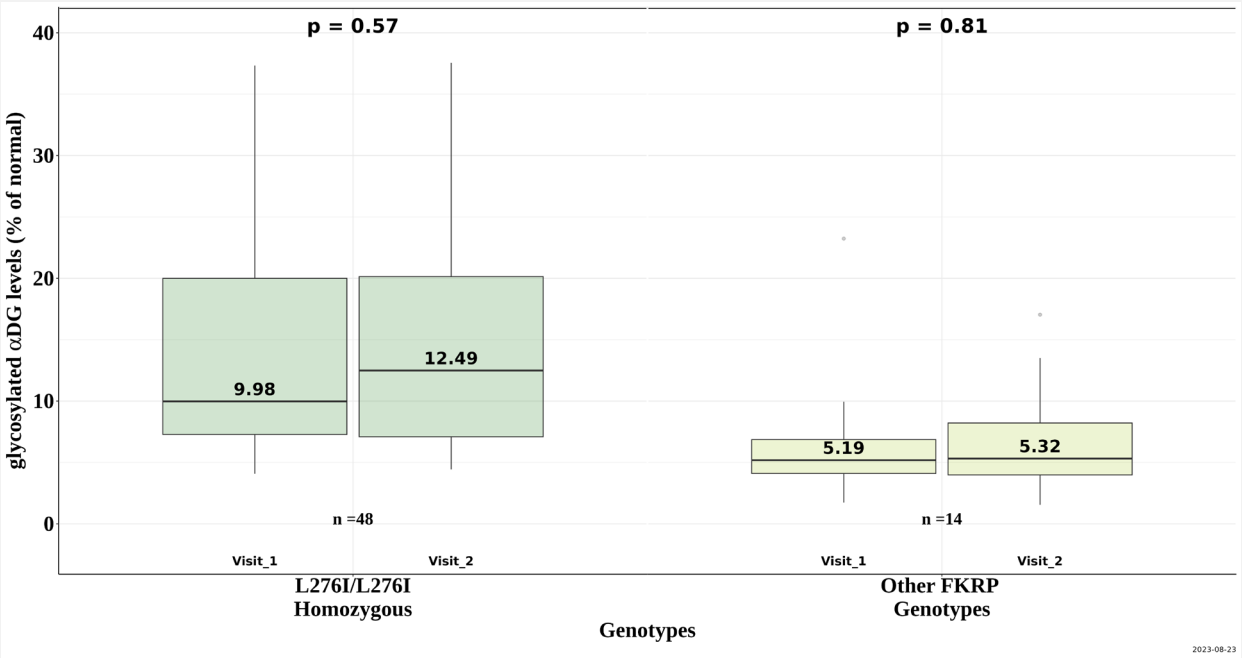
Potential partial restoration of αDG glycosylation

Natural history data supports the premise that glycosylation of αDG in muscle mirrors the severity of LGMD2I/R9 disease and remains stable over time

Reduced αDG glycosylation in other *FKRP* genotypes vs. L276I/L276I homozygous LGMD2I/R9 patients



Glycosylated αDG levels remain stable over 6–12 months in untreated LGMD2I/R9 patients

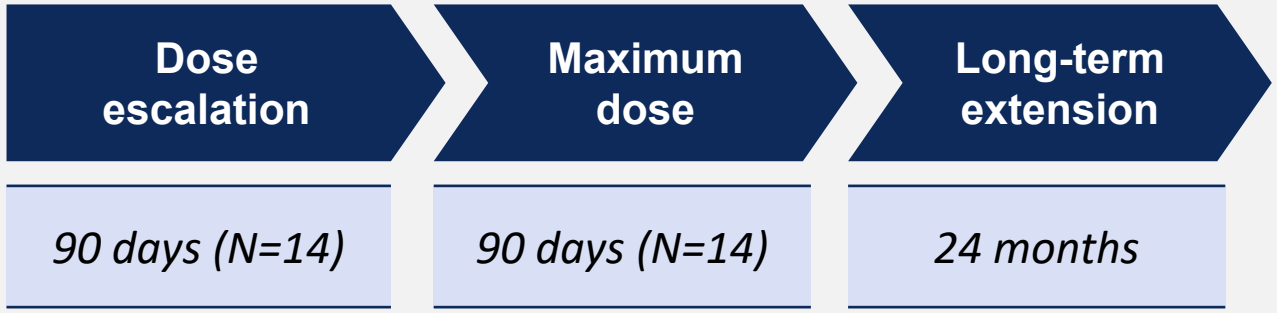


Other *FKRP* genotypes, which are more rare and typically have a more severe clinical presentation, have lower glycosylated αDG levels compared to L276I/ L276I homozygous patients; both groups have reduced levels compared to healthy individuals

