Preliminary results from MLB-01-003: an open label phase 2 study of BBP-418 in patients with Limb-girdle muscular dystrophy type 2I

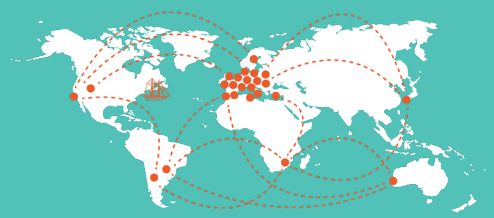
Douglas Sproule, MD – ML Bio Solutions, a Bridge Bio Company

WMS2022 Congress
11th-15th October 2022

WMS
World Muscle Society

Disclosure

- 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, 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

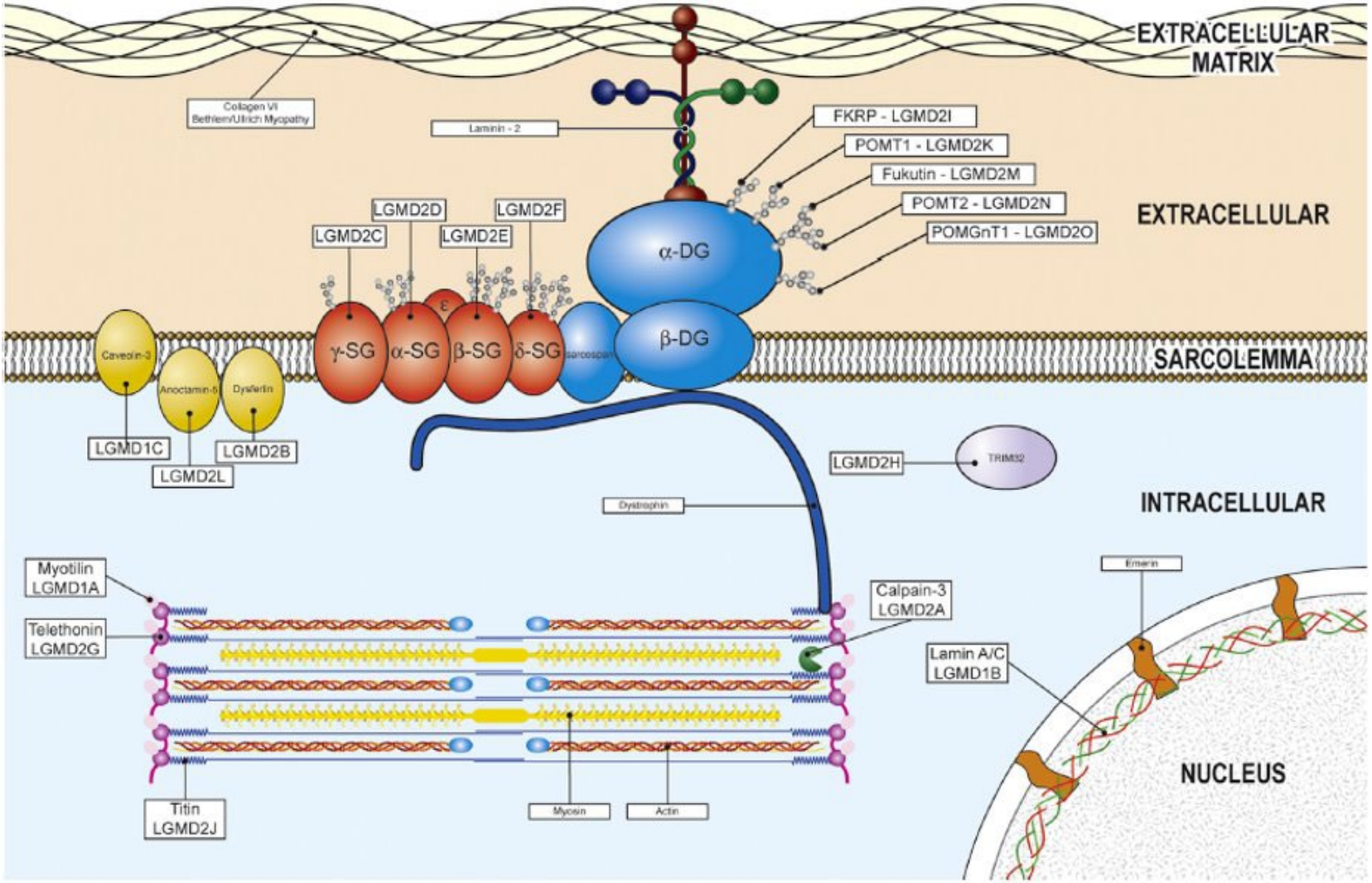


Figure from Wicklund et al., The limb-girdle muscular dystrophies. Neurologic Clinics, 2014.

Fukutin-Related Protein (FKRP) plays a critical role in priming αDG for additional glycosylation

