The Journey of BBP-418: From LGMD2I/R9 Disease Pathophysiology to Registrational Clinical Trials

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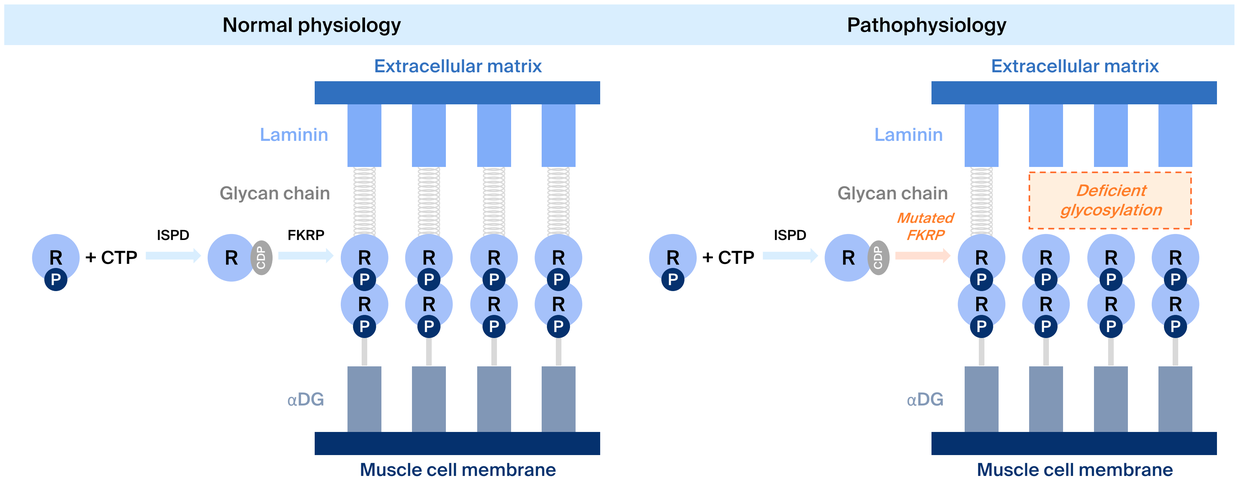
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OBJECTIVES

- Report preclinical and clinical findings on BBP-418 (ribitol), an investigational therapy for treatment of LGMD2I/R9
- Provide an overview of the clinical development pathway and key advancement milestones

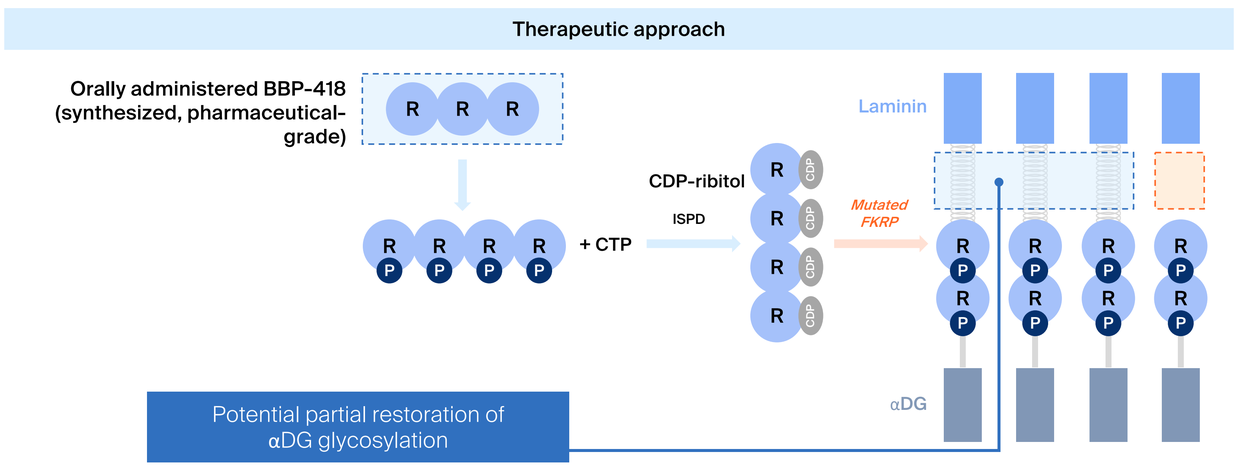
INTRODUCTION

Figure 1. LGMD2I/R9 Pathophysiology[1,2]



