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

Douglas Sproule, MD

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Disclosures

- I have the following conflict of interest to declare:
  - I am an employee of BridgeBio Pharma / ML Bio Solutions
- BBP-418 has not been approved to treat patients by any regulatory authority in any country.
- Phase 2 study is ongoing. Therefore, all results are preliminary and may be subject to change.

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

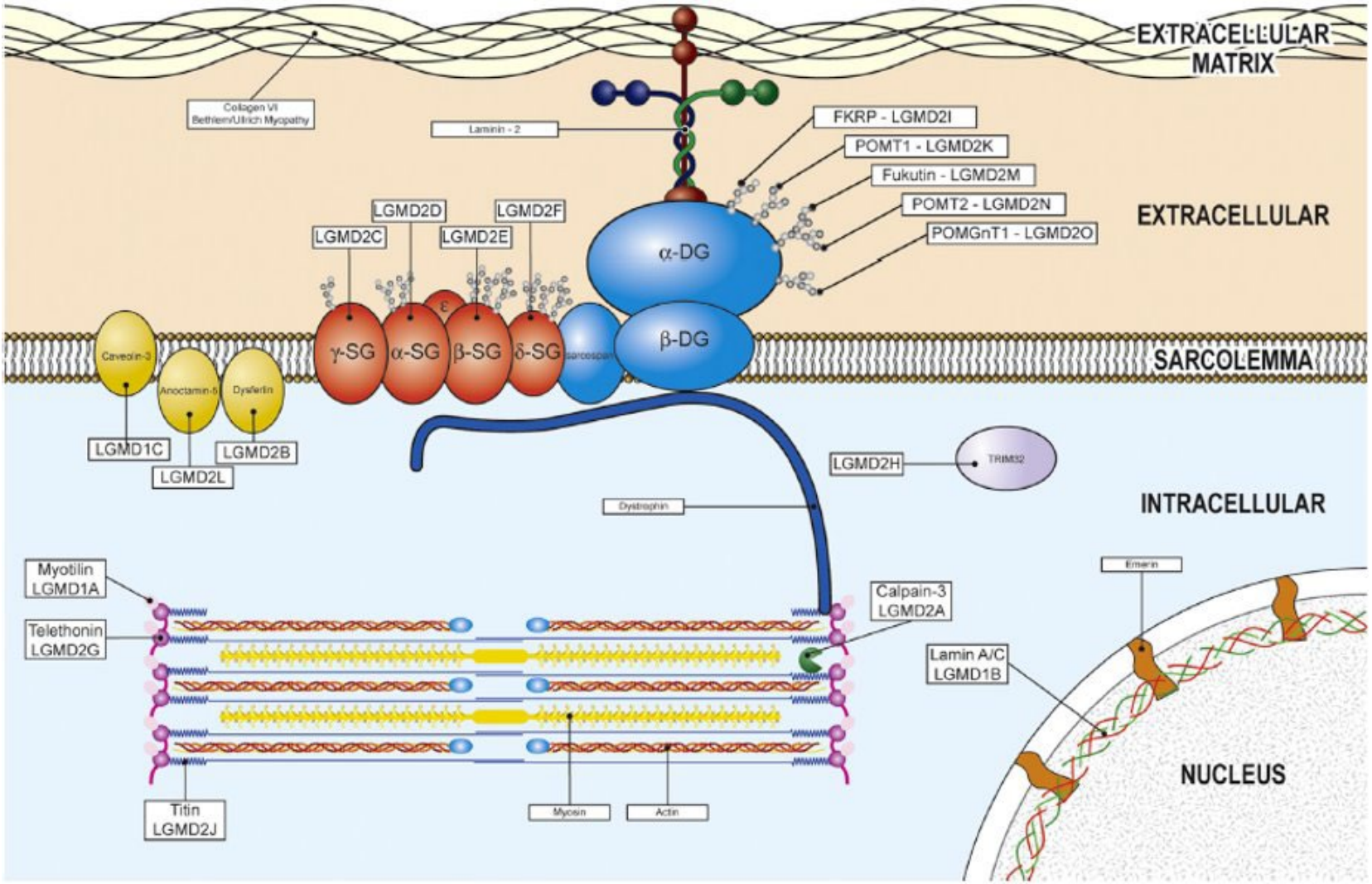


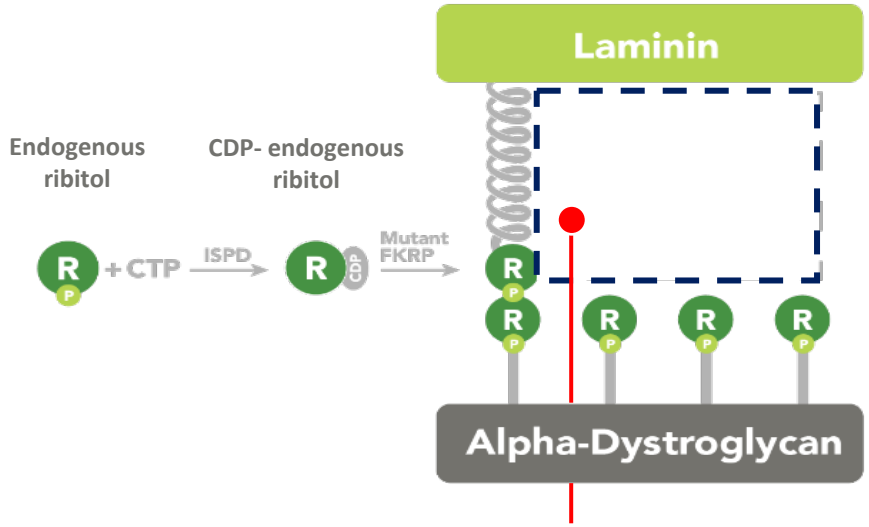
Figure from Wicklund et al., The limb-girdle muscular dystrophies. Neurologic Clinics, 2014.

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

LGMD2I 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

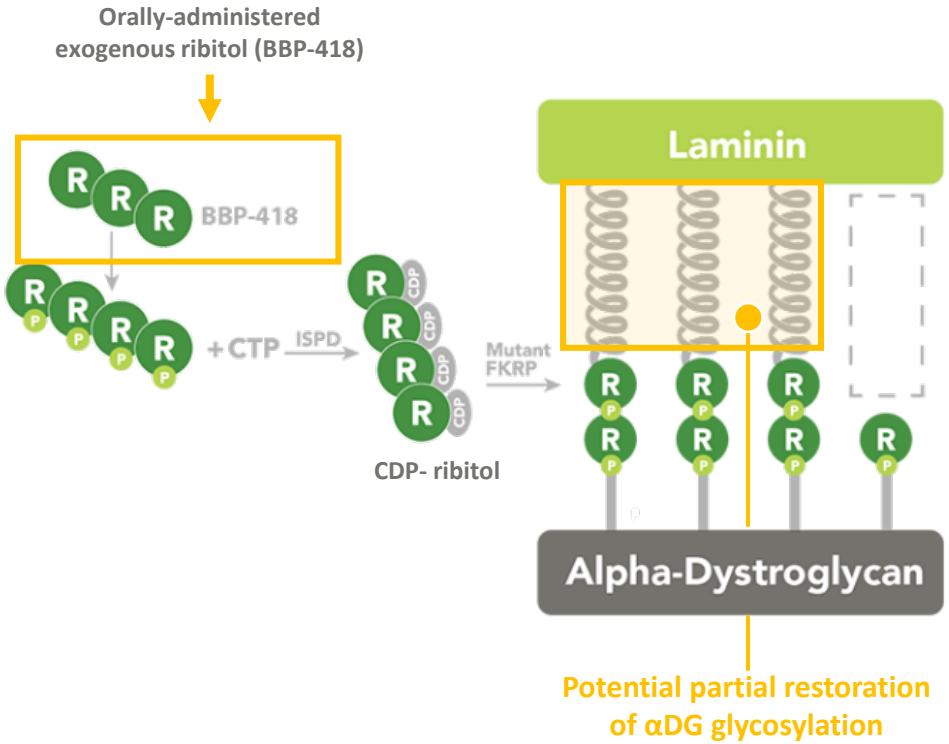
Partial loss of function mutation in FKRP results in dysfunctional, hypo-glycosylated αDG in myocytes which increases susceptibility to damage



