

# bridgebio

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## BBP-418 (Ribitol)

## Phase 2 Results

Prepared for ICNMD 2022

July 2022



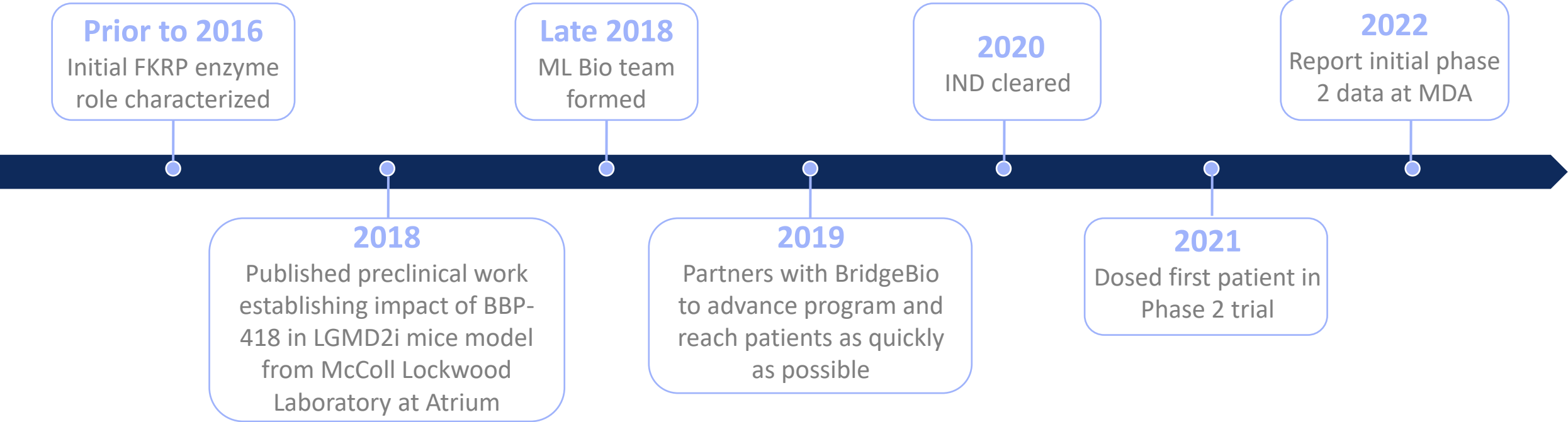
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# BBP-418 program history: From scientific breakthrough to clinical proof-of-concept in less than 3 years



- **BBP-418 rapidly progressed from pre-IND to Phase 2 in less than 3 years**
- **Initial phase 2 data showed improvements on all key endpoints at 90 days and 180 days**



# Limb-girdle muscular dystrophy type 2i (LGMD2i) overview

LGMD2i is an **autosomal recessive disease** caused by a **partial loss of function in the FKR gene**

An estimate of **~7k patients<sup>1</sup>** currently living with LGMD2i in US and EU

BBP-418 (ribitol), **substrate supplementation therapy**, is designed to treat LGMD2i at its source

**No approved disease modifying agents currently available** for LGMD2i patients

**BBP-418 is the only investigational oral therapy** designed to potentially increase FKR enzymatic activity, in turn leading to increased fully glycosylated  $\alpha$ -DG



Sammi

**Living with LGMD2i**

<sup>1</sup>Includes potential treatable mutations

# LGMD2i a progressive neuromuscular disease with high unmet need

## Disease overview

**7k**

Prevalence (US & EU)<sup>1</sup>

**L276I**

Most common genetic mutation

**Early childhood**

Symptom onset

## Clinical manifestations



**Loss of ambulation:** beginning as early as late teens



**Respiratory decline:** invasive assistance potentially required by early 30s



**Cardiac dysfunction:** up to 25% by age 30

- **No approved disease modifying agents for LGMD2i**
- **Current standard of care is aimed at symptom management and includes physical therapy, steroids and pain management**
- **Standard of care does not prevent continuous progressive decline in LGMD2i patients**

