# Durable Responses to Low-Dose Investigational Gene Therapy BB-301 in Patients with Oculopharyngeal Muscular Dystrophy (OPMD) with Dysphagia and Summary of Interim Clinical Results for High-Dose BB-301

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## Abstract

OPMD is an autosomal-dominant degenerative muscle disorder characterized by progressive life-threatening dysphagia and ptosis. BB-301, a gene therapy designed to reduce dysphagic symptoms in OPMD, is being evaluated in a phase 1b/2a, first-in-human study (NCT06185673).

Patients diagnosed with OPMD who were enrolled into the Benitec OPMD 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 during the statistical assessments of efficacy. Serial clinical and radiographic assessments of swallowing function are conducted during the pre-treatment and post-treatment periods to facilitate the characterization of post-treatment improvements on a per-patient basis. Efficacy assessments comprise videofluoroscopic swallowing studies [VFSS], a validated patient reported outcome instrument (Sydney Swallow Questionnaire [SSQ]) and a cold water timed drink test (CWDT).

A Responder Analysis incorporating the results of the VFSS, SSQ and CWDT assessments was developed to facilitate the standardized evaluation of BB-301 efficacy.

Six Patients in Cohort 1 were treated with low-dose BB-301 and have completed the 12-month statistical follow-up period for the phase 1b/2a study (completers). All Cohort 1 completers were formal Responders to BB-301, demonstrating durable responses to BB-301. At 24-months post-BB-301 treatment, patient 1 and patient 2 of Cohort 1 continued to demonstrate robust, disease-modifying, outcomes in the key drivers of their respective dysphagic symptom burdens.

Three patients have been treated with high-dose BB-301 in Cohort 2, and the assessments for safety and efficacy are ongoing. The interim clinical results for the first 3 patients treated with high-dose BB-301 in Cohort 2 demonstrate clinically significant improvements in swallowing function with all three patients achieving formal response to BB-301.

There have been no serious adverse events in any patient treated with BB-301 to date.

## 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 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.

**Silence and Replace:** BB-301 is designed to block production of 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.

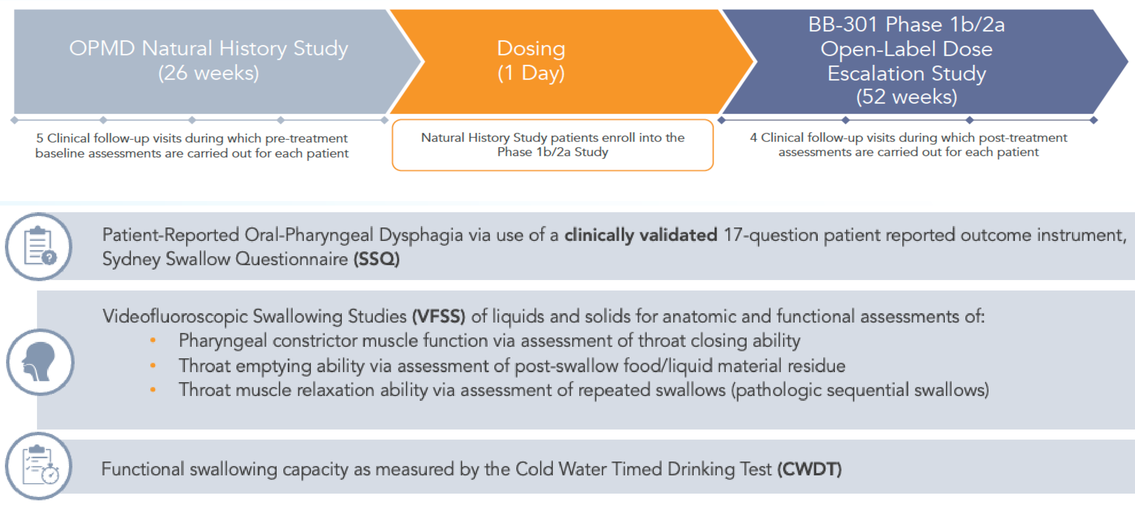



Figure 1 (top) BB-301 Clinical Development Program and key components of study design; Figure 2 (bottom) Key Assessments: Subject-Reported and VFSS Endpoints. Efficacy assessments were derived from literature-based methods assessing throat closing ability, throat emptying ability, throat muscle relaxation ability.