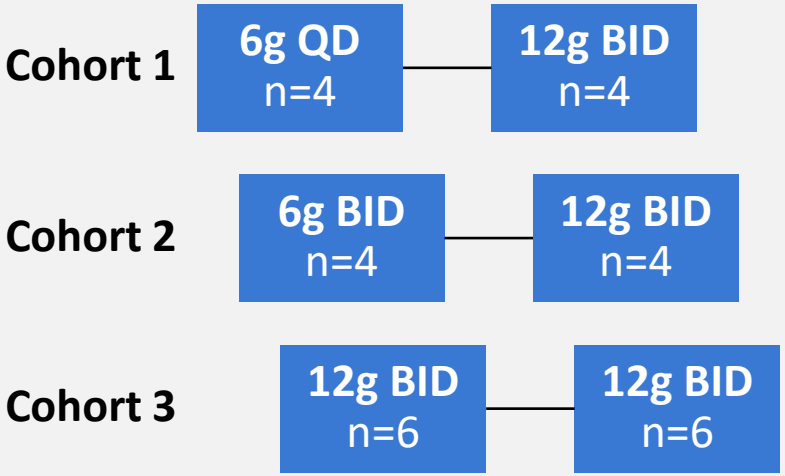
Patient samples were interpolated to standard curve to determine % of normal glycosylation of αDG; lines show medians; figure includes all patients with biopsies in MLB-01-001

Patient samples were interpolated to standard curve to determine % of normal glycosylation of αDG; median and 25-75% percentile are shown; figure includes all patients with repeat biopsies in MLB-01-001

BBP-418 is under investigation in a small, open label Phase 2 study in individuals with LGMD2I/R9



After Part 1, all participants transitioned to highest dose 12g BID



Key Endpoints

- NSAD
- 10-meter walk test/100-meter timed test
- FVC
- PUL2.0
- Glycosylated αDG levels
- Serum creatine kinase (CK)

Key inclusion criteria

- Age between 12-55 years at enrollment
- Genetically confirmed LGMD2I/R9
- Body weight >30kg
- Able to complete 10MWT ≤12 seconds unaided (moderate disease) or unable to (severe disease)

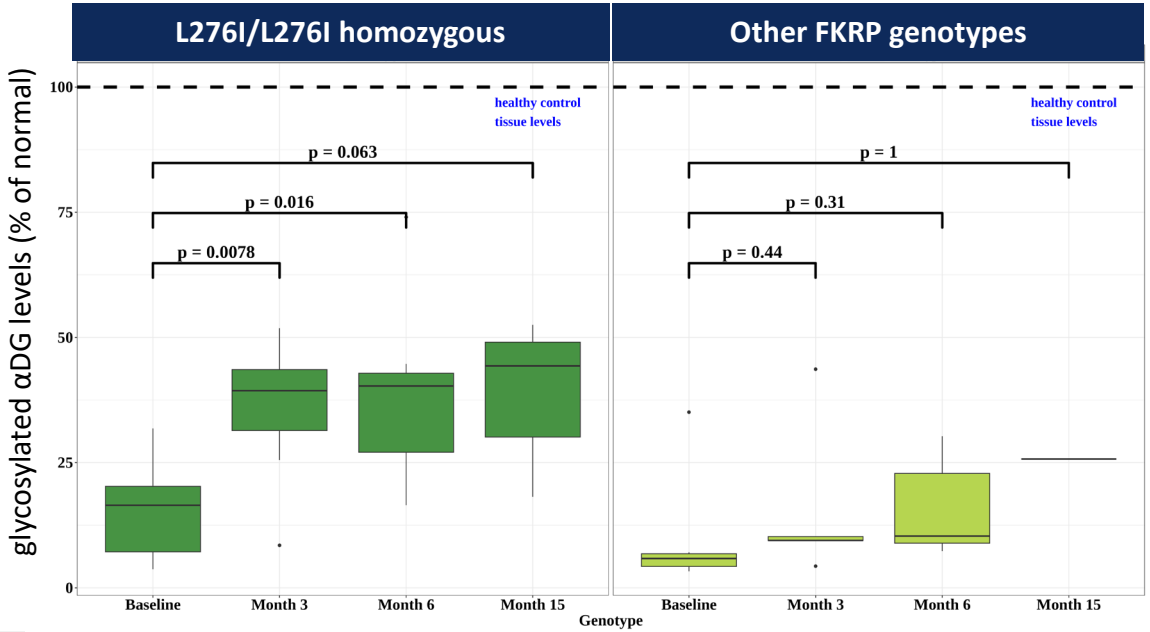
BBP-418 has been well tolerated, with only minor GI related adverse events recorded in the Phase 2 study