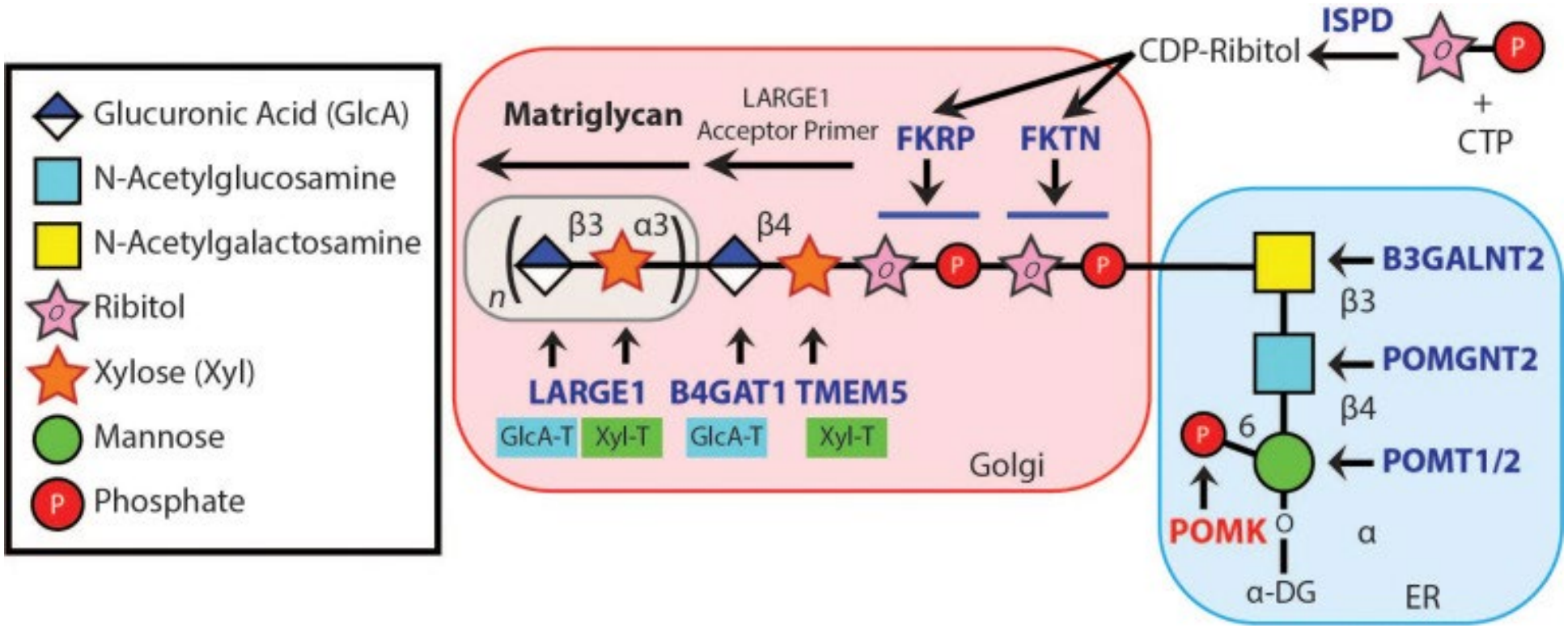


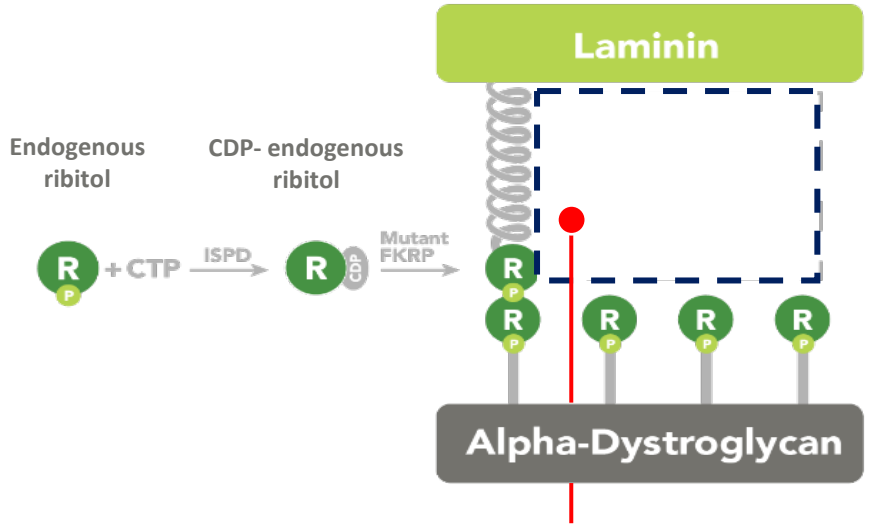
Figure from Walimbe et al., POMK regulates dystroglycan function via LARGE1-mediated elongation of matriglycan. eLife, 2020.

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

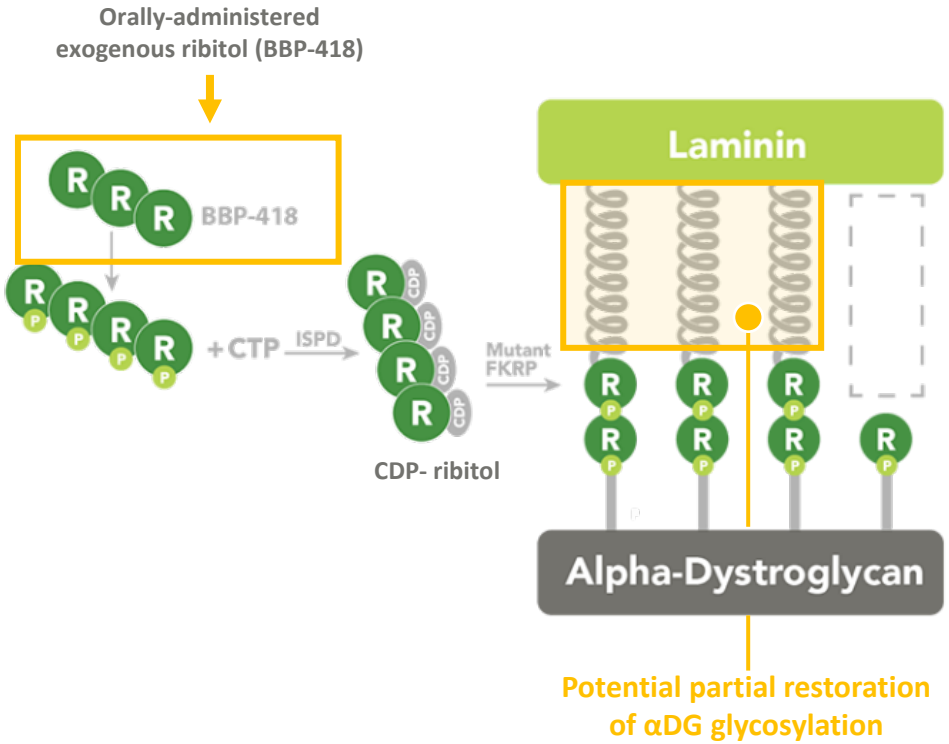
Partial loss of function mutation in FKRP results in dysfunctional, hypo-glycosylated αDG in myocytes which increases susceptibility to damage



