UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): April 18, 2024

BENITEC BIOPHARMA INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-39267**	**84-4620206**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

3940 Trust Way, Hayward, California	**94545**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's Telephone Number, Including Area Code: (510) 780-0819

(Former Name or Former Address, if Changed Since Last Report): Not Applicable

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, par value $0.0001	BNTC	The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter)

Emerging Growth Company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure

On April 18, 2024, Benitec Biopharma Inc. (the "Company") issued a press release announcing interim clinical trial data from itsBB-301 Phase 1b/2a study. The Company is presenting this data at a live virtual R&D event to be held on April 18, 2024. Copies of the press release and the presentation to be used at the R&D event, which are attached hereto as Exhibit 99.1 and Exhibit 99.2, are furnished pursuant to this Item 7.01.

The information contained in Item 7.01 of this Current Report on Form8-K, including Exhibit 99.1 and Exhibit 99.2, shall not be incorporated by reference into any filing of the Company, whether made before, on or after the date hereof, regardless of any general incorporation language in such filing, unless expressly incorporated by specific reference to such filing. The information contained in Item 7.01 of this Current Report on Form 8-K Report, including Exhibit 99.1 and Exhibit 99.2, shall not be deemed to be "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press Release
99.2	Presentation
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

BENITEC BIOPHARMA INC.

Date: April 18, 2024

/s/ Jerel A. Banks
Name: Jerel A. Banks
Title: Chief Executive Officer

Exhibit 99.1

Benitec Biopharma Reports Positive Interim Clinical Trial Data for First OPMD Subject Treated with BB-301 in Phase 1b/2a Study

-First efficacy signals demonstrated for a gene therapy under development for Oculopharyngeal Muscular Dystrophy (OPMD) which affects ~15,000 patients worldwide-

- BB-301 facilitated improvements across multiple measures of swallowing function in the first Phase 1b/2a clinical study subject as compared to pretreatment assessments conducted during the observational natural history portion of the study-

-Virtual R&D Day being held today at 9:00 am EDT, details below-

HAYWARD, Calif., April 18, 2024 (GLOBE NEWSWIRE) — Benitec Biopharma Inc. (NASDAQ: BNTC) ("Benitec" or "Company"), a clinical-stage, gene therapy-focused, biotechnology company developing novel genetic medicines based on its proprietary "Silence and Replace" DNA-directed RNA interference ("ddRNAi") platform, today announces positive interim clinical data from the 90-day timepoint following the administration of BB-301 to the study's first subject (Subject 1) treated in the BB-301 Phase 1b/2a single-arm, open-label, sequential, dose-escalation cohort study (NCT06185673) in Oculopharyngeal Muscular Dystrophy (OPMD). BB-301 has been granted Orphan Drug designation by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) Committee for Orphan Medicinal Products (COMP).

"To date, no clinical studies have systematically demonstrated a clinical improvement in OPMD patients across both objective and subjective measures of swallowing. We are, therefore, pleased to report positive interim clinical data from multiple radiographic measures as well as subject-reported outcome measures from the first subject treated with BB-301," said Jerel A. Banks, M.D., Ph.D., Executive Chairman and Chief Executive Officer of Benitec. "We are highly encouraged by these early clinical trial results and for the hope that they may offer to patients and caregivers, and we look forward to reporting additional results and continuing to treat patients as they enter the dosing portion of the study from the Natural History observational lead-in period."