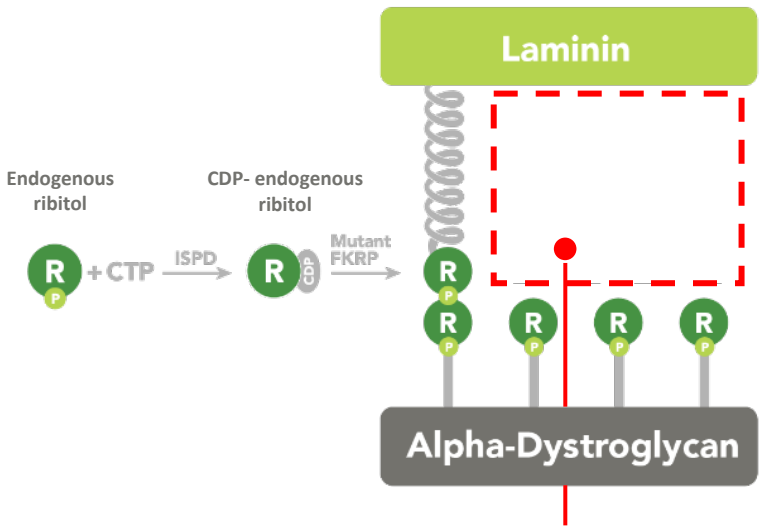
<sup>1</sup>Includes potential treatable mutations

Source: Sveen et al, Annals of Neurology, 2006; Richard et al, Neuromuscular Disorders, 2016; Gedlinske et al, Neurology, 2020.

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

## Disease Mechanism

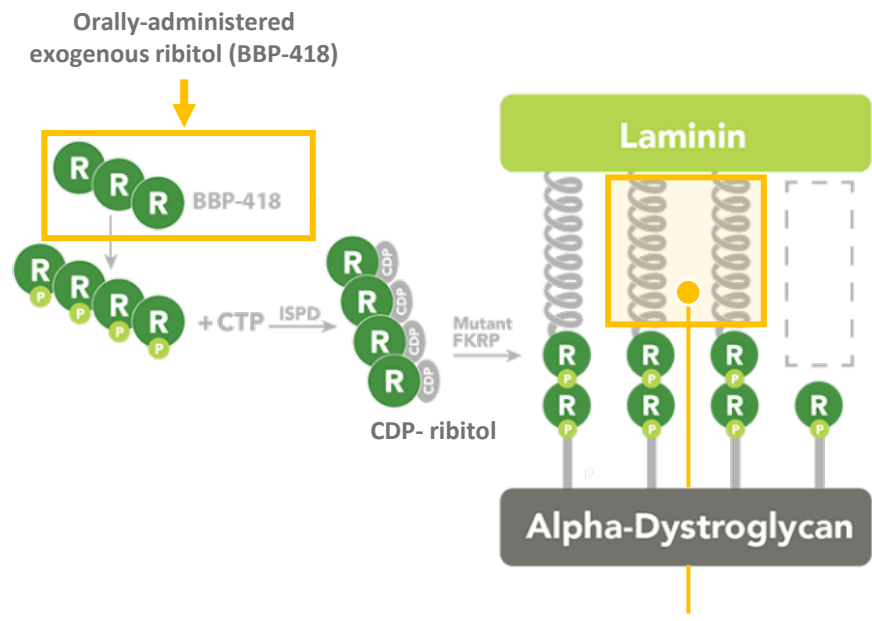
- ✓ Functional FKRP fully glycosylates alpha-dystroglycan ( $\alpha$ -DG) which stabilizes cells by binding extracellular ligands
- ✗ Partial loss of function mutation in FKRP result in dysfunctional, hypo-glycosylated  $\alpha$ -DG in muscle cells which increases cell susceptibility to damage