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

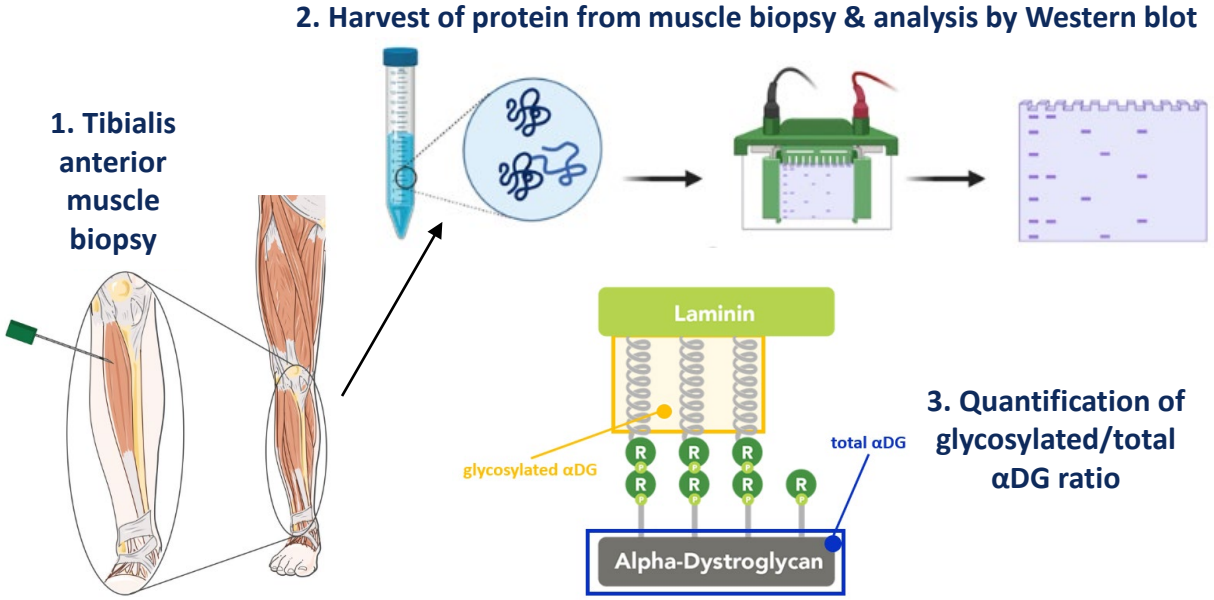
Supply supraphysiological levels of ribitol upstream to drive residual activity of mutant FKRP enzyme and increase αDG glycosylation levels



LGMD2i is caused by hypo-glycosylation of αDG due to reduced FKRP enzyme activity; we have developed a novel assay to measure glycosylated & total αDG

Overview of αDG assay

What is the assay?
The assay measures protein levels of glycosylated αDG and total αDG from tibialis anterior muscle biopsy samples



How is the assay relevant in LGMD2i disease?
Given hypo-glycosylation of αDG is established as the root cause of LGMD2i, measurement of αDG glycosylation is a novel tool to show resolution of the disease at its source

αDG assay Proof of Concept Overview

1. Mouse models of LGMD2i have reduced glycosylation of αDG compared to WT animals; glycosylation follows the severity of disease in mice, mice with a more severe mutation have reduced glycosylation compared to animals with a less severe mutation

2. LGMD2i patients have a reduced ratio of glycosylated αDG to total αDG compared to healthy individuals

3. More severely affected compound pathogenic heterozygote LGMD2i patients have reduced glycosylation of αDG vs. individuals who are homozygous with the common mutation L276I / L276I