- 189 adverse events (AEs) were recorded in the study with 19 possibly or probably related to BBP-418 treatment and 4 definitely related to BBP-418
- 19 possibly/probably related AEs include: diarrhea, dehydration, nausea, vomiting, dyspepsia, gastroenteritis, and headaches
- 4 definitely related AEs include: nausea, diarrhea, and abdominal pain
- No discontinuations or interruptions in therapy due to AEs
- 3 severe adverse events recorded unrelated to the treatment

TEAE	# of incidents	Severity
Diarrhea	9	66% mild, 33 % moderate
Dehydration	1	100% mild
Nausea	3	66% Grade 1, 33% moderate
Vomiting	2	100% mild
Dyspepsia	1	100% mild
Gastroenteritis	1	100% moderate
Constipation	1	100% mild
Bloating	3	66% mild, 33% moderate
Headaches	1	100% moderate
Abdominal pain	1	100% moderate
Overall	**23**	

Sustained increases in levels of glycosylated αDG in muscle and decreases in serum creatine kinase observed in Phase 2 study of BBP-418

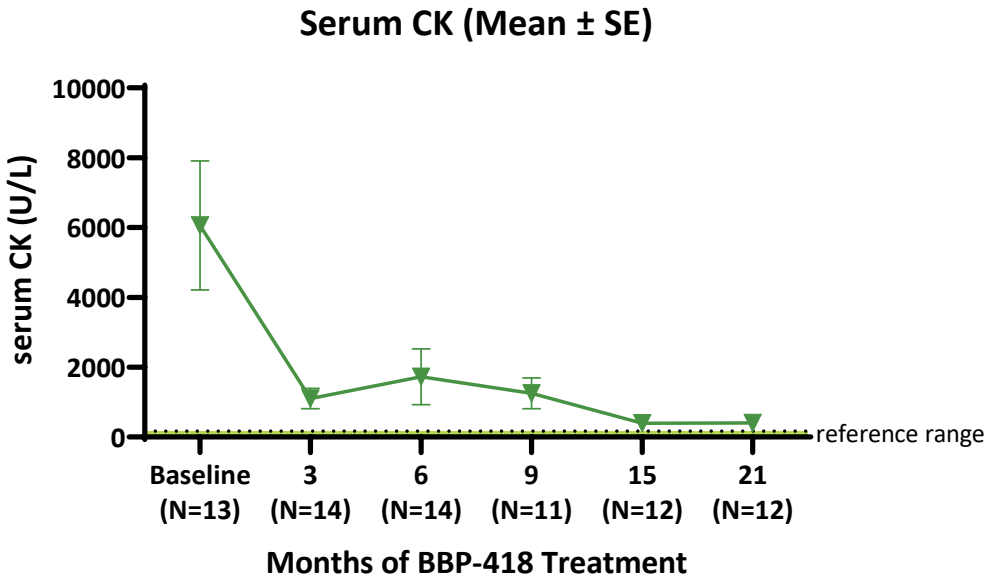
Increase in glycosylated αDG in muscle observed post dosing with BBP-418 (median ± 95% CI)



Median (%)	16.5	39.4	39.7	44.3	5.9	9.5	10.4	25.7
N	8	8	7	6	6	5	6	1

Patient samples were interpolated to standard curve to determine % of normal glycosylation of αDG
+ 3 mo = Part 1, 90-day; +6 mo = Part 2, Month 3; + 9 mo = Part 3, Month 3; + 15 mo = Part 3, Month 9
Median and 25-75% percentile are shown, Wilcoxon test was used to determine significance