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

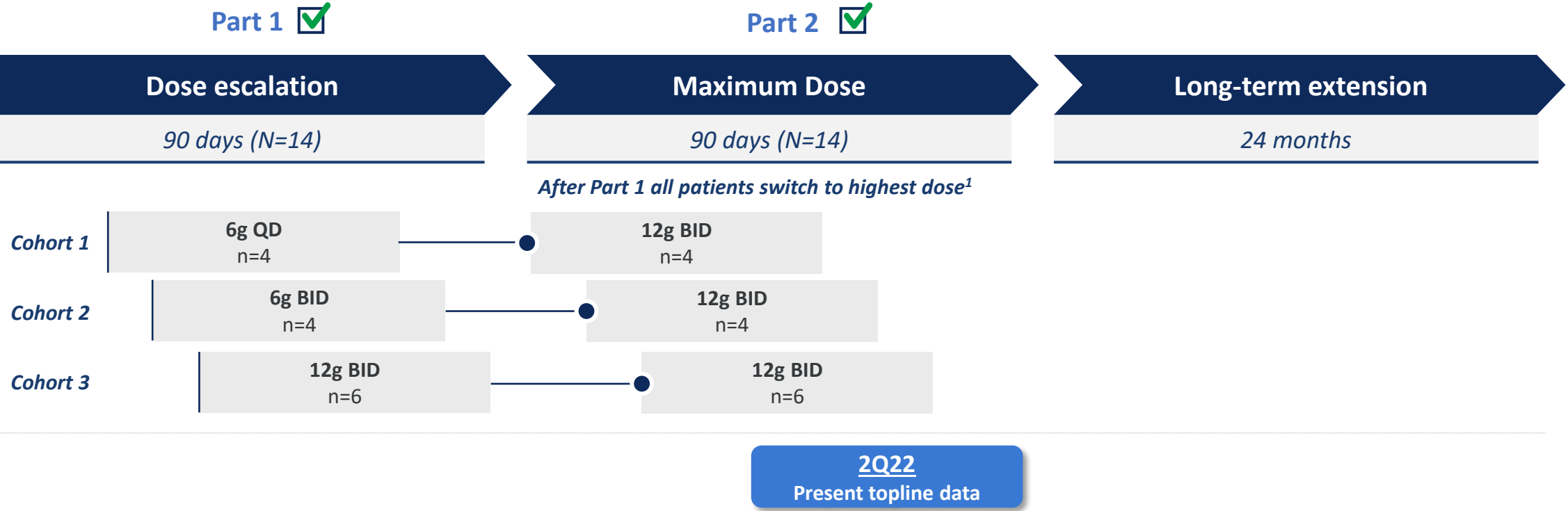
## Potential Therapeutic Approach

- 💡 Supply supraphysiological levels of ribitol upstream to drive residual activity of mutant FKRP enzyme and increase  $\alpha$ -DG glycosylation levels



Potential partial restoration of  $\alpha$ -DG glycosylation

# Full part 1 and partial part 2 data from Phase 2 is available



### Key study objectives:

- Safety and tolerability
- Dose selection for Phase 3
- Key biomarker parameters

### Key endpoints:

- Creatine Kinase
- Ratio of glycosylated  $\alpha$ -DG to total  $\alpha$ -DG
- NSAD
- PUL2.0
- 10MWT
- FVC

Note: Doses were adjusted for weight using the following schema: 0-50 kg 6g BID, >50-70kg 9g BID, >70kg 12g BID. <sup>1</sup>Cohort 3 continues same dose

The MLB-01-003 study is currently ongoing, and the data presented may change as more data become available, as additional analyses are conducted, or as audit and verification procedures are performed on such preliminary data

# BBP-418 (Ribitol) increased glycosylated alpha-dystroglycan, decreased creatine kinase and increased velocity in 10MWT at 90 days

	Ratio of Glycosylated $\alpha$ DG / total $\alpha$ DG	Creatine Kinase (CK)	10 Meter Walk Test (10MWT)
Normal Range	1.0	32 - 267 IU/L	No change
LGMD2i Natural History <sup>2</sup>	0.6 <sup>1</sup>	1000 - 5000 IU/L	0.12 m/sec annual decline
Expected threshold to address phenotype <sup>3, 4</sup>	<u>10% increase</u> from baseline	<u>50% decrease</u> from baseline	<u>Slowing of decline</u> vs. natural history
<b>BBP-418 Phase 2 result</b>	<u>43% increase</u> from baseline	<u>68% decrease</u> from baseline	<u>0.14 m/sec increase</u> from baseline <u>0.24 m/sec increase</u> from natural history

<sup>1</sup>Data on file. <sup>2</sup>Sveen et al, Annals of Neurology, 2006. <sup>3</sup>Cataldi, et al, 2018, Nature Comms. <sup>4</sup>KOL interviews, 2021. Note: Heterozygote average ratio of glycosylated aDG / total aDG