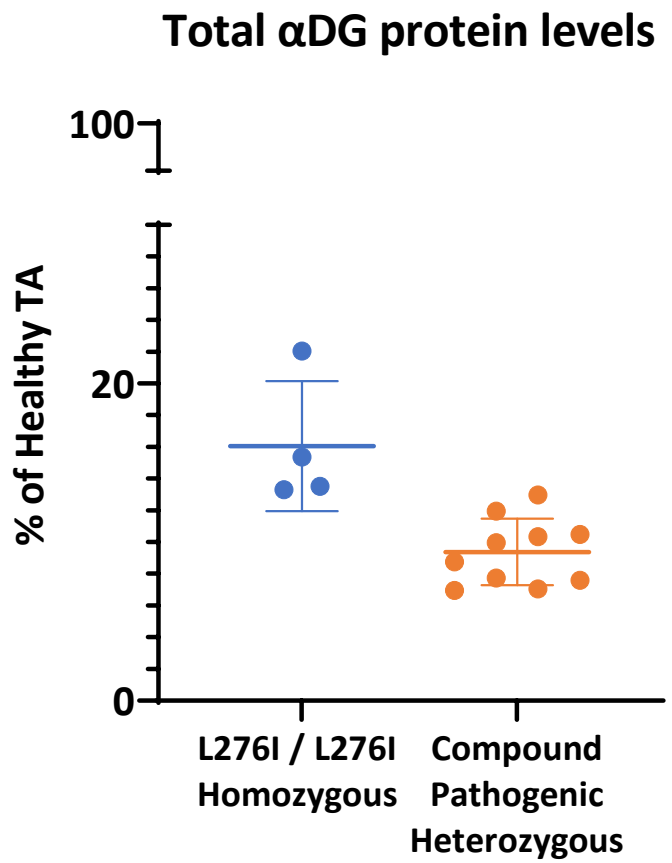
4. Treatment of LGMD2i patients with BBP-418 improved the ratio of glycosylated αDG / total αDG after 90 days of treatment

For more details on the αDG assay, please see WMS poster #171

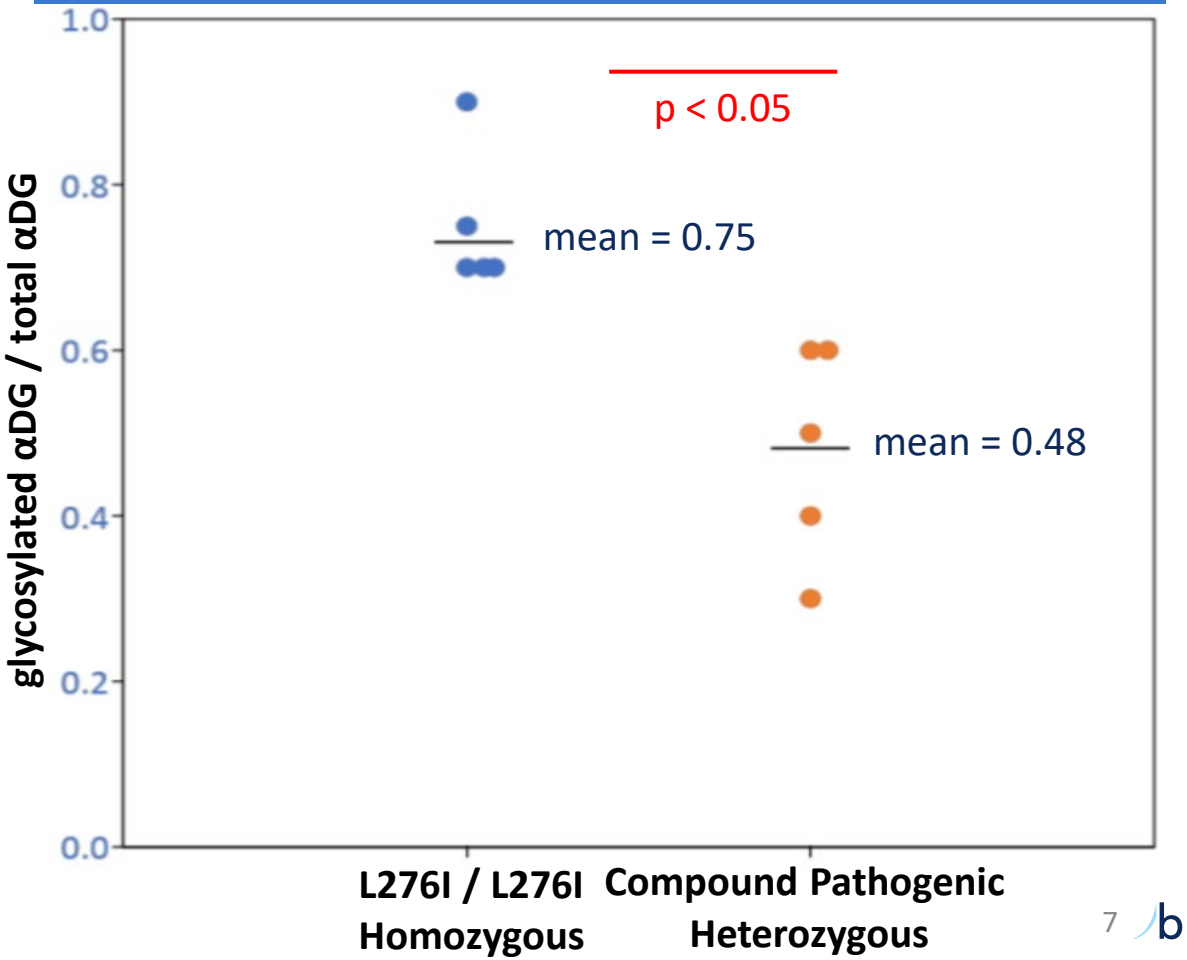
Glycosylation of αDG mirrors the severity of LGMD2i disease

Compound pathogenic heterozygotes show reduced glycosylation compared to L276I (“common”) homozygotes. Both groups are reduced compared with healthy individuals: homozygotes have 12% and compound pathogenic heterozygotes have 5% of healthy.

