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

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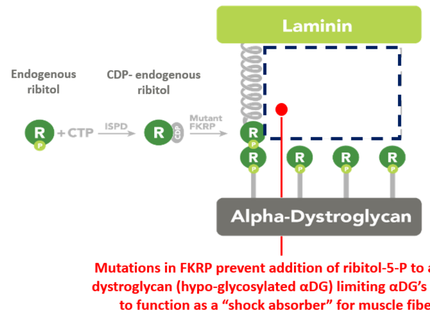
Introduction

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

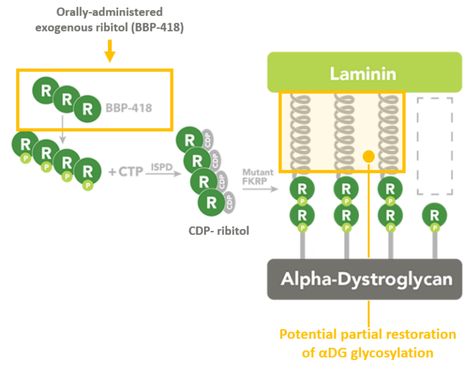
Partial loss of function mutation in FKRP results in dysfunctional, hypo-glycosylated αDG in myocytes which increases susceptibility to damage



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



Study Design

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

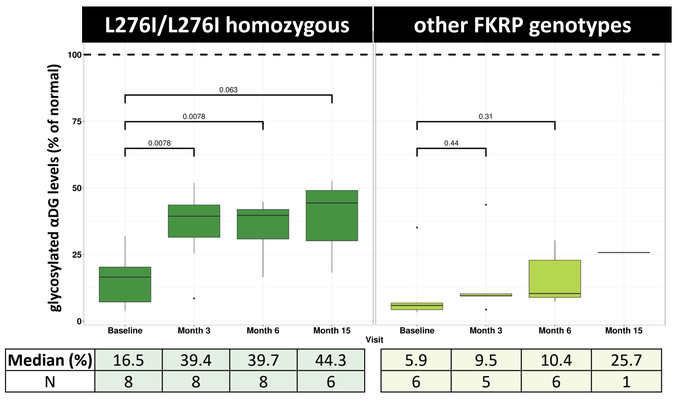
Part 3 Dosing
Dose for patients assigned to Part 3 receiving 12 g BID was adjusted as follows:
- Patient weight is >50 kg: 12 g BID
- Patient weight is >30 kg - 50 kg: 9 g BID

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)

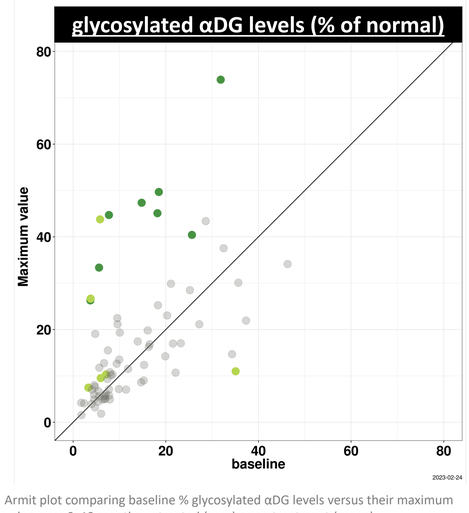
3 months = Part 1, 90-day; 6 months = Part 2, Month 3; 9 months = Part 3, Month 3; 15 months = Part 3, Month 9

Biomarkers: Glycosylated αDG



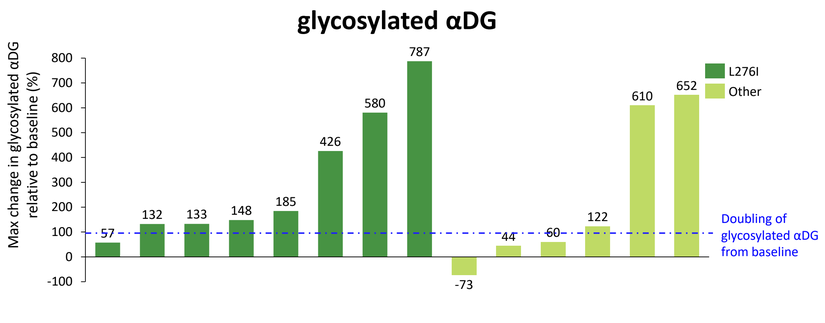
	L276I/L276I homozygous				other FKRP genotypes			
Median (%)	16.5	39.4	39.7	44.3	5.9	9.5	10.4	25.7
N	8	8	8	6	6	5	6	1