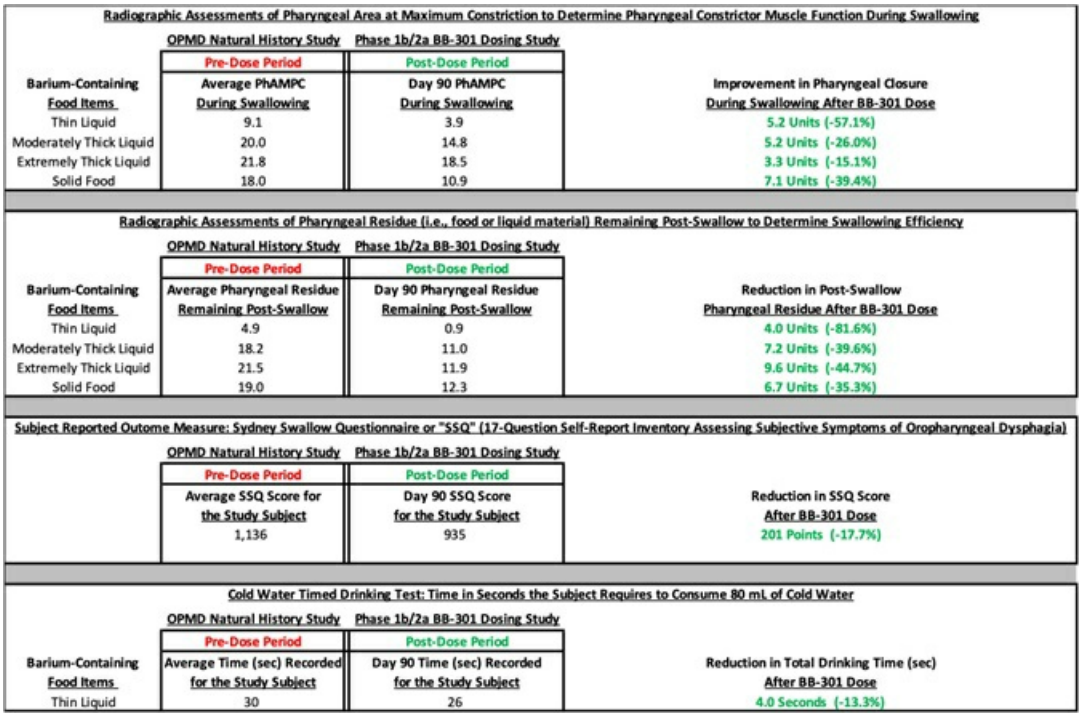
BB-301 Interim Clinical Study Results:

During the OPMD Natural History Study, which represents the pre-dose observational period for each subject, Subject 1 experienced progressive worsening of dysphagia as demonstrated by the results of the videofluoroscopic swallowing studies (VFSS), the cold water timed drinking test, and the key subject-reported outcome measure (the Sydney Swallow Questionnaire). Videofluoroscopic swallowing studies represent the gold standard analytical method for the quantitative assessment of dysphagia (swallowing difficulty) in the clinical setting.

At the 90-day timepoint following the administration of BB-301, Subject 1 demonstrated improvements in key videofluoroscopic assessments which correlated with the observation of similar improvement in the key subject-reported outcome measure as compared to the average values for the respective assessments completed during the pre-dose observational period (as summarized in Figure 1). Notably, the results of many assessments completed at the 90-day timepoint demonstrated improvements over the initial measurements assessed at the subject's first visit for the natural history observational study which occurred more than 12 months prior to the 90-day assessment.

The most significant VFSS improvements at Day 90 were observed for swallowing tasks centered on the evaluation of pharyngeal constrictor muscle function and swallowing efficiency in the context of the consumption of thin liquids, solid foods and thick, non-solid foods (e.g., yogurt or pudding) (Figure 1). The VFSS improvements correlated with an improvement in the key subject-reported outcome measure the Sydney Swallow Questionnaire, indicating an improvement in swallowing function as reported by Subject 1 (Figure 1).

Figure 1: Improvement in All Outcomes at 90-Days Post-BB-301 Injection*



Radiographic Assessments of Pharyngeal Area at Maximum Constriction to Determine Pharyngeal Constrictor Muscle Function During Swallowing

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Average PhAMPC During Swallowing	Day 90 PhAMPC During Swallowing	Improvement in Pharyngeal Closure During Swallowing After BB-301 Dose
Thin Liquid	9.1	3.9	5.2 Units (-57.1%)
Moderately Thick Liquid	20.0	14.8	5.2 Units (-26.0%)
Extremely Thick Liquid	21.8	18.5	3.3 Units (-15.1%)
Solid Food	18.0	10.9	7.1 Units (-39.4%)

Radiographic Assessments of Pharyngeal Residue (i.e., food or liquid material) Remaining Post-Swallow to Determine Swallowing Efficiency

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Average Pharyngeal Residue Remaining Post-Swallow	Day 90 Pharyngeal Residue Remaining Post-Swallow	Reduction in Post-Swallow Pharyngeal Residue After BB-301 Dose
Thin Liquid	4.9	0.9	4.0 Units (-81.6%)
Moderately Thick Liquid	18.2	11.0	7.2 Units (-39.6%)
Extremely Thick Liquid	21.5	11.9	9.6 Units (-44.7%)
Solid Food	19.0	12.3	6.7 Units (-35.3%)