Reduced total αDG in LGMD2i vs. healthy individuals

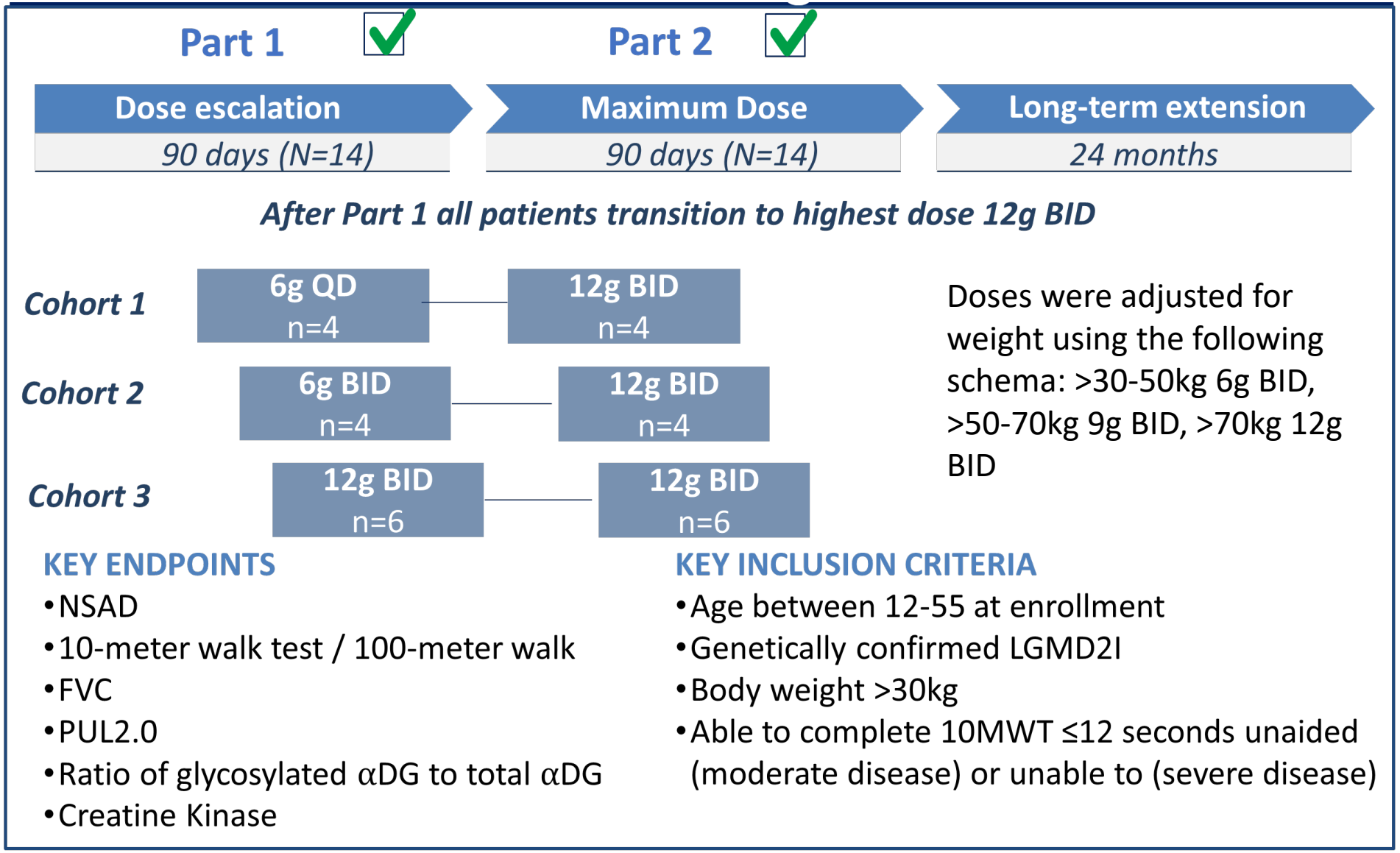


Reduced αDG glycosylation in LGMD2i



*αDG data represent preliminary results from the Phase 2 study (MLB-01-003)

BBP-418 is being investigated in an open label Phase 2 Study (MLB-01-003)



Doses were adjusted for weight using the following schema: >30-50kg 6g BID, >50-70kg 9g BID, >70kg 12g BID

KEY ENDPOINTS

- NSAD
- 10-meter walk test / 100-meter walk
- FVC
- PUL2.0
- Ratio of glycosylated αDG to total αDG
- Creatine Kinase