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

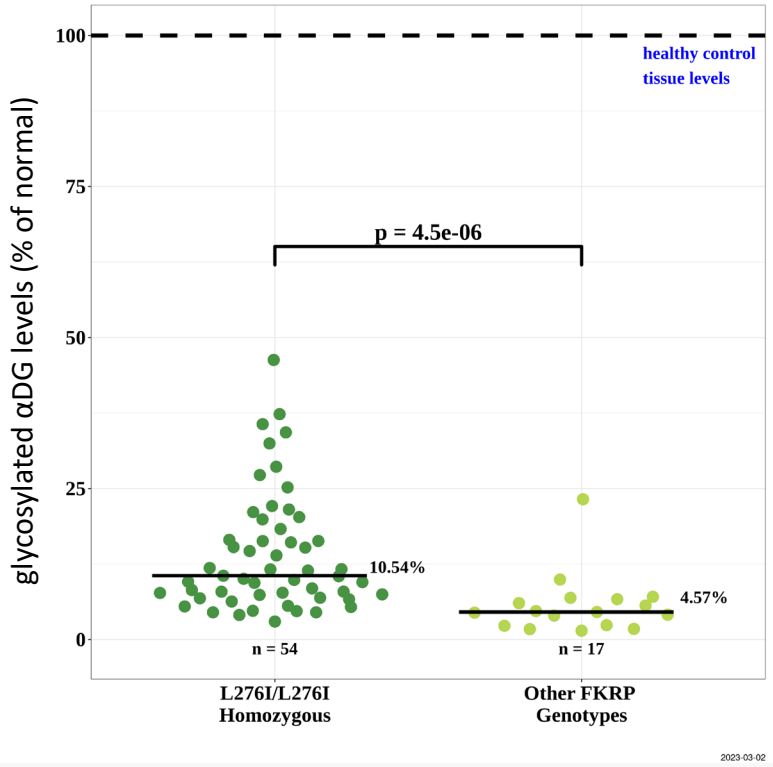
BBP-418 Therapeutic Approach

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

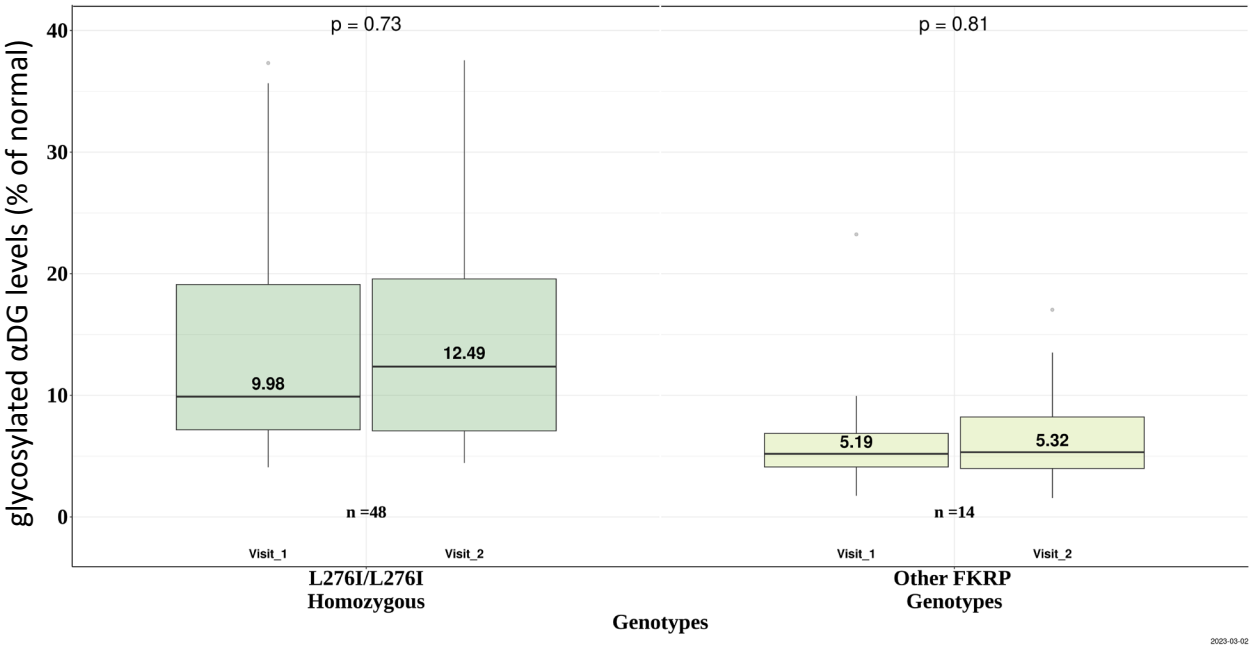


Degrees of hypoglycosylation of αDG mirror the severity of LGMD2I disease and remain stable over time