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



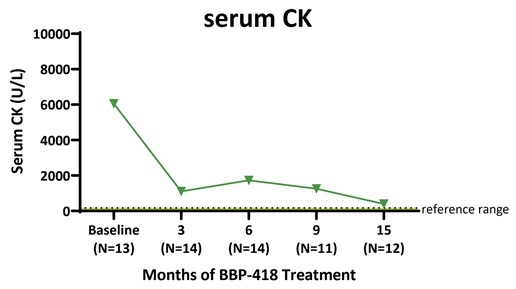
Armit plot comparing baseline % glycosylated αDG levels versus their maximum value over 6–12 months untreated (grey) or on treatment (green)
For natural history samples, visit 2 data are shown; For Phase 2 samples, maximum value is shown

- Glycosylated αDG levels approximately double with BBP-418 treatment vs. baseline values
- Increases in glycosylated αDG on treatment are markedly different from natural history study in which glycosylated αDG levels are stable over time



- 13 of 14 patients show an increase in glycosylated αDG levels with BBP-418 treatment vs. pre-treatment baseline levels
- 10 of 14 patients have ≥100% increase, or a doubling, in glycosylated αDG levels relative to their pre-treatment levels

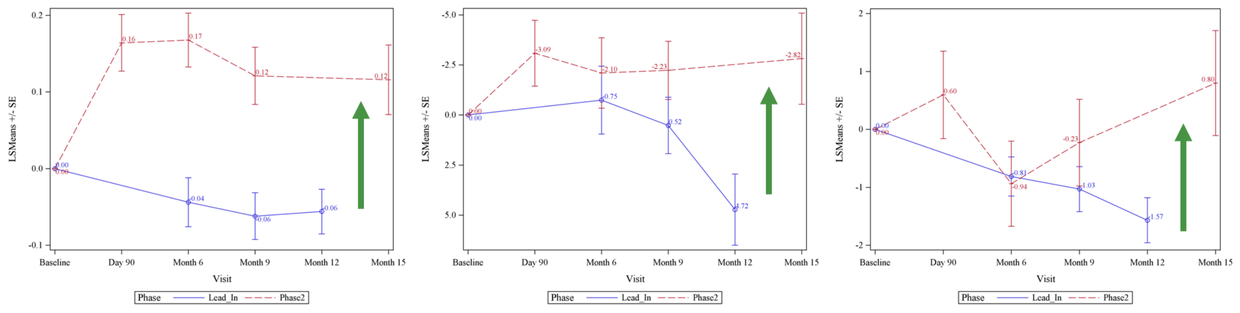
Biomarkers: Serum CK



- Sustained reduction in serum CK of >75% was observed over 15 months of treatment

Ambulatory & Clinical Measures

Change from baseline 10MWT (m/s) **Change from baseline 100MTT (s)** **Change from baseline 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
6 months = Part 2, Month 3; 9 months = Part 3, Month 3; 15 months = Part 3, Month 9

Safety

- 14 out of 136 adverse events (AEs) were recorded as 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 events due to underlying disease were recorded; all were deemed 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

Conclusions

- BBP-418 supplementation therapy provides supraphysiological levels of ribitol upstream of the mutant FKRP enzyme to drive residual activity of the enzyme and increase levels of glycosylated αDG.
- Preliminary results of BBP-418 treatment showed increased levels of glycosylated αDG at 3 months in a Phase 2 study, which was sustained over time (15 months).
  - Approximate doubling of glycosylated αDG was observed in both L276I/ L276I homozygous and other FKRP genotype LGMD2I patients.
- Consistent with the changes in glycosylated αDG observed, a sustained reduction in serum CK of >75% was observed over 15 months of treatment.
- An improvement in NSAD and ambulatory measures was observed with 15 months of BBP-418 treatment.
- BBP-418 was well tolerated with only minor GI adverse events.
- Based on the encouraging data from a Phase 2 study (MLB-01-003), a global, double-blind placebo-controlled Phase 3 study is planned.

Disclosures

- BBP-418 is an investigational drug; BBP-418 has not yet been evaluated or approved to treat LGMD2I or any other disease or condition by any regulatory health authority.
- Presenters are employees of ML Bio Solutions, Inc. and BridgeBio Pharma, Inc.
- References made to a Phase 2 clinical trial (ClinicalTrials.gov Identifier: NCT04800874) refer to a trial that is currently ongoing and all results are preliminary and subject to change.