KEY INCLUSION CRITERIA

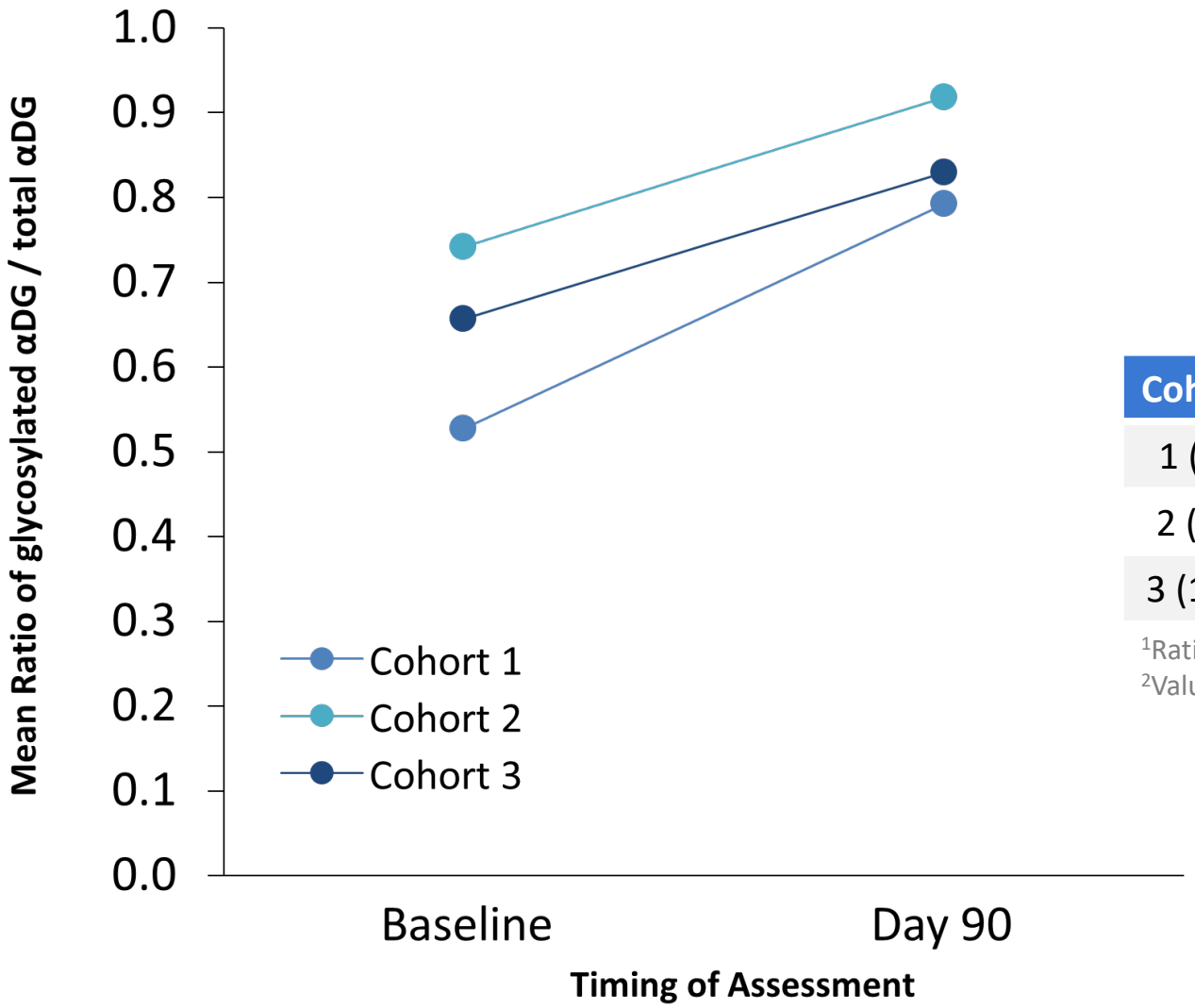
- Age between 12-55 at enrollment
- Genetically confirmed LGMD2I
- Body weight >30kg
- Able to complete 10MWT ≤12 seconds unaided (moderate disease) or unable to (severe disease)

MLB-01-003 Subject Demographic and Baseline Characteristics

	Cohort 1 (N=4)	Cohort 2 (N=4)	Cohort 3 (N=6)	Overall (N=14)
Age Group at Enrollment				
12 – ≤18 years	2	2	2	6
>18 – 30 years	0	1	0	1
>30 years	2	1	4	7
Sex				
Male	2	1	1	4
Female	2	3	5	10
Genotype				
Homozygotes	3	2	3	8
Heterozygotes	1	2	3	6
Ambulatory Status at Baseline*				
Ambulatory	3	3	5	11
Non-Ambulatory	1	1	1	3
Time Since LGMD Diagnosis				
Mean (years)	2.8	6.7	9.9	7.0

**ambulatory defined as able to complete the 10-meter walk test in ≤ 12 seconds unaided*

Data to date suggest that BBP-418 improves the ratio of glycosylated αDG / total αDG after 90 days of treatment

