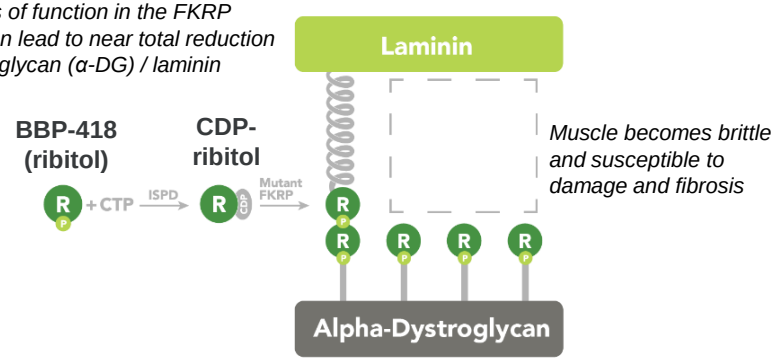
ML Bio Solutions overview: BBP-418 (ribitol) for Limb-girdle muscular dystrophy type 2I (LGMD2i)

Mechanism of Disease

Partial loss of function in the FKRP enzyme can lead to near total reduction in α-dystroglycan (α-DG) / laminin binding



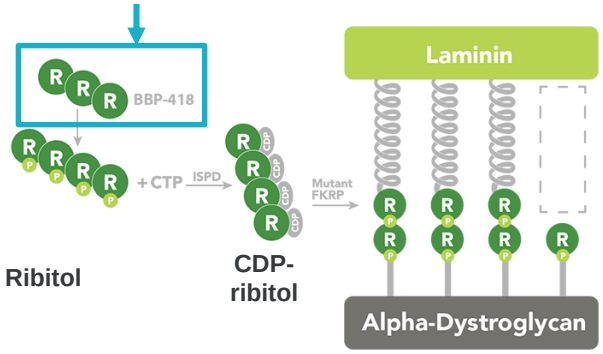
Muscle becomes brittle and susceptible to damage and fibrosis

Impact on patients:

- Progressive muscle weakness, leading to loss of ambulation, respiratory function, and cardiac function
- Increased mortality in even the mildest forms of the disease
- No currently approved therapies

Mechanism of Drug

Exogenous BBP-418 (ribitol) partially restores glycosylation



Program Highlights

7000+

LGMD2i pts in US+EU

Development status:

Pre-IND	Phase 1	Phase 2	Phase 3

BBP-418

Catalysts:

- Natural history study start 2H19
- IND filing in 2020

Key info:

- In preclinical tolerability studies of BBP-418 in LGMD2i mice, a ~20x window between minimum effective dose and maximum tolerated dose was observed.
- Preclinical studies of BBP-418 in the mouse model of severe LGMD2i (P448L) showed:
  - **Clear BBP-418 uptake in target tissues and efficient conversion into FKRP substrate:** 4x increases in '418 levels in heart and in leg tissue with similar increases in ribitol-5P and CDP-ribitol
  - **Restored *α-DG* glycosylation in skeletal, cardiac, and diaphragm muscle**
  - **Improved disease pathology and function:** Increase in running time and distance, increase in muscle, decrease in fibrosis, and increase in respiratory function
- **FDA Orphan Drug Designation** for the treatment of LGMD2i

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Mechanism of disease and therapeutic rationale

We have a clear quantitative understanding of LGMD2i pathophysiology…

FKRP mutants result in partial loss of enzyme	• ~70% or more of enzyme function can be lost • May result in complete loss of α-DG glycosylation
Up to 100% loss of α-DG glycosylation	• Results in dissociation of muscle fibers from the extracellular matrix • Muscles become "brittle"
Patients with mutation have 4-12% muscle mass	• 30-40% is average for an adult without FKRP mutations
Reduction in strength by 33-100%	• Based on strength testing across flexors/extensors in human subjects
45%+ lose ambulation, 30%+ cardiomyopathy Increased mortality	• For the mildest form • Severe forms impact respiratory & brain function

…and a therapeutic rationale based on quantitative understanding of our product candidate, BBP-418

Dose of 2g daily dissolved in water	• Based on the human equivalent dose from animal studies in the severe form of LGMD2i
Leads to >6x CDP-ribitol in target tissues	• Based on animal PK studies and ~70-90% BBP-418 to FKRP substrate conversion rate in human muscle
Leading to a 2x or greater increase in catalytic rate of mutant FKRP	• Based on our estimates from preclinical studies in the severe LGMD2i mouse model
50%+ magnitude of benefit on symptoms	• Given significant functional benefits observed in the treated severe LGMD2i mouse model

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