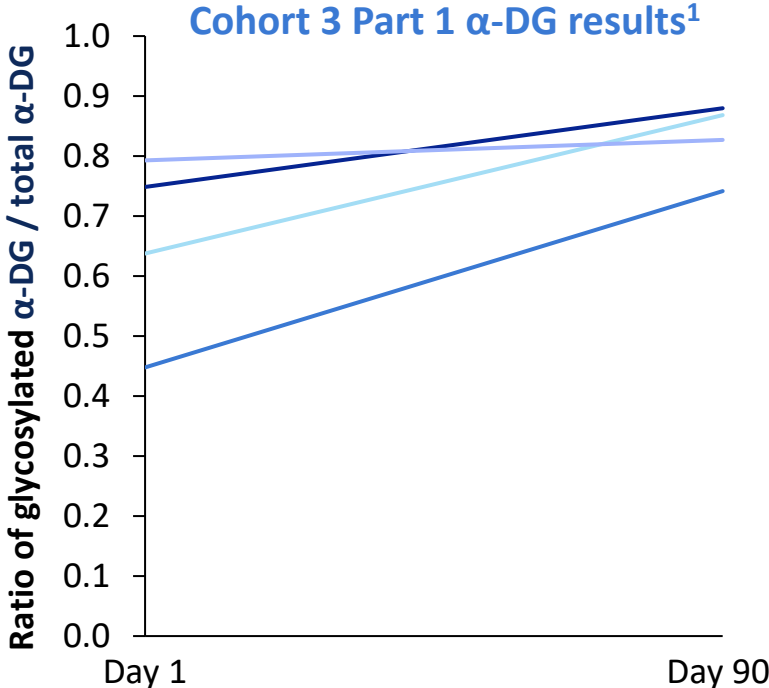
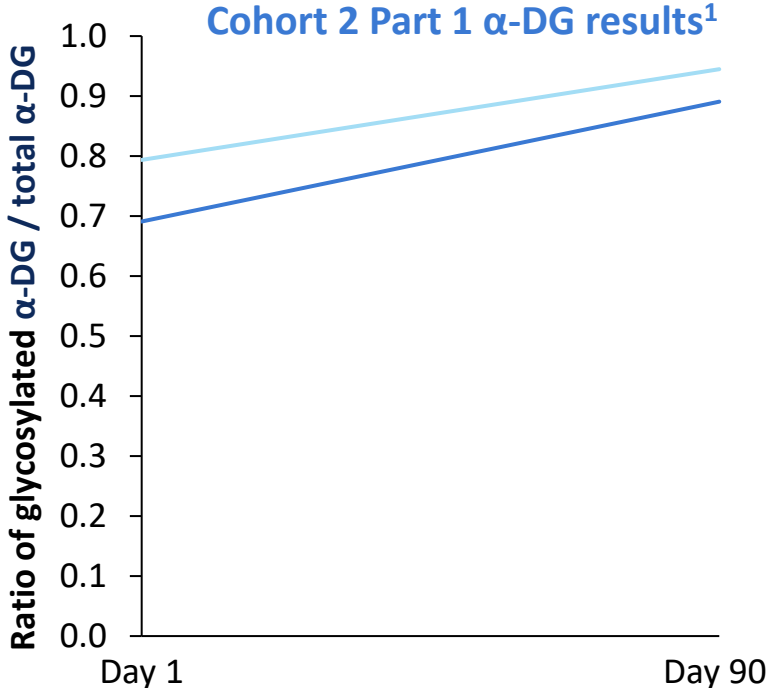
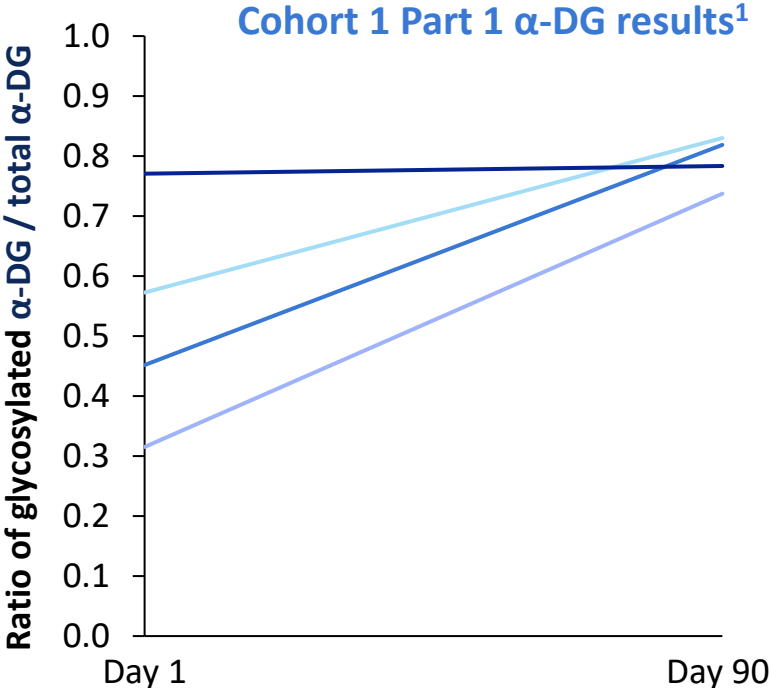
# BBP-418 (Ribitol) exhibits a well-tolerated safety profile to date with only GI related adverse events in Phase 2

