Durable Responses to Low Dose BB-301 in Oculopharyngeal Muscular Dystrophy at 12- and 24-months and Improved Depth of Response to High Dose BB-301

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Abstract

BB-301, a gene therapy designed to reduce dysphagic symptoms in OPMD, is being evaluated in a phase 1b/2a, first-in-human (FIH) study (NCT06185673). OPMD, driven by poly(A)-binding protein nuclear 1 gene mutation, is a rare muscular dystrophy characterized by severe, universally progressive dysphagia. Treatment-induced stabilization, or reduction, of dysphagic symptom burden represents a clinically meaningful outcome.

Patients diagnosed with OPMD who were enrolled into the Benitec Natural History (NH) study for ≥ 6 months, are eligible to screen onto the BB-301 phase 1b/2a study. Each patient serves as their own control, with all clinical and radiographic assessments conducted during the pre-treatment period being compared to an identical set of post-treatment assessments. Serial efficacy assessments comprise videofluoroscopic swallowing studies [VFSS] and a validated patient-reported outcome instrument (Sydney Swallow Questionnaire [SSQ]).

A Responder Analysis was developed to facilitate standardized evaluation of BB-301 efficacy. Parameters underlying Response characterization were derived from literature-based methods and include: SSQ, VFSS (post-swallow pharyngeal residue and throat closure), and cold water timed drinking test.

Six patients in cohort 1 safely received the lowest-dose of BB-301, with no treatment related serious adverse events (SAEs). Four cohort 1 patients have completed the 12-month statistical follow-up period for the phase 1b/2a study (completers), with 24-month post-treatment results available for Patient 1.

All cohort 1 completers were formal Responders to BB-301, demonstrating durable response to BB-301.

At 24-months post-BB-301 treatment, Patient 1 continued to demonstrate robust, disease-modifying, outcomes, with deepening improvements in both post-swallow pharyngeal residue and total dysphagic symptom burden.

Patient 1 of cohort 2 safely received the highest-dose of BB-301, with no treatment-related SAEs. The preliminary interim clinical results demonstrate improved depth of response at the 3-month post-treatment timepoint, with significant improvements noted for throat closure, post-swallow pharyngeal residue, and total dysphagic symptom burden.

Methodology

- BB-301 is an adeno-associated virus serotype 9 (AAV9)-based investigational gene therapy under development by Benitec Biopharma, Inc. for the treatment of moderate dysphagia in adult patients diagnosed with OPMD.
- Progressive dysphagia impacts 97% of OPMD patients and is a severe, life-threatening complication of OPMD which can lead to chronic choking, malnutrition, aspiration pneumonia, and death.
- In OPMD, the pharyngeal constrictor muscles are weakened and atrophic and unable to support the propulsion of food or liquid towards the esophagus.
- In the current clinical study, BB-301 is delivered to the pharyngeal constrictor muscles via direct intramuscular injection in the operating room.
- Potential BB-301-derived increases in muscle cross-sectional area, muscle mass, and muscle force, as observed in preclinical BB-301 studies, should enhance the functional capacity of the pharyngeal muscles of OPMD patients, thereby reducing the dysphagic symptom burden.

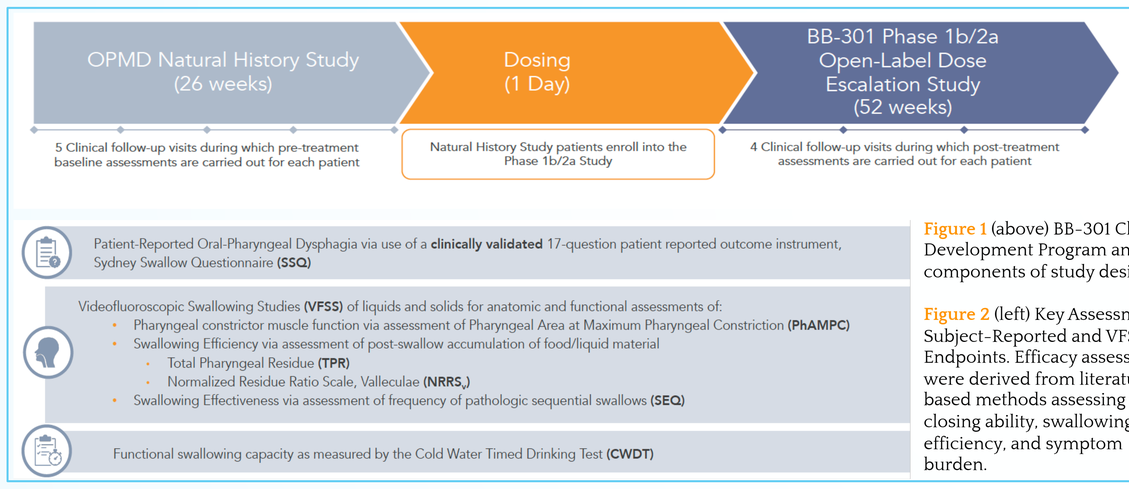


Figure 1 (above) BB-301 Clinical Development Program and key components of study design

Figure 2 (left) Key Assessments: Subject-Reported and VFSS Endpoints. Efficacy assessments were derived from literature-based methods assessing throat closing ability, swallowing efficiency, and symptom burden.