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



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



Rarer, non-L276I homozygous genotypes, which 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: **see poster #140 for more details**

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 being investigated in an open label Phase 2 Study (MLB-01-003)

Part 1	*Part 2*	*Part 3*
Dose escalation	**Maximum Dose**	**Long-term extension**
90 days (N=14)	*90 days (N=14)*	*24 months*

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

Cohort 1	6g QD n=4	12g BID n=4
Cohort 2	6g BID n=4	12g BID n=4
Cohort 3	12g BID n=6	12g BID n=6

Part 2 Dosing

Dose for patients in Part 2 of the study was 12 g BID, adjusted as follows:

- Patient weight is >70 kg: 12 g BID
- Patient weight is >50 kg–70 kg: 9 g BID
- Patient weight is >30 kg–50 kg: 6 g BID

Part 3 Dosing

Dose for patients assigned to Part 3 receiving 12 g BID was adjusted as follows:

- Patient weight is >50 kg: 12 g BID
- Patient weight is >30 kg–50 kg: 9 g BID

KEY ENDPOINTS

- NSAD
- 10-meter walk test / 100-meter timed test
- FVC
- PUL2.0
- glycosylated αDG levels
- serum creatine kinase

KEY INCLUSION CRITERIA

- Age between 12–55 years at enrollment
- Genetically confirmed LGMD2I
- 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

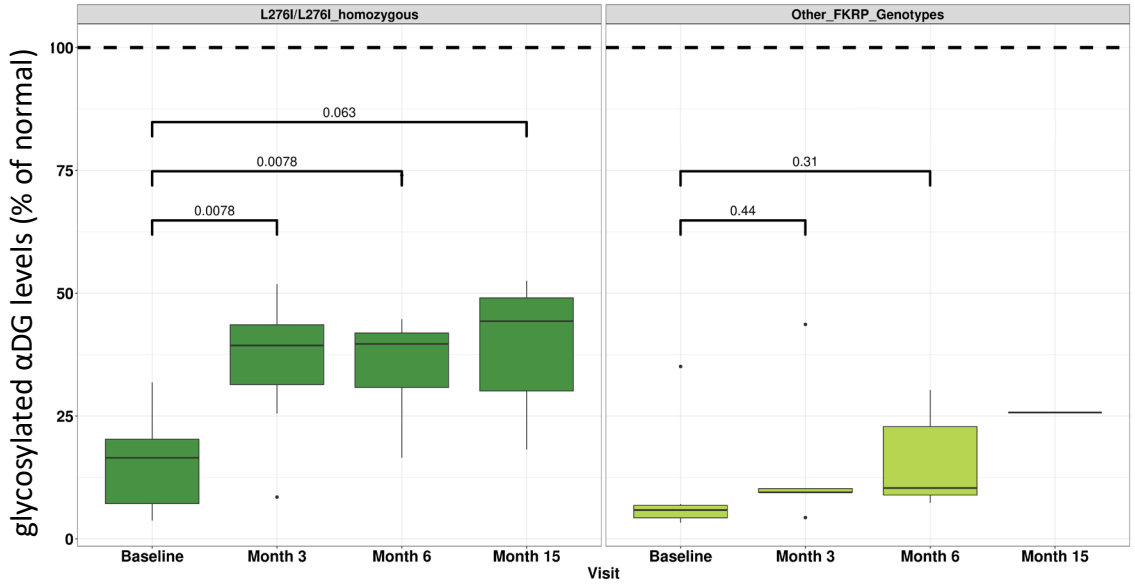
- 136 adverse events (AEs) were recorded in the study with 14 possibly or probably related to BBP-418 treatment
- 14 possibly/probably related AEs include: diarrhea, dehydration, nausea, vomiting, dyspepsia, gastroenteritis, and headaches
- No discontinuations or interruptions in therapy
- 3 severe adverse event recorded unrelated to the treatment

