A Phase 1 Randomized, Blinded, Placebo-Controlled Study of the Safety, Tolerability, and PK of BBP-418 (ribitol) in Healthy Subjects

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Abstract

Introduction:

LGMD Type 2I/R9 is caused by bi-allelic loss-of-function of the Fukutin-Related Protein (FKRP) gene, which results in hypoglycosylation of alpha-dystroglycan (αDG). BBP-418 (Ribitol) is an investigational drug being evaluated as an oral-administered substrate supplementation therapy intended to saturate the FKRP enzyme to drive increased glycosylation of the αDG, thus addressing the root cause of disease in LGMD Type 2I/R9.

Objectives:

The MLB-01-002 Phase 1 study intended to explore safety and tolerability of single (SAD) and multiple (MAD) ascending doses of BBP-418 following administration to healthy subjects. Investigators sought to characterize single dose and steady state pharmacokinetics (PK) of BBP-418 and evaluate the effect of a standardized high calorie meal on the PK profile of BBP-418.

Methods:

Phase 1 explored the safety of administration of BBP-418 to 93 healthy subjects. The SAD part of this study included 1 food effect (FE) cohort. Vital signs, ECGs, evaluation of AEs and blood draws for PK and safety laboratory tests were obtained serially. SAD dosing was assessed across 7 cohorts to a maximum dose of 15g. Five MAD cohorts were enrolled to a maximum dose of 9g BID.

Trial Design

Cohort type	Dose level							
SAD	0.5g	1.5g	3.0g	3.0g	6.0g	9.0g	12.0g	15.0g
MAD		1.5g QD	3.0g QD	3.0g BID	6.0g BID	9.0g BID		

single (SAD) and multiple (MAD) ascending doses

Randomized, blinded, placebo-controlled

(N = 85 Healthy Volunteers)

PRIMARY OBJECTIVE

- Safety & Tolerability
- Single Dose and Steady-State PK
- Effect of high standardized high calorie meal on the PK profile

PRIMARY ENDPOINTS

- TEAEs

SERIALLY OBTAINED:

- Vital signs
- ECGs
- Evaluation of AEs
- Blood draws for PK and safety laboratory tests

AE: adverse event, SAE: serious adverse event, TEAE: treatment emergent adverse events

Safety & Tolerability

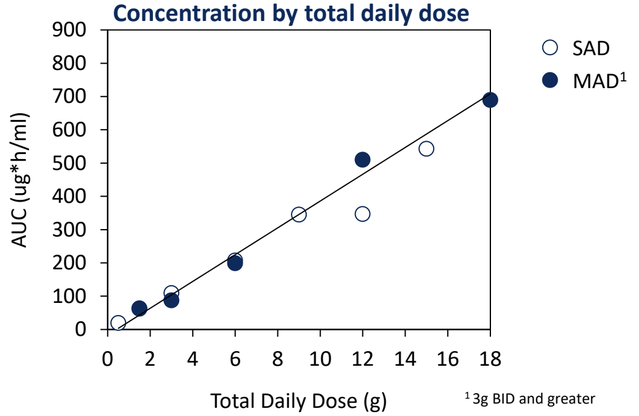
No dose-limiting toxicity observed

# of Adverse Events	Severity
28 (68%)	Grade 1 Mild
12 (29%)	Grade 2 Moderate
1 (2%)	Grade 3 Severe

- 41 adverse events were reported across the MAD (n=21) and SAD (n=20) cohorts
- Most possibly (n=15) or probably (n=6) related AEs were gastrointestinal
- There were no deaths, SAEs, or subjects discontinued due to AEs during the SAD or MAD portions of the study

Pharmacodynamic Results

Concentration by total daily dose



[1] 3g BID and greater

- The geometric mean (%CV) for Cmax and AUC(0-∞) following a single 15 g dose were 221 (12.6%) µg/mL and 543 (12.3%) µg*hr/mL, respectively
- Effective half-life was ~4-5 hours
- No clinically significant differences in exposure occurred when administered under fed conditions

Conclusions

Phase 1 Trial in healthy volunteers revealed:

- Good overall tolerability profile across a wide range of doses
- PK assessment with dose proportional exposure following both single and multiple dose administrations
- Initial weight-based dosing model to be used in ongoing Phase 2 trial supporting doses of up to 12g BID (24g total daily dose)

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