- LGMD2I/R9 is an autosomal-recessive neuromuscular disorder caused by pathogenic variants in the *FKRP* gene, which lead to impaired glycosylation of α-dystroglycan (αDG; matriglycan)
- Glycosylated αDG is a critical component of the dystrophin-associated glycoprotein complex, which is responsible for anchoring the muscle cell cytoskeleton to the ECM
- Complete glycosylation of αDG supports the physical link between the ECM and the muscle cell membrane, conferring stability and resistance to activity-induced damage
- There are no approved therapies for LGMD2I/R9, representing a significant unmet medical need

Figure 2. BBP-418[3]



- Pharmaceutical grade BBP-418 is an orally administered small molecule that is currently being evaluated in a Phase 3 clinical trial (NCT05775848) for the treatment of LGMD2I/R9
- When administered in supraphysiological levels, BBP-418 drives the residual activity of the mutant FKRP enzyme and increases glycosylation of αDG in patients with LGMD2I/R9

BBP-418: PRECLINICAL FINDINGS

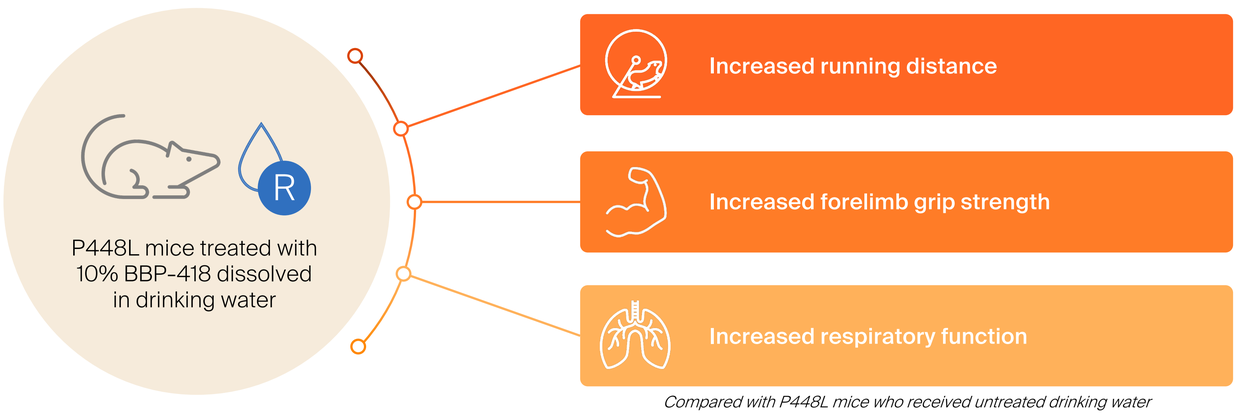
Figure 3. Key Data From a Murine Model of LGMD2I/R9



P448L mice are an FKRP-deficient model of LGMD2I/R9

- When orally gavaged with BBP-418, P448L mice had increased matriglycan levels in the tibialis anterior, diaphragm, and heart compared with saline-treated mice[4]