TEAE	# of incidents	Severity
Diarrhea*	6	25% Grade 2, 75% Grade 1
Dehydration	1	100% Grade 1
Nausea	2	100% Grade 1
Vomiting	2	100% Grade 1
Dyspepsia	1	100% Grade 1
Gastroenteritis	1	100% Grade 2
Headaches	1	100% Grade 2
Overall	**14**	

*includes diarrhea and diarrhea intermittent

BBP-418 demonstrated sustained increases in levels of glycosylated αDG and sustained decreases in CK over time

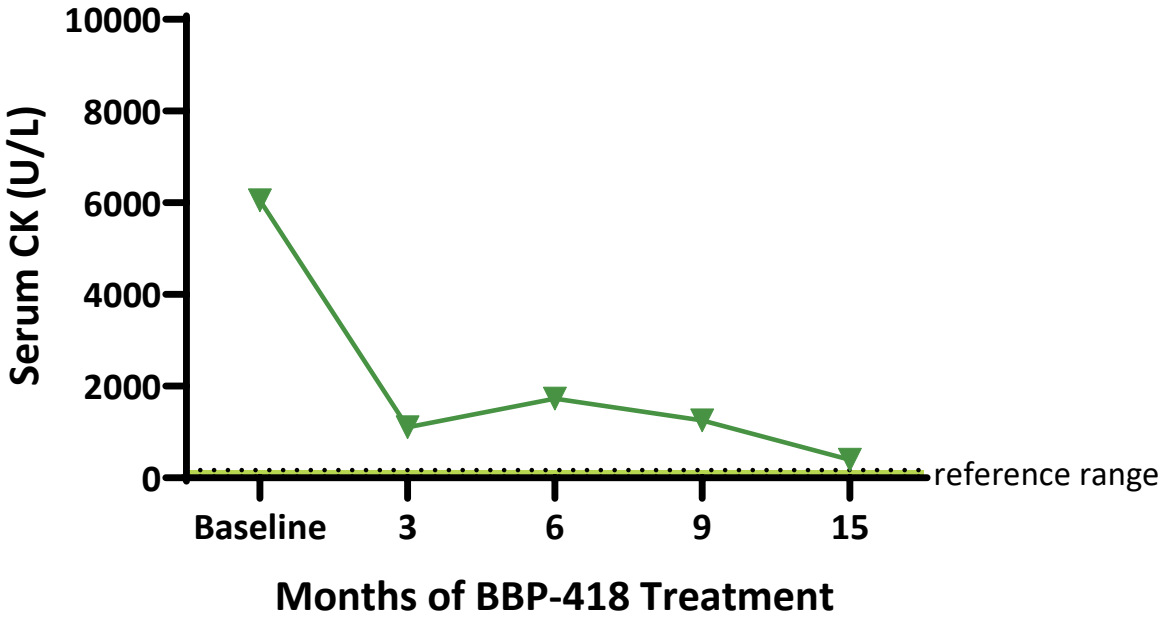
Change in glycosylated αDG post treatment (median ± 95% CI)



	L276I/L276I_homozygous				Other_FKRP_Genotypes			
Median (%)	16.5	39.4	39.7	44.3	5.9	9.5	10.4	25.7
N	8	8	8	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, + 15 mo = Part 3, Month 9
Median and 10–90% percentile are shown
Wilcoxon test was used to determine significance