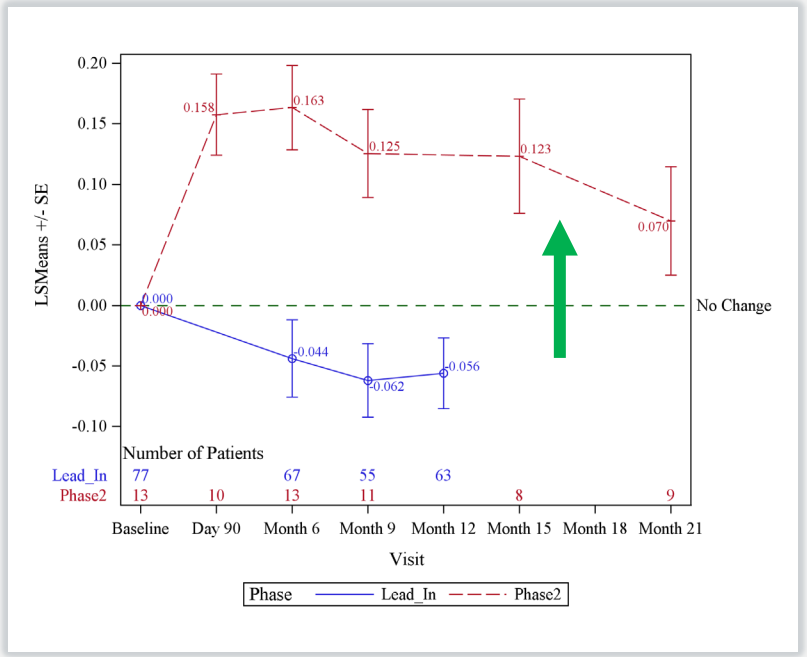
Reduction in mean serum creatine kinase (CK) observed post dosing with BBP-418



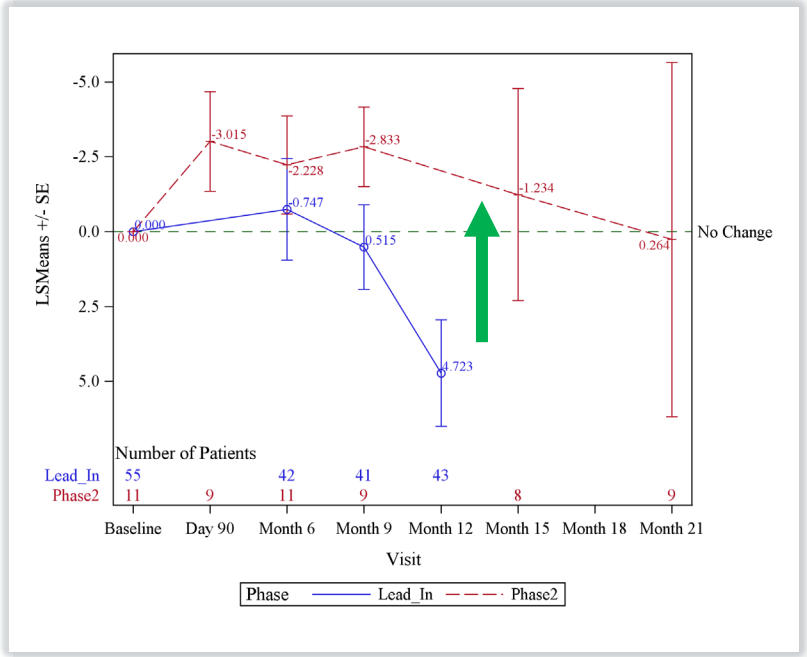
Cohort 1 Day 1 CK draws taken after functional assessments; all other draws done prior to functional assessment
After Day 90, all subjects received 12 g BID (weight-adjusted)
+ 3 mo = Part 1, 90-day; +6 mo = Part 2, Month 3; + 9 mo = Part 3, Month 3; + 15 mo = Part 3, Month 9; +21 mo = Part 3, Month 15; Reference range for CK is 55–170 units/L for men and 30–135 units/L for women, figure shows reference range from 30–170 units/L