## Results

### Durable Responses to Low Dose BB-301: Cohort 1 (1.2e13 vg/subject), 12-months Post-Treatment

**100% of Patients in Cohort 1 (n=6) Are Responders to BB-301**

| Patient | Post-Treatment Statistical Follow-Up Period | Response Criteria Achieved | Total Responder Score | Responder |
|---|---|---|---|---|
| 1 | 12- months | SSQ, throat closing ability, throat emptying ability, CWDT | 4 | ✓ |
| 2 | 12- months | SSQ, throat closing ability, throat emptying ability, throat muscle relaxation ability, CWDT | 5 | ✓ |
| 3 | 12- months | SSQ, throat closing ability, throat emptying ability, throat muscle relaxation ability | 4 | ✓ |
| 4 | 12- months | SSQ, throat closing ability, throat emptying ability | 3 | ✓ |
| 5 | 12- months | SSQ, throat closing ability, CWDT | 3 | ✓ |
| 6 | 12-months | SSQ, throat closing ability, throat emptying ability | 3 | ✓ |

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

### 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.
- Following treatment with BB-301, significant improvements were noted for: throat closing ability, throat emptying ability, throat muscle relaxation ability, functional swallowing capacity and total dysphagic symptom burden.

## Results Continued

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

**Interim Clinical Results: Cohort 2, all patients are Responders to BB-301**

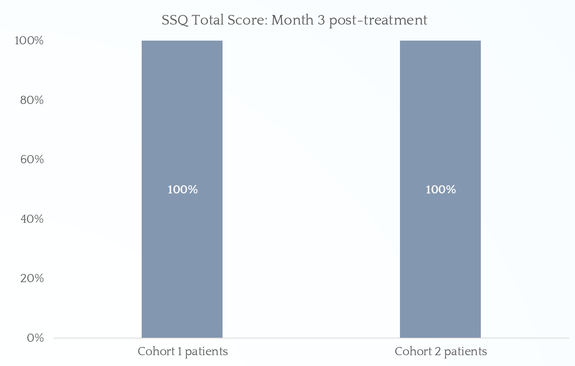
| Patient | Post-Treatment Statistical Follow-Up Period | Response Criteria Achieved | Total Responder Score | Responder |
|---|---|---|---|---|
| 7 | 9- months | SSQ, throat closing ability, throat emptying ability | 3 | ✓ |
| 8 | 3- months | SSQ, throat closing ability, throat emptying ability, CWDT | 4 | ✓ |
| 9 | 3- months | SSQ, throat emptying ability, CWDT | 3 | ✓ |

Figure 4 Interim clinical results for Cohort 2 indicate that all Cohort 2 patients are Responders to BB-301 treatment.

- Three patients have been treated with high-dose BB-301 in Cohort 2, completing the dosing for this cohort.
- There have been no treatment-related SAEs in Cohort 1 or Cohort 2 patients to date.
- Interim clinical results indicate that all Cohort 2 patients are formal responders to BB-301 treatment.

### Evaluation of Dose-Response: Full Cohort Comparisons (Cohort 1 compared to Cohort 2)

- Month 3 clinical results are currently available for all Cohort 1 and Cohort 2 patients.
- The response to BB-301 at the Month 3 post-treatment timepoint was used to evaluate dose-response relationships for Cohort 1 and Cohort 2 patients.