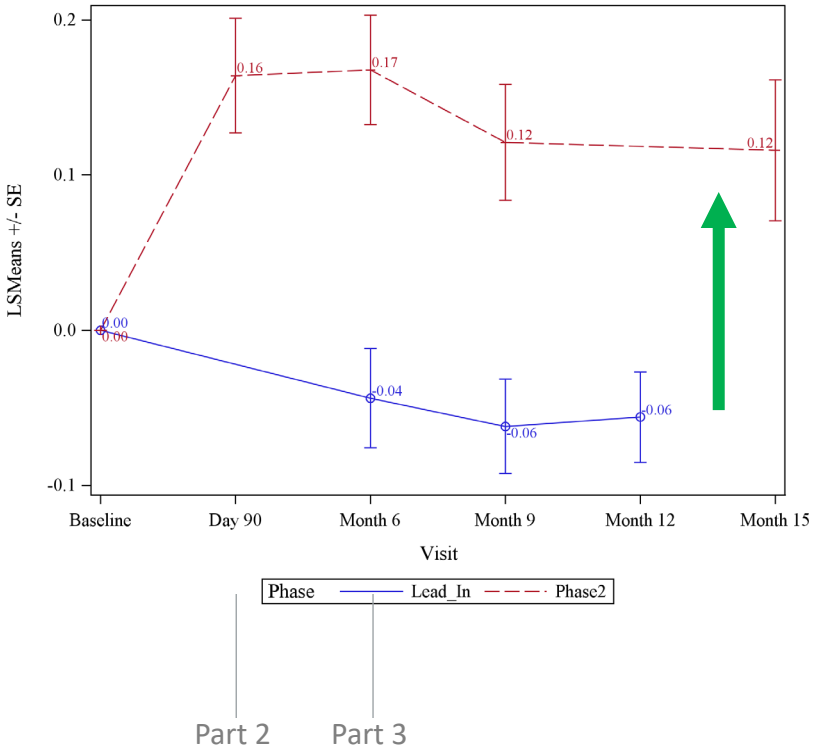
Mean Serum Creatine Kinase (CK)



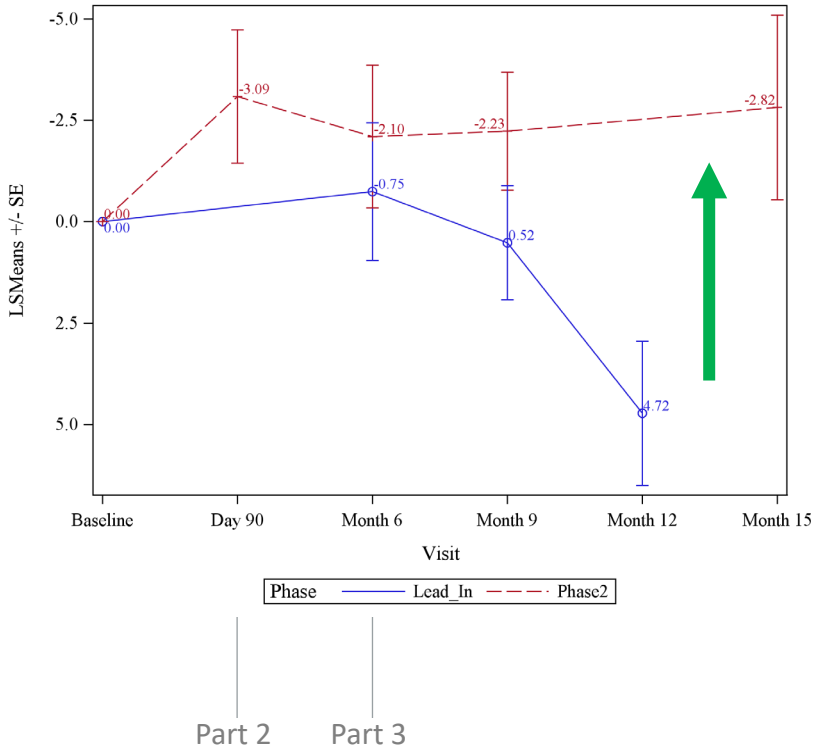
Cohort 1 Day 1 CK draws taken after functional assessments; all other draws done prior to functional assessment
After Day 90, all subjects received 12 g BID (weight-adjusted)
+ 3 mo = Part 1, 90-day, +6 mo = Part 2, Month 3, + 9 mo = Part 3, Month 3, + 15 mo = Part 3, Month 9
Reference range for CK is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

Improvement in ambulatory and clinical measures observed after 15 months of treatment with BBP-418