Stabilization in ambulatory and clinical measures observed after 21 months of treatment with BBP-418 in Phase 2 study

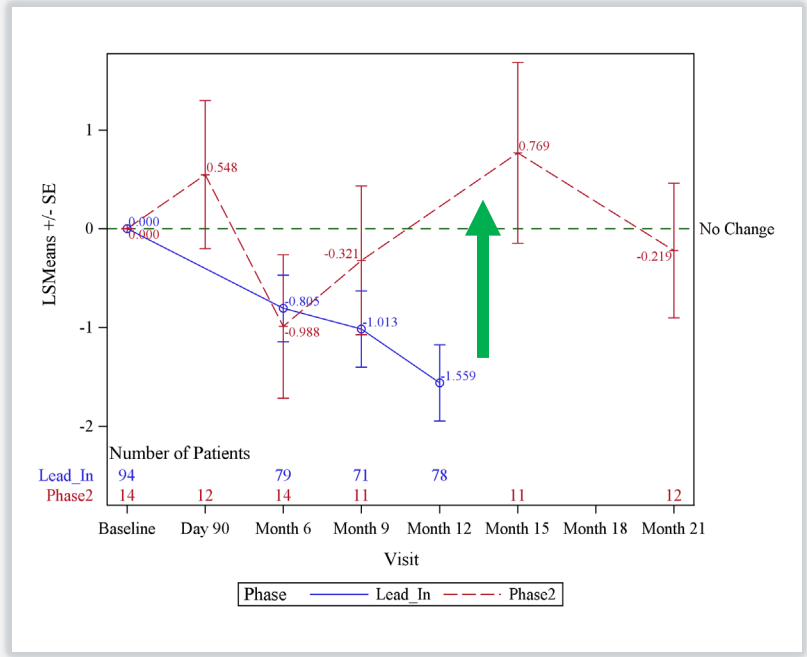
Change from baseline in 10MWT (m/s)



Change from baseline in 100MTT (s)



Change from baseline in NSAD

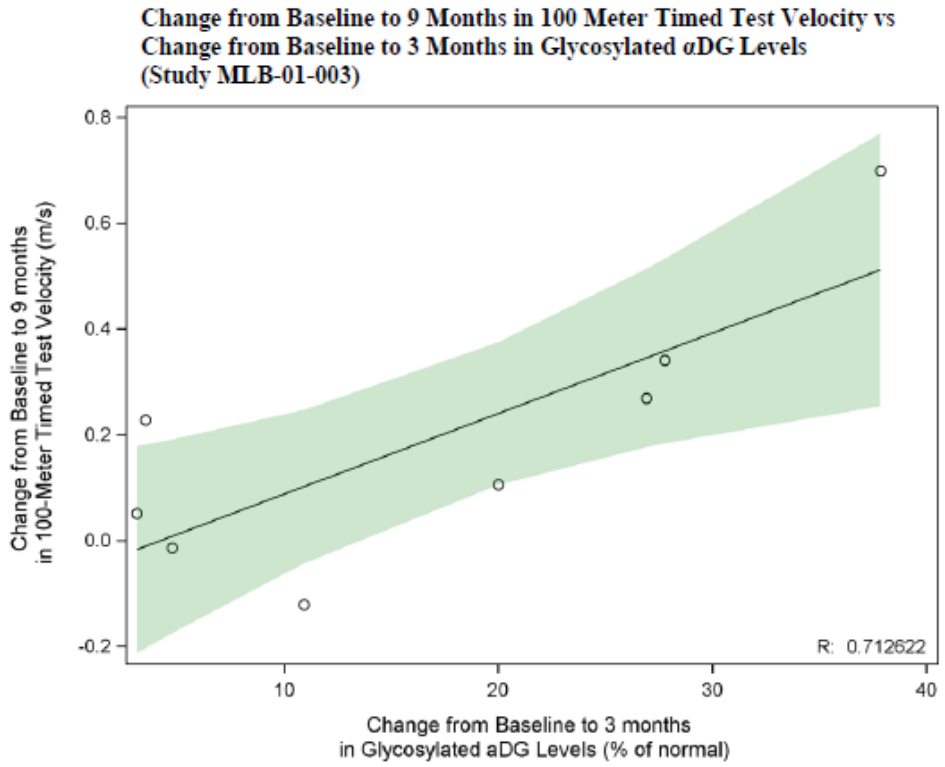


Blue lines denote natural history data and **red lines** denote on-treatment data collected during the Phase 2 study