Scoring Clinical Success: If a patient achieves the statistical criteria for improvement in at least 2 out of 5 measures, they are considered a Responder to BB-301.

Results

Figure 3 All Cohort 1 Study Completers (patients that have reached the 12-month post-BB-301-treatment assessment timepoint) are Responders to BB-301 Treatment

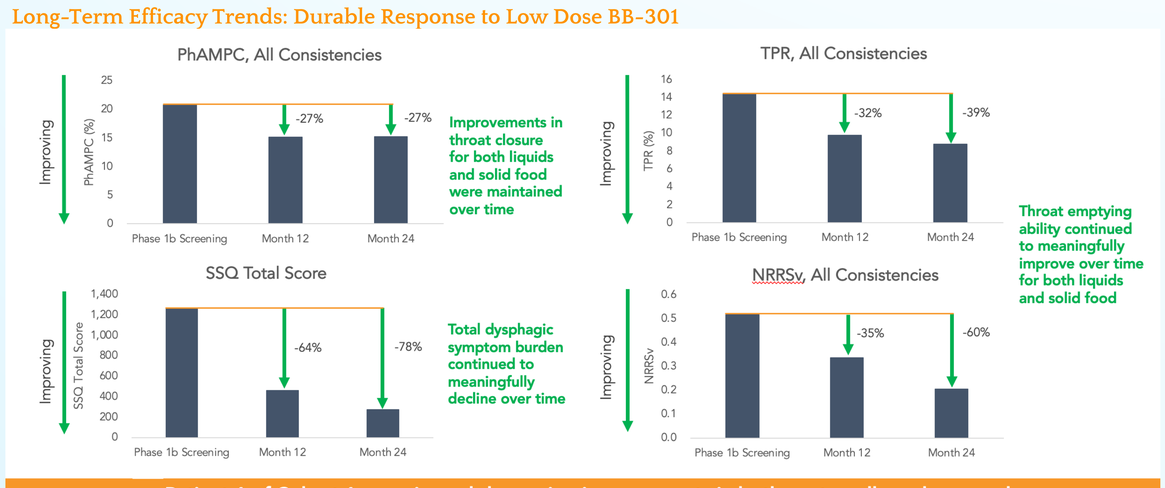
Patient	Post-Treatment Statistical Follow-up Period	Response Criteria Achieved	Total Responder Score	Responder
1	12- months	SSQ, PhAMPC, Pharyngeal residue, CWDT	4	✓
2	12- months	SSQ, PhAMPC, SEQ, CWDT	4	✓
3	12- months	SSQ, PhAMPC, SEQ, Pharyngeal residue	4	✓
4	12- months	SSQ, PhAMPC, Pharyngeal residue	3	✓

Silence and Replace: BB-301 is designed to block production of the the harmful mutant PABPN1 protein and restore normal muscle function by supplying a new, functional version of the protein, potentially providing a permanent solution with a single administration.

Cohort 1 Study Completers Experienced Clinically Meaningful Improvements

- Each patient serves as their own control, enabling unambiguous characterization of post-treatment changes to each clinical, radiographic, and patient-reported metric (FDA specifically recommended this approach to clinical study design for the development of gene therapy products in orphan populations in the Sept 2025 Draft Guidance for Industry "Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations").
- Post-BB-301-treatment, post-swallow pharyngeal residue, pharyngeal constrictor muscle function, timed drinking test results and patient-reported outcome scores showed significant improvement.