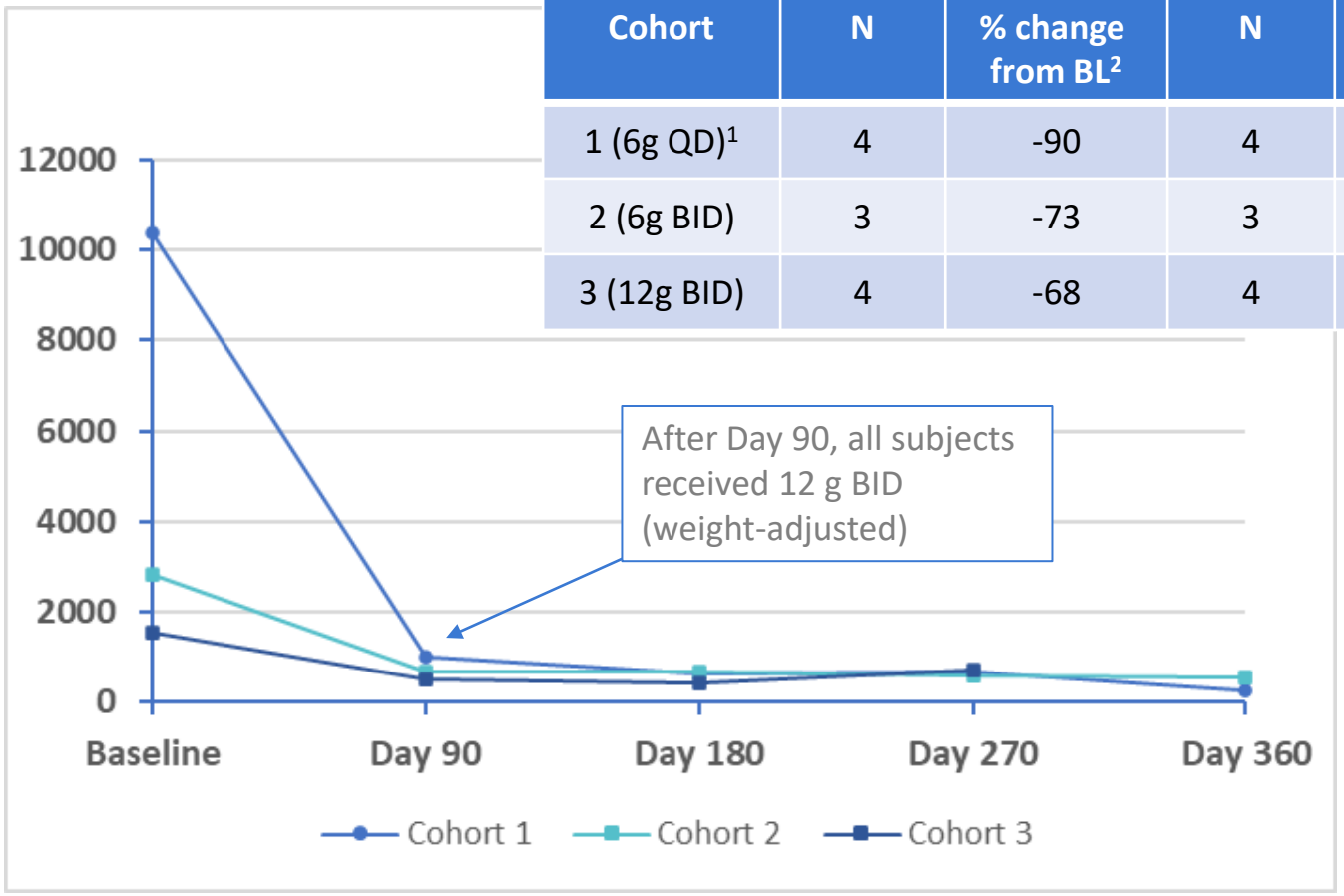


Cohort	N	Average αDG change from baseline (day 90)[1]
1 (6g QD)	4	0.28
2 (6g BID)	2[2]	0.18
3 (12g BID)	4	0.17

[1]Ratios are normalized against healthy control samples
[2]Values excluded where signal intensities were below reliable quantification threshold

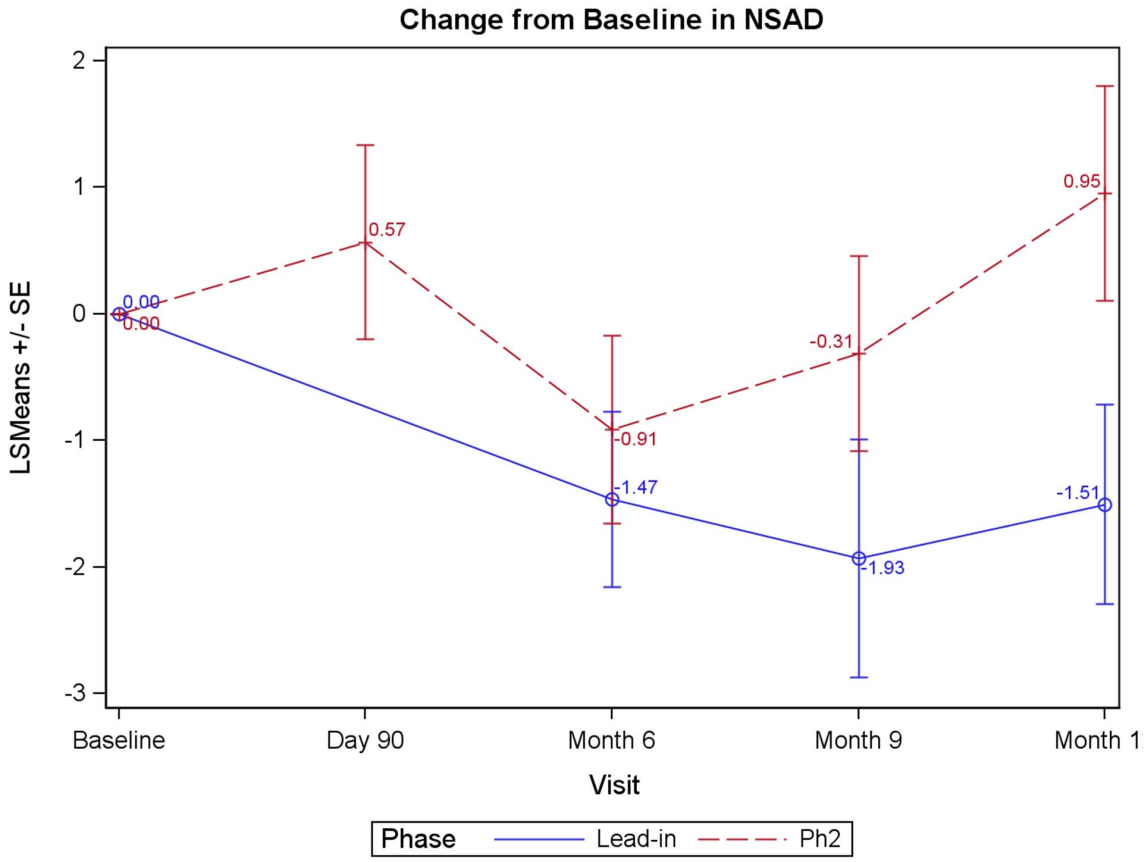
All cohorts show marked declines in creatine kinase, ~77% from baseline at day 90, ~80% at day 180, and ~76% at day 270