- 62 adverse events were recorded with 11 possibly or probably related to treatment (in 7 patients)

TEAE	Number of incidents	Severity
Diarrhea	4	75% Grade 1 , 25% Grade 2
Nausea / Dyspepsia	3	100% Grade 1
Vomiting	2	100% Grade 1
Other	2	50% Grade 1, 50% Grade 2
<b>Overall</b>	<b>11</b>	<b>82% Grade 1</b>

Phase 2 safety data aligns with both preclinical and Phase 1 data suggesting strong safety and tolerability

# Glycosylated $\alpha$ -DG / total $\alpha$ -DG ratio increased across all study cohorts following 90 days of treatment with BBP-418

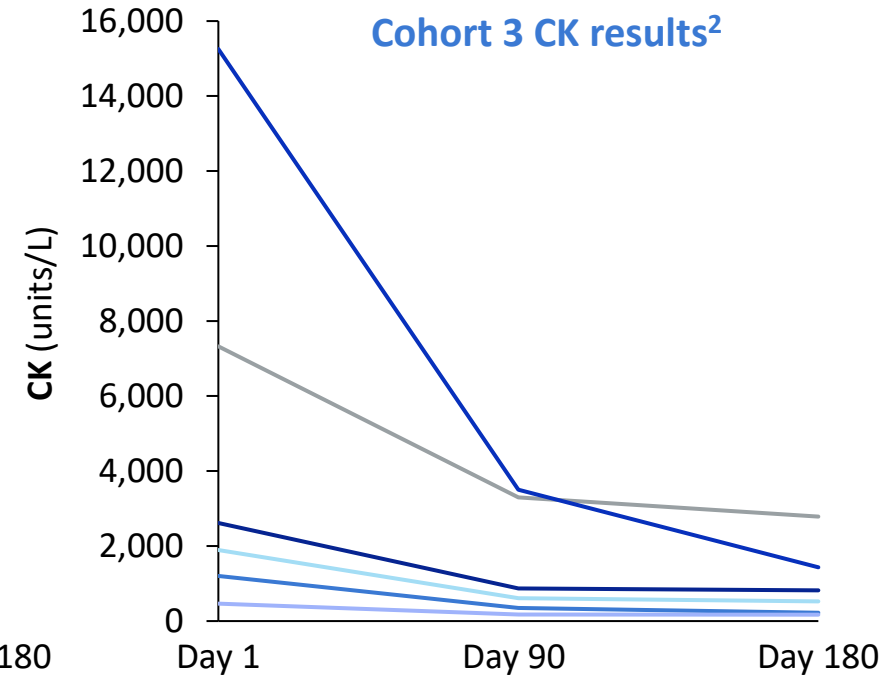
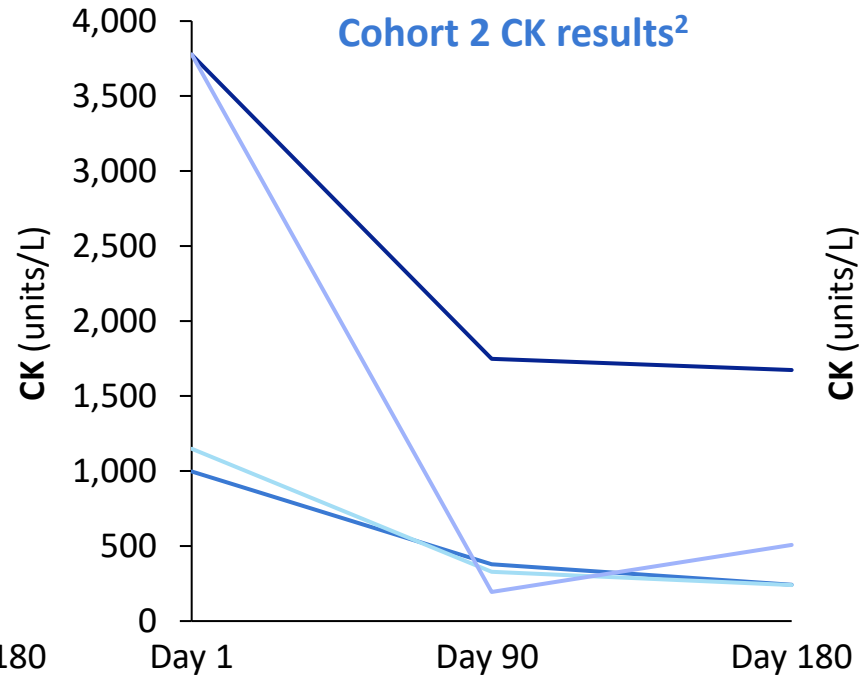
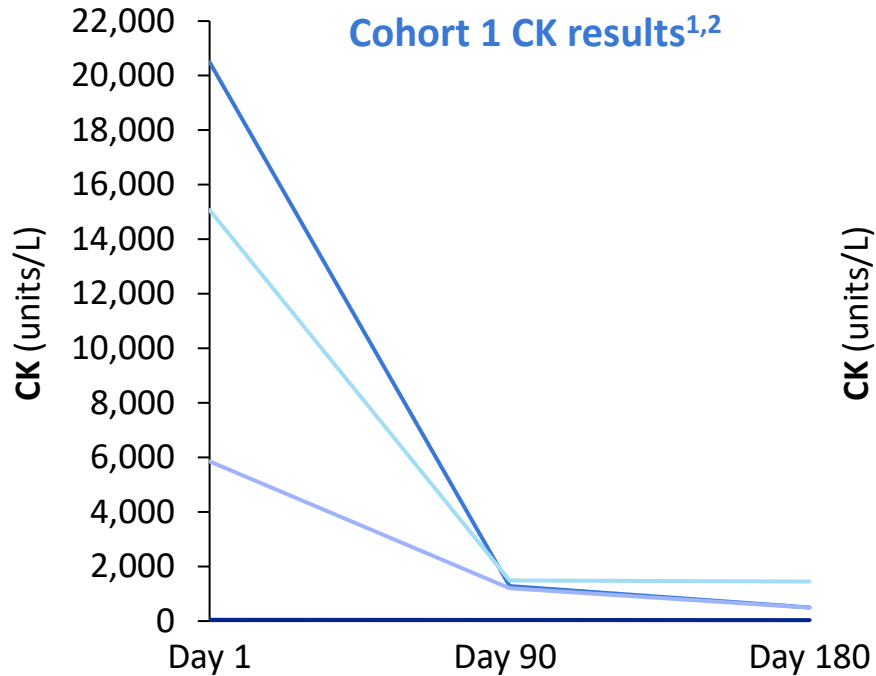