Long-Term Efficacy Trends: Durable Response to Low Dose BB-301



Patient 1 of Cohort 1 experienced deepening improvements in both post-swallow pharyngeal residue and total dysphagic symptom burden 24-months post-BB-301 treatment

Figure 4 Patient 1, Cohort 1 (low dose BB-301, 1.2e13 vg/subject) Demonstrates Continued, Robust, Disease-Modifying, Outcomes 24-months Post-BB-301 Treatment

Results Continued

Interim Clinical Results: Patient 1, Cohort 2 (high dose BB-301, 1.8e13 vg/subject)

- Patient A (low dose BB-301 (1.2e13 vg/subject), Cohort 1) and Patient B (high dose BB-301 (1.8e13 vg/subject), Cohort 2) had comparable baseline functional and anatomic deficits.
- When comparing the 3-month post-BB-301-treatment timepoint for both patients, Patient B (who safely received the high dose of BB-301) exhibited greater depth of response as compared to Patient A.

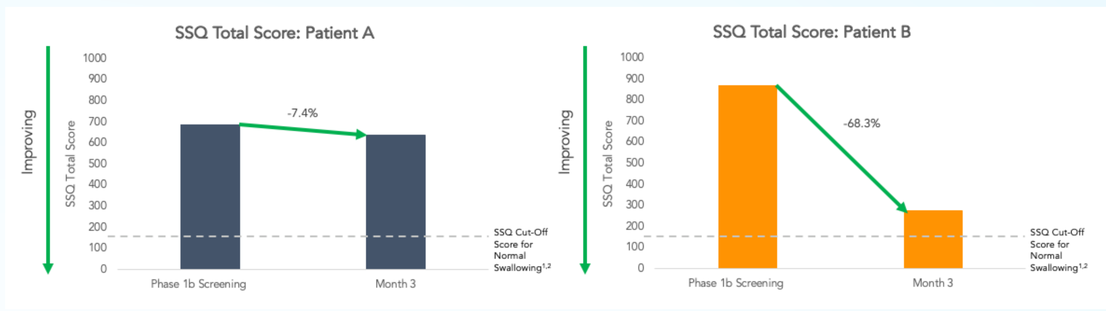


Figure 5 (above) When comparing the 3-month post-BB-301-treatment timepoints of patients with similar baseline dispositions (Patient A of Cohort 1 and Patient B of Cohort 2), Patient B experienced significantly greater reductions in total dysphagic symptom burden; 1. Bua, B.A. and Bülow, M., BMC Research Notes (2014) 7:742, 2. Audag N., et al., Dysphagia (2019) 34:556-566

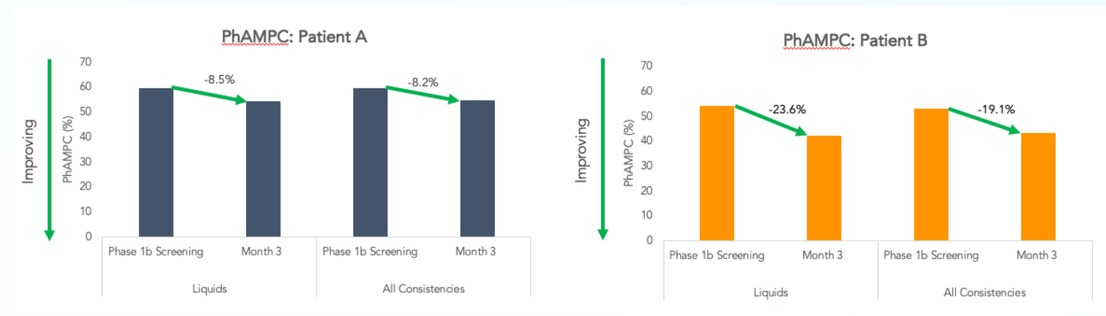


Figure 6 (above) When comparing the 3-month post-BB-301-treatment timepoints of patients with similar baseline dispositions (Patient A of Cohort 1 and Patient B of Cohort 2), Patient B experienced significantly greater improvements in throat closure

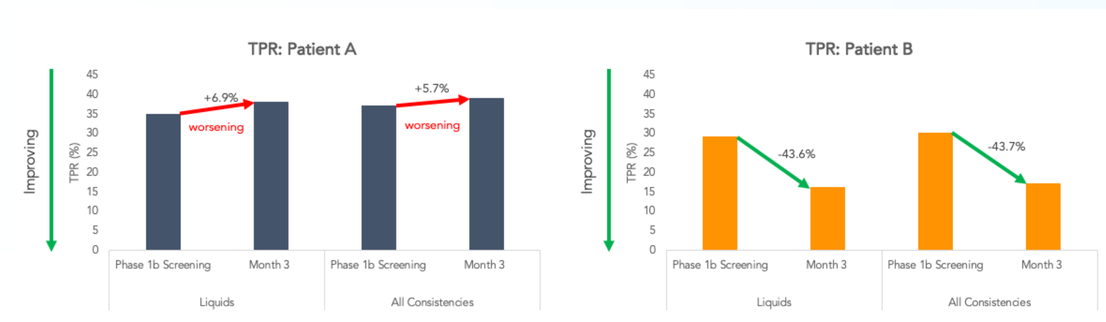


Figure 7 (above) and Figure 8 (below) When comparing the 3-month post-BB-301-treatment timepoints of patients with similar baseline dispositions (Patient A of Cohort 1 and Patient B of Cohort 2), Patient B experienced significantly greater improvements in throat emptying

