FORTIFY: A Phase 3 Study to Evaluate Efficacy & Safety of BBP-418 in Individuals With Limb Girdle Muscular Dystrophy 2I (LGMD2I), LGMDR9 FKRP-Related

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What does FORTIFY mean for the LGMD2I/R9 Community?

- FORTIFY (NCT05775848) will evaluate the efficacy and safety of BBP-418 in individuals with limb girdle muscular dystrophy type 2I, R9 FKRP-related (LGMD2I/R9), a disease for which no approved therapies currently exist.
- Biomarker and clinical endpoints will be measured at 12 months for an interim assessment of BBP-418 efficacy.
- Clinical endpoints and safety will also be measured at 36 months to provide confirmatory clinical data.
- After completion of the study, individuals in FORTIFY may be eligible to enroll into an extension study to assess the long-term safety and efficacy of BBP-418.

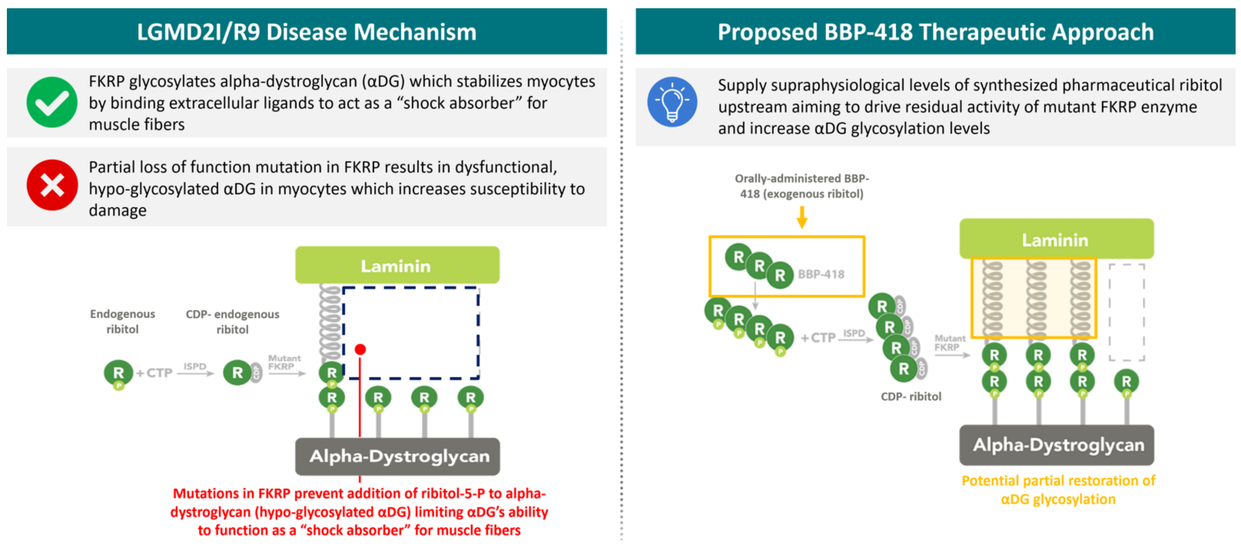
Study Objectives

- To evaluate the efficacy and safety of BBP-418, as measured by physical, respiratory, and cardiac activity; and glycosylated αDG levels in individuals with LGMD2I/R9.

Study Background

- Oral BBP-418 is substrate supplementation therapy designed to drive residual activity of mutant FKRP in LGMD2I/R9, targeting the disease at its source.
- BBP-418 is an oral therapy dissolved in water for convenient oral dosing twice daily.

Figure 1. Overview of BBP-418 Mechanism in the Context of LGMD2I/R9 Disease



- ML Bio has conducted a natural history study in individuals with LGMD2I/R9. Oral BBP-418 has also been evaluated in several clinical studies in unaffected individuals and in a clinical study in individuals with LGMD2I/R9.

Figure 2. Summary of Clinical Trials of BBP-418

	Study	Phase	Description	Key Takeaways
1	MLB-01-002 MLB-01-004	Phase 1 (N=109)	▪ Two US Phase 1 studies in unaffected individuals to evaluate the safety and pharmacokinetics of BBP-418	▪ No serious adverse events or discontinuations due to adverse events related to BBP-418 ▪ Pharmacokinetics of BBP-418 with and without food defined
2	MLB-01-001 NCT04202627	Natural History (N=101)	▪ Large natural history in US and Denmark study to define LGMD2I/R9 phenotypes ▪ Validate muscle biomarker for LGMD2I/R9 to support therapeutic development	▪ Defined disease trajectory over ~1 year ▪ Muscle biomarker reflected genotype/phenotype in LGMD2I/R9 ▪ Defined natural variability of muscle biomarker over ~1 year
3	MLB-01-003 NCT04800874	Phase 2 (N=14)	▪ Open label, dose-finding US study to evaluate safety and tolerability of BBP-418 in LGMD2I/R9	▪ Encouraging safety profile in individuals with LGMD2I/R9 ▪ Bioassay data suggest BBP-418 impacts disease at the molecular level ▪ Encouraging data supporting clinical activity