Cohort	# pt	Baseline $\alpha$ DG ratio	Absolute change $\alpha$ DG ratio at day 90 (%)
1 (6g QD)	n=4	0.53	+0.28 (65%)
2 (6g BID)	n=2 <sup>2</sup>	0.74	+0.18 (24%)
3 (12g BID)	n=4	0.66	+0.17 (31%)
<b>Total</b>	<b>N=10</b>	<b>0.62</b>	<b>+0.21 (43%)</b>

<sup>1</sup>Ratios are normalized against healthy control samples; normalization technique under development and subject to change

<sup>2</sup>Values excluded where signal intensities were below reliable quantification threshold

# All cohorts show declines in creatine kinase, ~68% from baseline at day 90 and ~75% at day 180



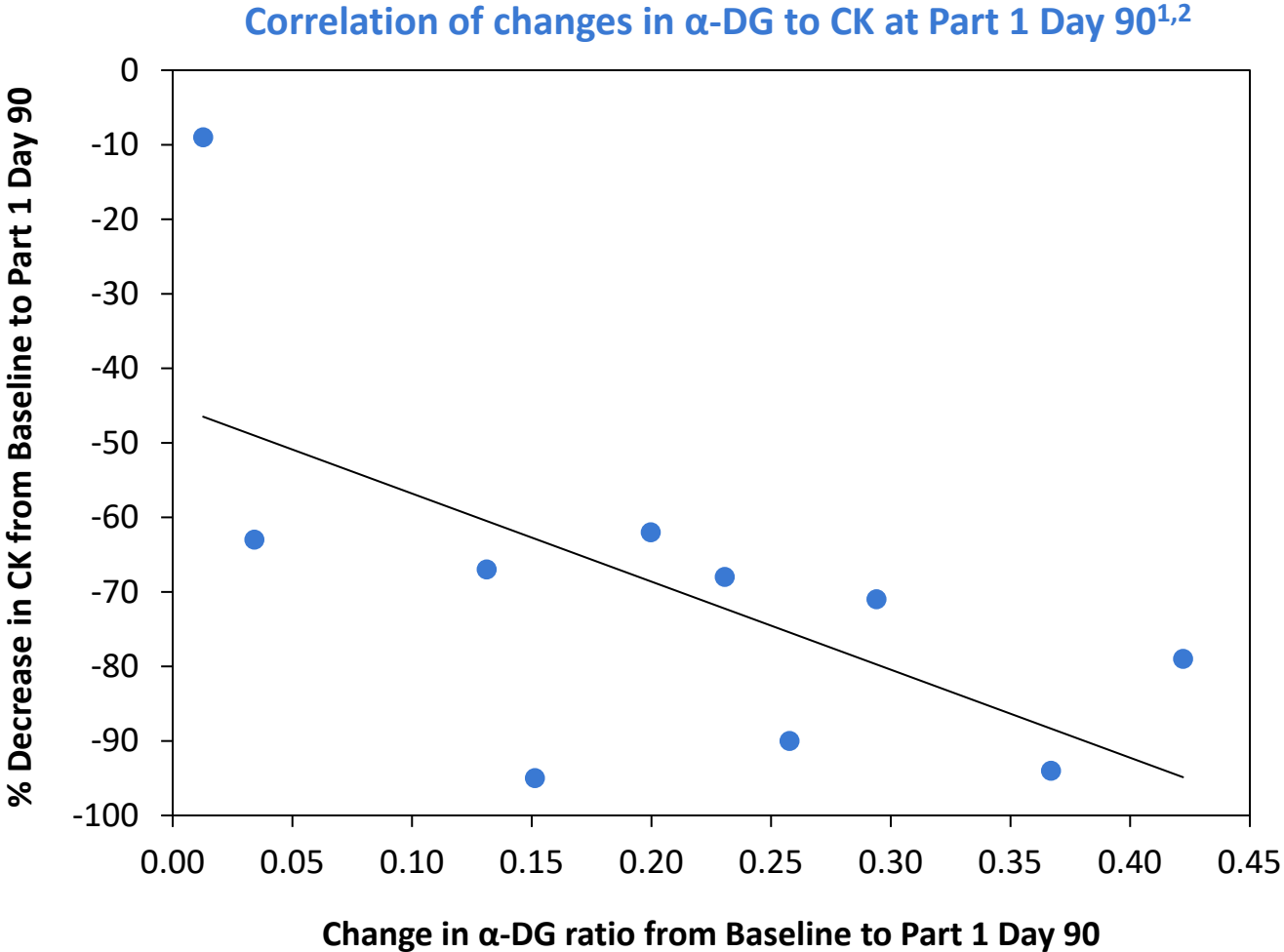
Cohort	# pts	Baseline CK Day 1	Average % change part 1 day 90	Average % change part 2 day 90
1 (6g QD)	N=4	10,364 <sup>1</sup>	-68%	-77%
2 (6g BID)	N=4	2,425	-71%	-74%
3 (12g BID)	N=6	4,791	-67%	-73%
<b>Total</b>	<b>N=14</b>	<b>5,707</b>	<b>-68%</b>	<b>-75%</b>

<sup>1</sup>Cohort 1 Day 1 CK draws taken after functional assessments; all other draws done prior to functional assessment. Comparing cohort 1 lead-in CK values to baseline Ph2 values suggests little impact of function assessments on CK. Note differences in scale.

<sup>2</sup>Reference range for CK is 55-170 units/L for men and 30-135 units/L for women

<sup>3</sup>CK change from baseline at part 1 day 90 is statistically significant with P < 0.05