Figure 4. Functional Outcomes in an Independent Murine Model of LGMD2I/R9



Compared with P448L mice who received untreated drinking water

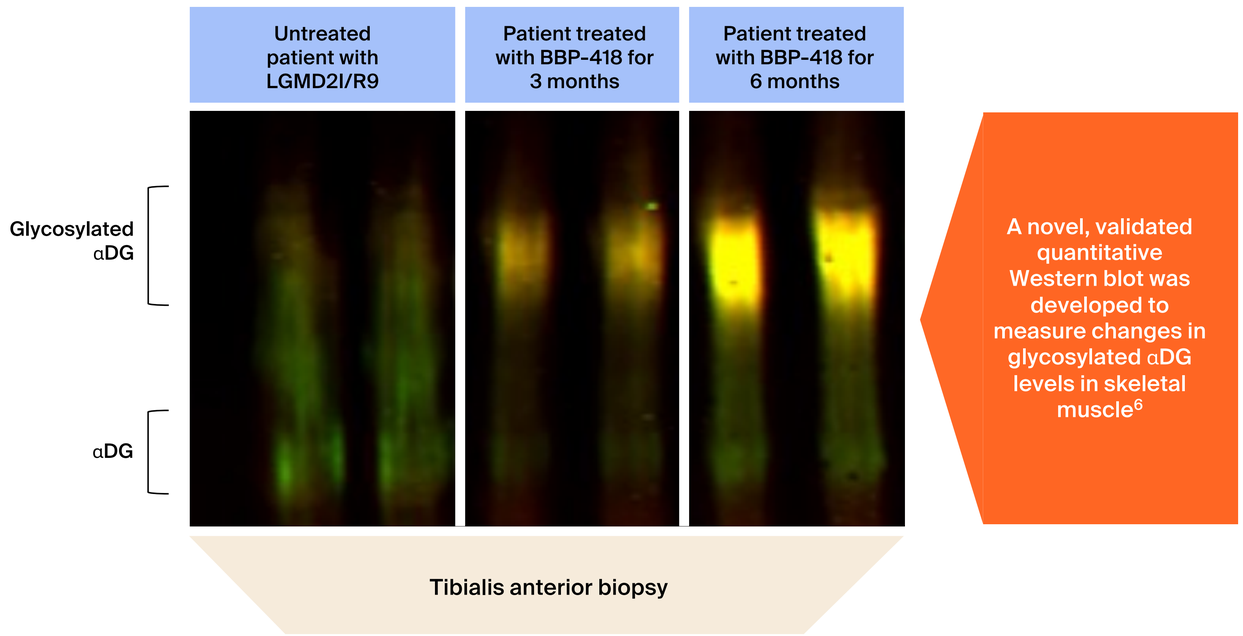
BBP-418 treatment improved skeletal muscle function and respiratory function in P448L mice[5]

CONCLUSION

- Over a decade of foundational research has elucidated the pathophysiology of LGMD2I/R9, identified a potential disease-modifying therapy, and enabled both functional outcomes and biomarker-driven clinical evaluation of BBP-418

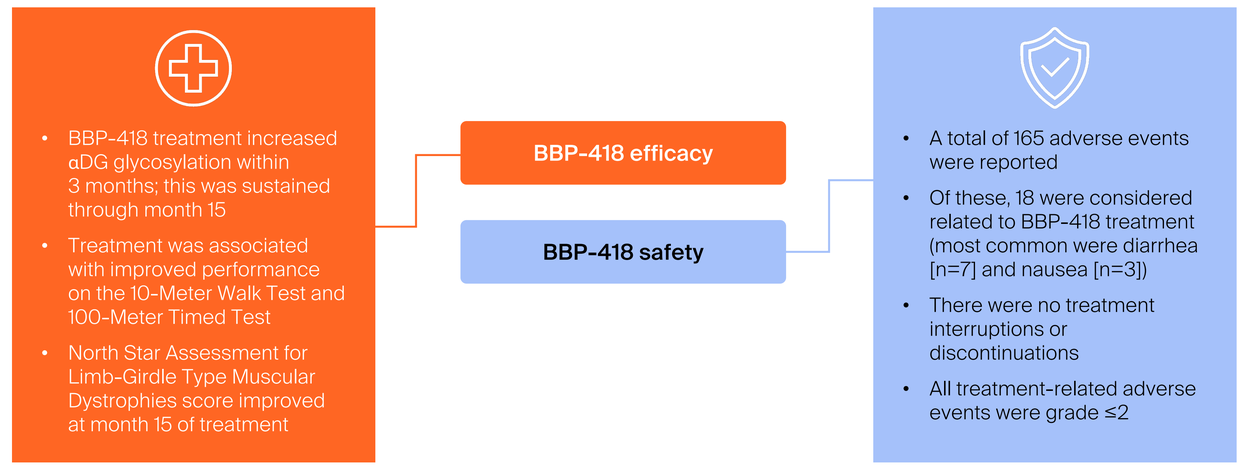
BBP-418: CLINICAL FINDINGS

Figure 5. Levels of Glycosylated αDG After Treatment With BBP-418



- Glycosylated αDG levels were increased in tibialis anterior muscle biopsy samples from patients with LGMD2I/R9 treated with BBP-418 for 3 and 6 months compared with untreated patients