Acknowledgements & Disclosures

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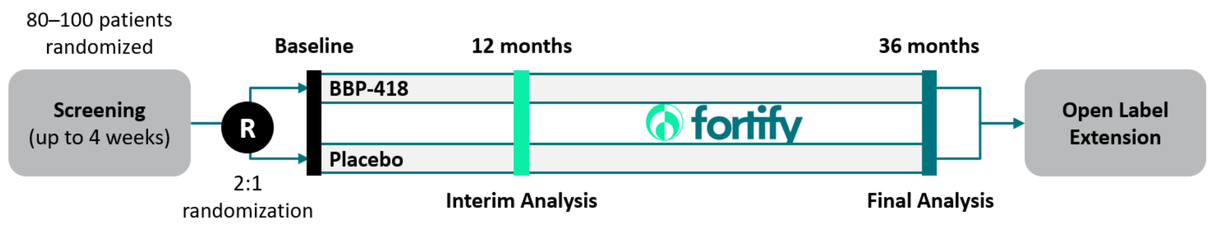
- The authors would also like to thank the individuals with LGMD2I/R9 and their families for their participation in ML Bio Solutions' natural history study and Phase 2 study that provided critical data to support the ongoing FORTIFY study.
- FORTIFY is sponsored and funded by ML Bio Solutions Inc., a BridgeBio Pharma, Inc. company, Palo Alto, CA, USA.
- DR, DW, TB, AR, LR, and DS are employees of ML Bio Solutions, a BridgeBio company, and may have equity compensation packages as part of such employment.

Conclusions

- FORTIFY is an ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial evaluating the safety and efficacy of BBP-418, an oral substrate supplementation therapy, in development as a potential therapy for LGMD2I/R9.
- Efficacy and safety will be evaluated through assessments of physical, cardiac, and respiratory function, as well as biomarker endpoints.
- For more information on FORTIFY, visit https://clinicaltrials.gov/study/NCT05775848

Study Design

Figure 3. FORTIFY Study Design Schematic



Eligibility

Key Inclusion Criteria*

- have a genetically confirmed diagnosis of LGMD2I/R9 & be clinically affected
- male or female participants 12 to 60 years of age (inclusive)**
- willing and able to complete all study procedures, including muscle biopsies

Key Exclusion Criteria*

- evidence of clinically significant concomitant disease
- score of zero on any one or more of the primary or key secondary endpoints at the time of screening***
- use of ribose or other sugar alcohol-containing supplement within 90 days of screening
- use of a systemic corticosteroid within 90 days of screening
- previously received gene therapy to treat LGMD2I/R9 experimental therapy or device within 90 days of screening

*Additional inclusion and exclusion criteria apply.
**Applicable to participants in US, UK, and AUS only. In EU, male or female participants 18 to 60 years of age (inclusive) are eligible.
***Not applicable to individuals who participated in ML Bio's natural history study MLB-01-001 (NCT04202627).

Study Endpoints

Primary Endpoint

Efficacy

- Change from baseline in NSAD at 36 months

Safety

- Frequency and severity of TEAEs and treatment-emergent SAEs
- Results of physical examinations including vital signs
- Chemistry and hematology laboratory analyses
- 12-lead ECG, including QTc intervals

Secondary Endpoints

- Change from baseline in 100mTT at 36 months
- Change from baseline in PUL2.0 at 36 months
- Change from baseline in FVC (% predicted, performed in a sitting position) at 36 months
- Change from baseline in 10MWT (velocity) at 36 months

Key Biomarker Objectives

- Change from baseline in total glycosylated αDG
- Change from baseline in pre-functional assessment serum CK
- Change from baseline in glycosylated αDG/total αDG ratio

Statistical Analyses

- The primary endpoint and key secondary endpoints in this study will each be analyzed using mixed models for repeated measures.
- Given the impact of genetic mutation (heterozygote vs. homozygote) and qualification status for the Primary Efficacy Analysis Population, analyses will be conducted for these subgroups to determine the impact on treatment effect.
- The PK parameters will be assessed using non-compartmental and population PK analysis methods.
- Safety analyses will be descriptive in nature and assessed based on the evaluation of AEs, SAEs, physical examination, clinical laboratory test results, ECG parameters, echocardiogram, and vital signs. Safety data will be summarized by treatment group.

Abbreviations

10MWT, 10-meter walk test; 100MTT, 100-meter timed test; αDG, alpha dystroglycan; AUS, Australia; CK, creatine kinase; ECG, electrocardiogram; EU, European Union; FKRP, fukutin-related protein; FVC, forced vital capacity; LGMD2I/R9, Limb-girdle muscular dystrophy type 2I, R9 FKRP-related; NSAD, North Star Assessment for Dysferlinopathy (also referred to as the North Star Assessment for Limb Girdle Muscular Dystrophy); PK, pharmacokinetics; PUL2.0, Performance of Upper Limb 2.0; QTc, corrected QT interval; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; UK, United Kingdom; US, United States

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