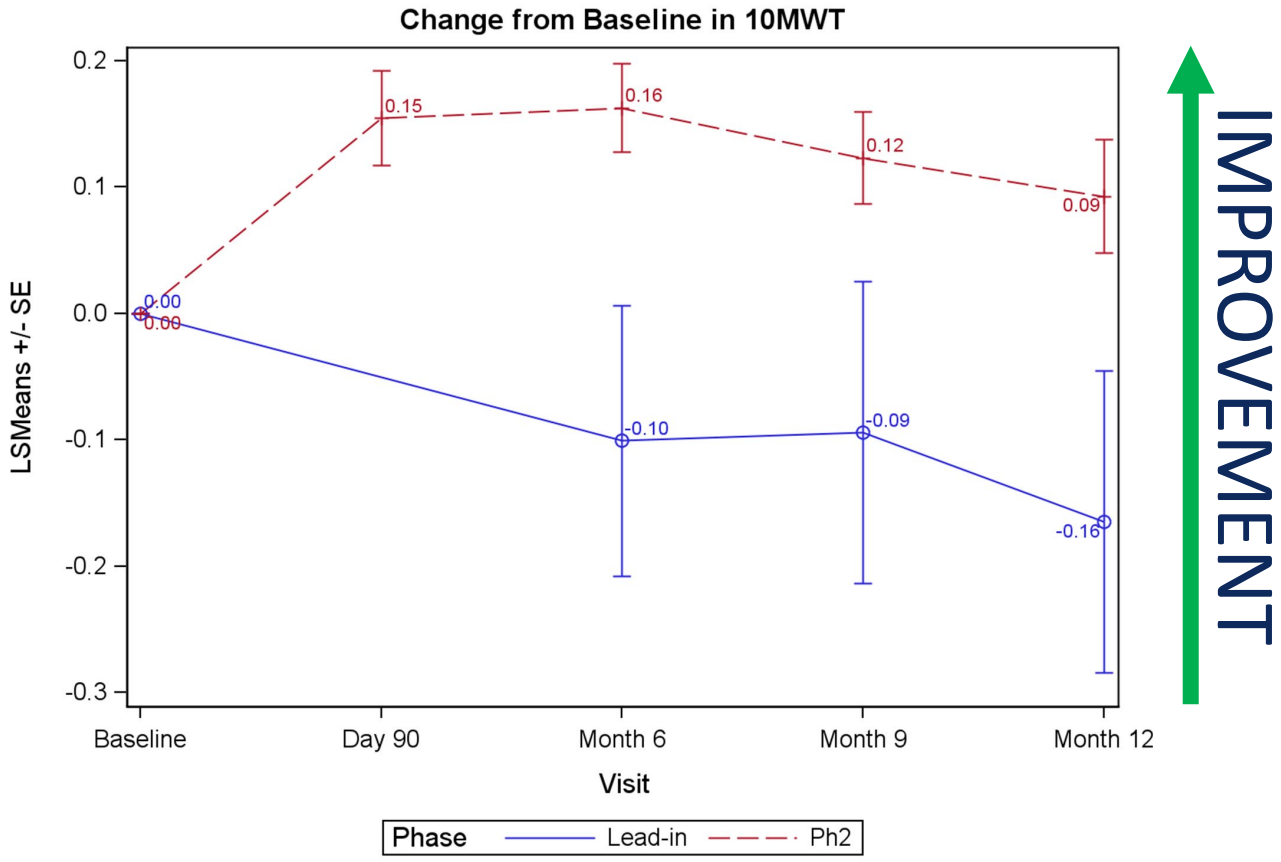
Cohort	N	D90 mean % change from BL[2]	N	D180 mean % change from BL[3]	N	D270 mean % change from BL	N	D360 mean % change from BL
1 (6g QD)[1]	4	-90	4	-94	3	-93	3	-97
2 (6g BID)	3	-73	3	-72	2	-73	3	-77
3 (12g BID)	4	-68	4	-72	3	-62	*data pending*	



[1]Cohort 1 Day 1 CK draws taken after functional assessments; all other draws done prior to functional assessment
[2]CK change from baseline as part 1 day 90 is statistically significant with $P < 0.05$
[3]First measurement since dose adjustment for all cohorts to 12g bid following D90
Reference range for CK is 55-170 units/L for men and 30-135 units/L for women

Increases in NSAD & 10MWT velocity observed after 12 months of treatment with BBP-418





Blue lines denote natural history data collected prior to Phase 2 enrollment and **red lines** denote on-treatment data collected during the Phase 2 study from the same patient population

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

- 100 adverse events (AEs) were recorded in the study with 12 possibly or probably related to BBP-418 treatment
- 12 possibly/probably related AEs include: diarrhea, dehydration, nausea, vomiting, dyspepsia, gastroenteritis, and headaches
- No discontinuations or interruptions in therapy
- 1 severe adverse event recorded unrelated to the treatment

TEAE	# of incidents	Severity
Diarrhea	4	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	12	83% Grade 1

BBP-418 was well-tolerated and αDG glycosylation, creatine kinase, NSAD, and 10MWT velocity improvements were observed in Phase 2 study

- Impaired glycosylation of αDG directly leads to the development of muscular dystrophy in LGMD2i patients
- Novel assay developed to measure glycosylated and total αDG; Increased glycosylation of αDG was observed in all cohorts, with an average increase in αDG ratio of +0.21 at day 90
- A large, sustained reduction in creatine kinase (>70%) was seen over an extended (up to 12-month) treatment period
- Improvements in NSAD & 10MWT velocity were observed over a 12-month treatment period
- No treatment-related SAEs or dose limiting toxicities were observed with BBP-418
- Plans for a Phase 3 study of BBP-418 in LGMD2i are in development

Thank You!

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