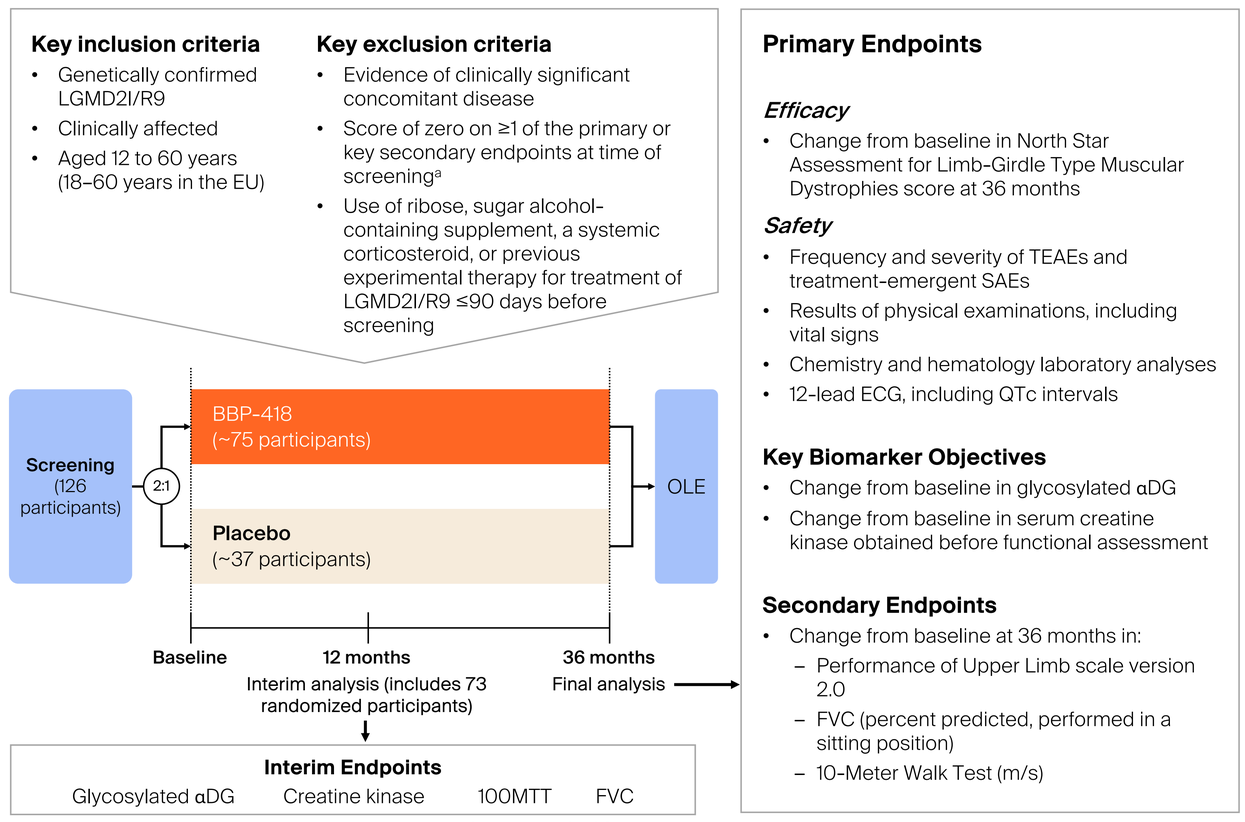
Figure 6. Phase 2 Clinical Efficacy and Safety of BBP-418 (MLB-01-003; NCT04800874; Open Label; n=14)



- BBP-418 treatment stabilized ambulatory and clinical measures after 21 months of treatment; treatment was well tolerated

BBP-418: ONGOING CLINICAL TRIALS

Figure 7. Phase 3 FORTIFY (NCT05775848), Active, Not Recruiting



[a]Participants who previously completed participation in Study MLB-01-001 and would be excluded due to this criterion may enroll in this study provided all inclusion and no other exclusion criteria are met.

A placebo-controlled phase 3 study (FORTIFY)[7] will further evaluate the mechanism of action of BBP-418, measuring functional endpoints and key biomarkers of muscular damage

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ABBREVIATIONS: 100MTT, 100-Meter Timed Test; αDG, α-dystroglycan; CDP, cytidine diphosphate; CTP, cytidine triphosphate; ECG, electrocardiogram; ECM, extracellular matrix; FKRP, fukutin-related protein; FVC, forced vital capacity; ISPD, isoprenoid synthase domain containing; LGMD2I/R9, limb-girdle muscular dystrophy type 2I/R9; OLE, open-label extension; P, phosphate group; R, ribitol; Ra, randomized; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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DISCLOSURES: CB, AT, KB, and DS are employees of and may own stock/options in ML Bio Solutions Inc., a BridgeBio company. **QLL** holds patent US-20200061092-A1 (Methods and Compositions for Treating Disorders Associated with Muscle Weakness) and consultant to ML-Bio Solutions Inc. TR has nothing to disclose.