Data exclude 1 subject from month 15 timepoint due to post-COVID decline
Phase 2 data: + 3 mo = Part 1, 90-day; +6 mo = Part 2, Month 3; + 9 mo = Part 3, Month 3; + 15 mo = Part 3, Month 9; +21 mo = Part 3, Month 15

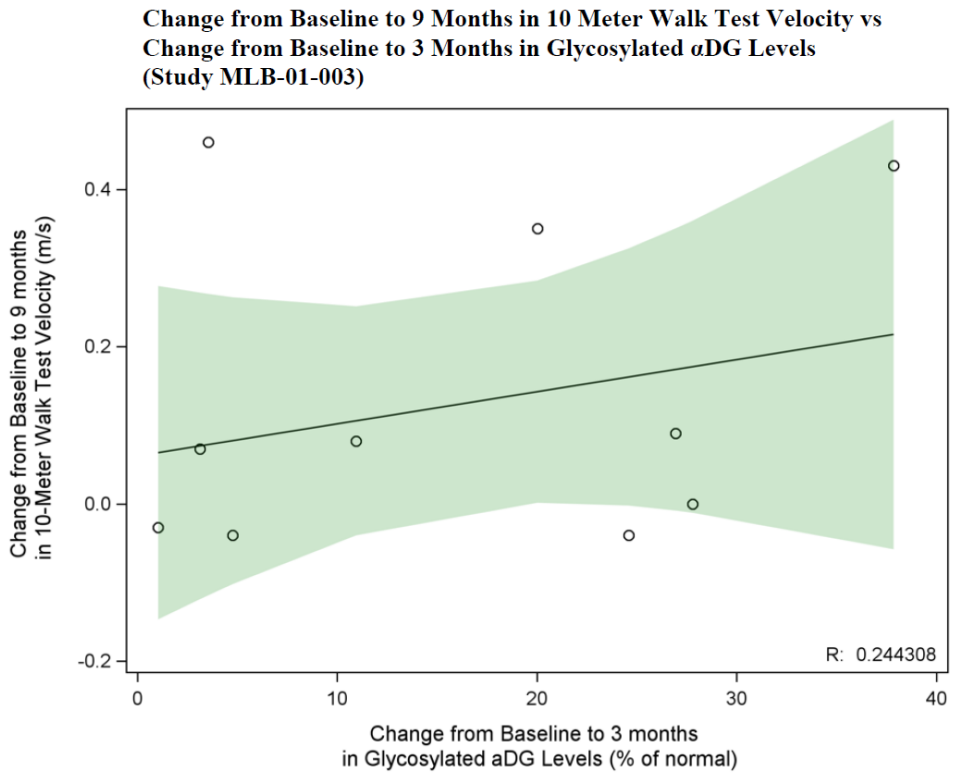
Phase 2 data support that early changes in glycosylated αDG levels at 3 months may be associated with subsequent clinical improvements

glycosylated αDG Levels at 3 months vs. 100MTT at 9 months



The line shows linear fit and R is the Pearson product moment correlation coefficient.
Source: MLB-01-003 Listings 16.2.2 and 16.4.1.

glycosylated αDG Levels at 3 months vs. 10MWT at 9 months



The line shows linear fit and R is the Pearson product moment correlation coefficient.
Source: MLB-01-003 Listings 16.2.1 and 16.4.1.

Summary

Phase 2 Study (MLB-01-003)

- Increased glycosylation of αDG observed following BBP-418 dosing which is sustained over time
- Large, sustained reduction in creatine kinase observed over an extended (up to 21-months) treatment period
- Stabilization in NSAD and ambulatory measures observed over 21-month treatment period
- No treatment-related SAEs or dose limiting toxicities observed with BBP-418

Phase 3 FORTIFY Study (MLB-01-005)

- The Phase 3 FORTIFY study is a double-blind, randomized, placebo-controlled clinical trial actively enrolling at sites in the US with expected additional sites in the EU, UK, and Australia

Thank You!

- ML Bio study participants
- LGMD2I/R9 patients, families, and patient advocates

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