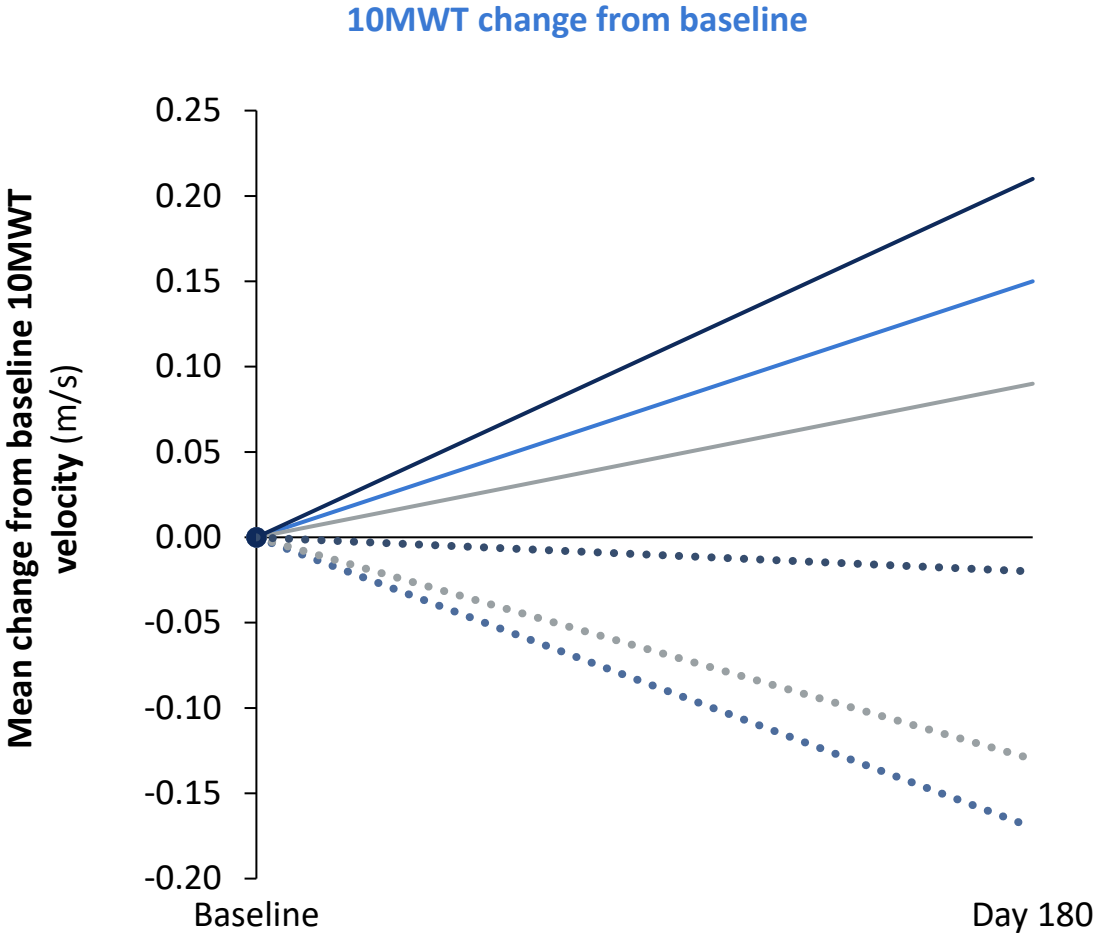
# Increases in $\alpha$ -DG glycosylation are correlated to decreases in CK observed over 90 days



<sup>1</sup>Ratios are normalized against healthy control samples; normalization technique under development and subject to change

<sup>2</sup>Values excluded where signal intensities were below reliable quantification threshold

# Increases were observed in the 10MWT in comparison to consistent declines noted in natural history



Natural history declines from baseline were measured from the MLB-01-001 Lead-in Natural history study for the same group of patients over six months and compared to velocities after 90 and 180 days of treatment

- Cohort 1
- Nat Hx 1
- Cohort 2
- Nat Hx 2
- Cohort 3
- Nat Hx 3

Cohort	# pts	Baseline	Part 2 Day 180
		Average 10MWT Velocity (m/sec) (Change from baseline)	
1 (6g QD)	N=3 <sup>1</sup>	2.72	2.87 (+0.15)
2 (6g BID)	N=4	1.48	1.57 (+0.09)
3 (12g BID)	N=5 <sup>1</sup>	1.68	1.89 (+0.21)
<b>Total</b>	<b>N=10</b>	<b>1.88</b>	<b>2.03 (+0.15)</b>

<sup>1</sup>Includes ambulatory patients only defined by the ability to complete the 10MWT ≤12 seconds



# Summary reported Phase 2 data and next steps

## Summary of BBP-418 development program

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- ✓ Phase 2 part 1 and part 2 data demonstrating a 43% increase in ratio of glycosylated  $\alpha$ -DG / total  $\alpha$ -DG and 68% reduction in creatine kinase from baseline at day 90 and 75% reduction at day 180
- ✓ Improvements in functional benefit observed at 90 days vs. natural history
- ✓ BBP-418 was well-tolerated across a wide range of dose levels with no treatment-related serious adverse events, dose limiting toxicities or discontinuations
- ✓ Granted Fast Track Designation (FTD) by FDA and Orphan Drug Designation (ODD) by the FDA and EMA<sup>1</sup>

### Next 12 months

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- Initiate Phase 3 registrational study

### Planned activities

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- Evaluate BBP-418 in expansion indications

<sup>1</sup>Orphan designation includes 7 years of market exclusivity in the US and 10 years in EU.

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# Thank you!