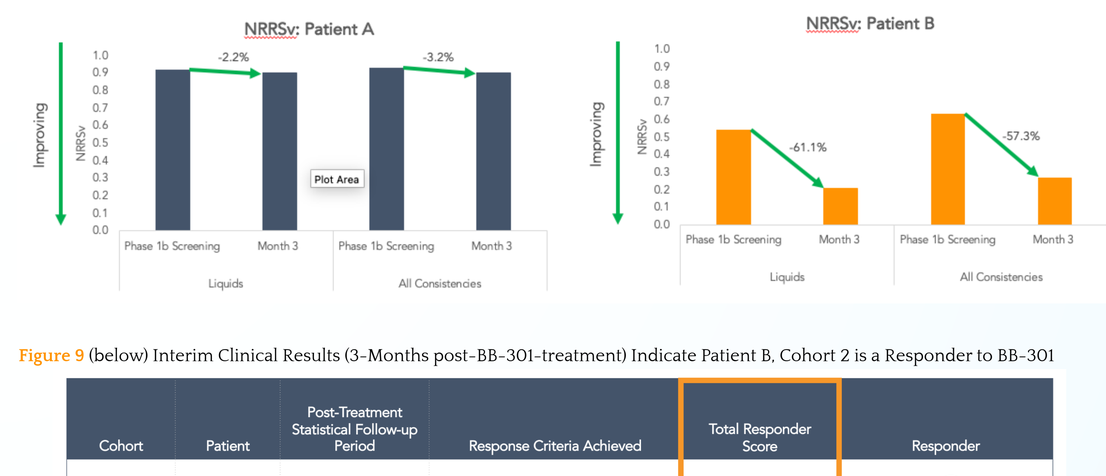


Figure 9 (below) Interim Clinical Results (3-Months post-BB-301-treatment) Indicate Patient B, Cohort 2 is a Responder to BB-301

Cohort	Patient	Post-Treatment Statistical Follow-up Period	Response Criteria Achieved	Total Responder Score	Responder
2	B	3-Months	SSQ, PhAMPC, Pharyngeal residue	3	✓

Figure 10 (below) Patient B, Cohort 2 safely received the high dose of BB-301 with no treatment related SAEs and preliminary interim clinical results demonstrate improved depth of response at the 3-months post-BB-301- treatment timepoint.

	SSQ	PhAMPC		TPR		NRRSv	
		Liquids	All Consistencies	Liquids	All Consistencies	Liquids	All Consistencies
Patient A Post-treatment Improvement	7.4% improvement	8.5% improvement	8.2% improvement	6.9% worsening	5.7% worsening	2.2% improvement	3.2% improvement
Patient B Post-treatment Improvement	68.3% improvement	23.6% improvement	19.1% improvement	43.6% improvement	43.7% improvement	61.1% improvement	57.3% improvement

Conclusions

- BB-301 is the first and only clinical stage therapy which has demonstrated durable, clinically meaningful improvements for OPMD-related dysphagia and has received Fast Track Designation from the FDA and Orphan Designation from the FDA/EMA.
- Six Patients with baseline characteristics regarding their respective functional and anatomic deficits and dysphagic symptom burdens have been safely treated with the low dose of BB-301, with no treatment-related SAEs
  - Four cohort 1 patients have completed the 12-month statistical follow-up period for the phase 1b/2a study (completers). All completers were formal Responders to BB-301, demonstrating durable response to BB-301.
- At 24-months post-BB-301 treatment, Patient 1 (Cohort 1) continued to demonstrate robust, disease-modifying, outcomes, with deepening improvements in both post-swallow pharyngeal residue and total dysphagic symptom burden.
- The first Patient in Cohort 2 (Patient B) has been safely treated with the high dose of BB-301 with no treatment-related SAEs.
- Patient A (Cohort 1) and Patient B (Cohort 2) had comparable baseline functional and anatomical deficits.
  - When comparing the 3-month post-treatment timepoints of Patient A (Cohort 1) and Patient B (Cohort 2), Patient B demonstrated improved depth of response to BB-301 with significant improvements noted for throat closure, post-swallow pharyngeal residue, and total dysphagic symptom burden.

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