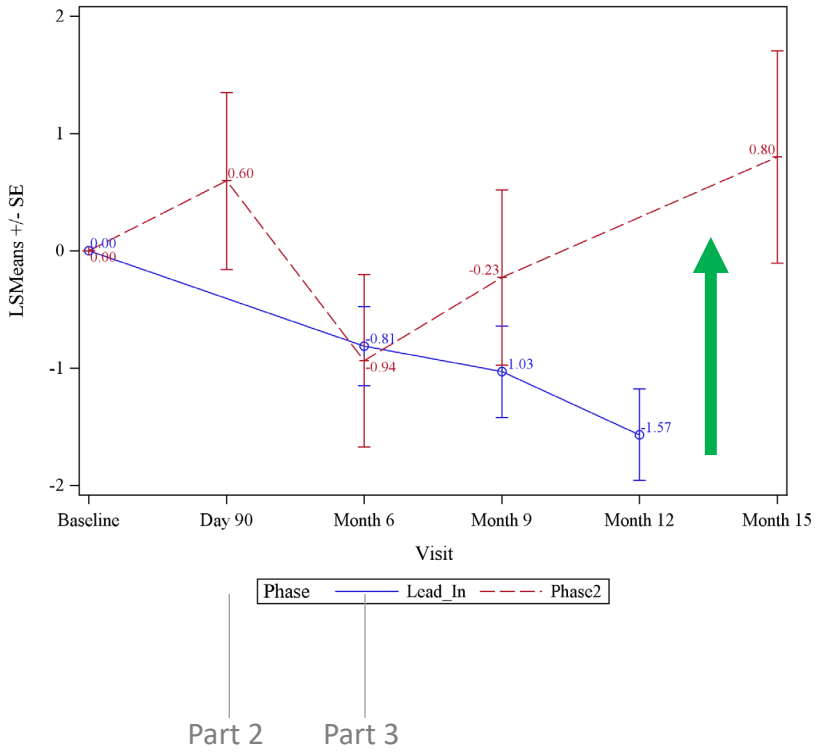
Change from baseline in 10MWT (m/s)



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. **Green arrows** indicate direction of improvement.

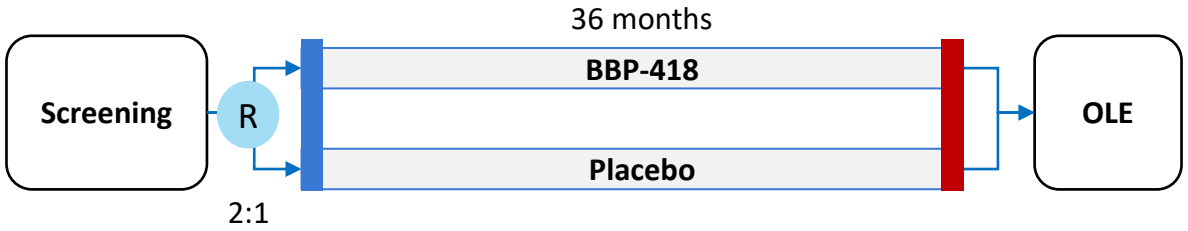
Data exclude 1 subject from month 15 timepoint due to post-COVID decline
Phase 2 data: 6 months = Part 2, Month 3, 9 months = Part 3, Month 3, 15 months = Part 3, Month 9

ML Bio Solutions is initiating a Phase 3 study of BBP-418 in LGMD2I

Phase 2 Summary

- Increased glycosylation of αDG was observed following treatment with BBP-418 and sustained over at least 15 months
- A large, sustained reduction in creatine kinase was seen over an extended (up to 15-month) treatment period
- Improvements in NSAD and ambulatory measures were observed over a 15-month treatment period
- No treatment-related SAEs or dose limiting toxicities were observed with BBP-418

A Phase 3 Randomized, Placebo-controlled, Double-blind Study to Evaluate the Efficacy and Safety of BBP-418 in LGMD2I



- ~80-100 patients, US/EMA/ROW
- **Key Enrollment Criteria:**
  - Genetically confirmed, symptomatic LGMD2I/R9
  - 12 to 60 years of age
- **Endpoints:**
  - NSAD
  - 100-meter timed test (s)
  - 10-meter walk test (m/s)
  - pulmonary function (FVC)
  - PUL 2.0
  - glycosylated αDG
  - serum CK

Thank You!

- Amy Harper, Ruby Langeslay and the team at VCU
- Patients, families and study participants

To learn more, please visit posters #139 and #140