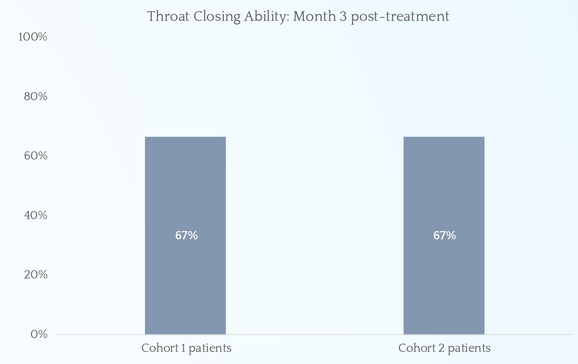
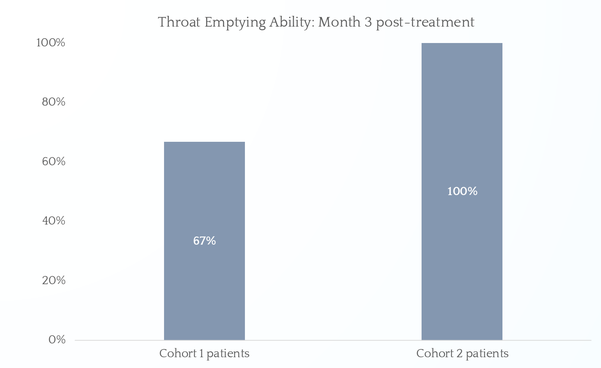




Figure 5 SSQ (above, left) At 3-months post-treatment, 100% of Cohort 1 patients and 100% of Cohort 2 patients meet the statistical criteria for response for total SSQ score.

Figure 6 Throat Closing Ability (above, right) At 3-months post-treatment, 67% of Cohort 1 patients and 67% of Cohort 2 patients meet the statistical criteria for response for throat closing ability.



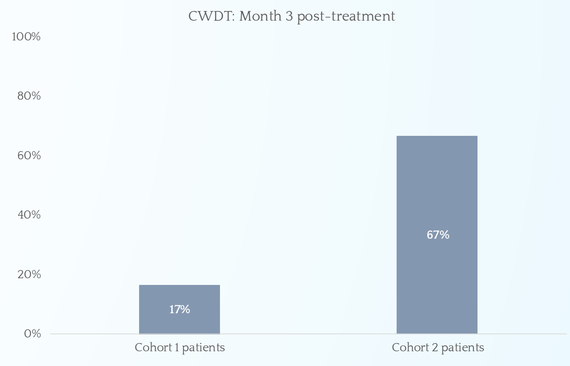




Figure 7 Throat Emptying Ability (above, left) At 3-months post-treatment, 67% of Cohort 1 patients meet the statistical criteria for response for throat emptying ability, and 100% of Cohort 2 patients meet the statistical criteria for response for throat emptying ability.

Figure 8 CWDT (above, right) At 3-months post-treatment, 17% of Cohort 1 patients and 67% of Cohort 2 patients meet the statistical criteria for response for functional swallowing capacity as assessed by CWDT.

- Improvements in total SSQ score and throat closing ability for Cohort 1 and Cohort 2 patients were equivalent at Month 3 post-BB-301 administration.
- A larger proportion of Cohort 2 patients exhibit an improvement in throat emptying ability and functional swallowing capacity at Month 3 post-BB-301 administration as compared to Cohort 1 patients.
- Additional safety and efficacy data collection for Cohort 2 patients is ongoing. Upon review of 12-months of safety and efficacy data for each patient in Cohort 2 the final dose selection for the pivotal study will be determined.

## Conclusions

- BB-301 is the first and only clinical stage gene 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 disparate baseline characteristics regarding their respective functional and anatomical deficits and dysphagic symptom burdens have been safely treated with the low dose of BB-301 in Cohort 1, with no treatment-related SAEs.
  - All Cohort 1 patients have completed the 12-month statistical follow-up period for the phase 1b/2a study (completers). All Cohort 1 patients are formal Responders to BB-301, demonstrating durable response to BB-301.
- Three patients have been safely treated with high-dose BB-301 in Cohort 2 with no treatment-related SAEs. The assessments for safety and efficacy are ongoing. The interim clinical results at 9-months and 3-months post-BB-301-administration, respectively, for Cohort 2 demonstrate clinically significant improvements in swallowing function with all patients achieving formal response to BB-301.

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