Subject Reported Outcome Measure: Sydney Swallow Questionnaire or "SSQ" (17-Question Self-Report Inventory Assessing Subjective Symptoms of Oropharyngeal Dysphagia)

OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
Pre-Dose Period	Post-Dose Period	
Average SSQ Score for the Study Subject	Day 90 SSQ Score for the Study Subject	Reduction in SSQ Score After BB-301 Dose
1,136	935	201 Points (-17.7%)

Cold Water Timed Drinking Test: Time in Seconds the Subject Requires to Consume 80 mL of Cold Water

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Average Time (sec) Recorded for the Study Subject	Day 90 Time (sec) Recorded for the Study Subject	Reduction in Total Drinking Time (sec) After BB-301 Dose
Thin Liquid	30	26	4.0 Seconds (-13.3%)

* *Company data on file*

Regarding the BB-301 safety profile observed to date, no Serious Adverse Events have been observed for the two subjects that have receivedBB-301. Transient Grade 2 Gastroesophageal Reflux Disease or "GERD" (i.e., "acid reflux" or "heartburn") was observed for the two subjects that received BB-301. For both subjects, the GERD resolved following the completion of a short course of common prescription medications approved for the treatment of GERD.

OPMD is a rare progressive muscle-wasting disease caused by a mutation in the poly(A)-binding protein nuclear 1 (PABPN1) gene, for which there is currently no effective drug therapy. The disease is characterized by swallowing difficulties (dysphagia), limb weakness and eyelid drooping (ptosis). Dysphagia worsens over time and can lead to chronic choking, regurgitation, aspiration pneumonia, and in severe cases, death. Available clinical and surgical interventions are limited in scope and effectiveness and do not address the underlying progressive muscle weakness.

Virtual R&D Event Information:

This live virtual R&D Event, featuring two OPMD key opinion leaders, will be held at 9:00AM EDT today, April 18th, 2024 and can be accessed here. The event replay will be placed on the News & Events tab on the Investor page of the Benitec website.

About BB-301

BB-301 is a novel, modified AAV9 capsid expressing a unique, single bifunctional construct promoting co-expression of both codon-optimized Poly-A Binding Protein Nuclear-1 (PABPN1) and two small inhibitory RNAs (siRNAs) against mutant PABPN1. The two siRNAs are modeled into microRNA backbones to silence expression of faulty mutant PABPN1, while allowing expression of the codon-optimized PABPN1 to replace the mutant with a functional version of the protein. We believe the silence and replace mechanism of BB-301 is uniquely positioned for the treatment of OPMD by halting mutant expression while providing a functional replacement protein.

About Benitec Biopharma, Inc.

Benitec Biopharma Inc. ("Benitec" or the "Company") is a clinical-stage biotechnology company focused on the advancement of novel genetic medicines with headquarters in Hayward, California. The proprietary "Silence and Replace" DNA-directed RNA interference platform combines RNA interference, or RNAi, with gene therapy to create medicines that simultaneously facilitate sustained silencing of disease-causing genes and concomitant delivery of wildtype replacement genes following a single administration of the therapeutic construct. The Company is developing Silence and Replace-based therapeutics for chronic and life-threatening human conditions including Oculopharyngeal Muscular Dystrophy (OPMD). A comprehensive overview of the Company can be found on Benitec's website at www.benitec.com.

Forward Looking Statements

Except for the historical information set forth herein, the matters set forth in this press release include forward-looking statements, including statements regarding Benitec's plans to develop and potentially commercialize its product candidates, the timing of completion of pre-clinical and clinical trials, the timing of the availability of data from our clinical trials, the timing and sufficiency of patient enrollment and dosing in clinical trials, the timing of expected regulatory filings, the clinical utility and potential attributes and benefits of ddRNAi and Benitec's product candidates, the intellectual property position, and other forward-looking statements.

These forward-looking statements are based on the Company's current expectations and subject to risks and uncertainties that may cause actual results to differ materially, including unanticipated developments in and risks related to: unanticipated delays; further research and development and the results of clinical trials possibly being unsuccessful or insufficient to meet applicable regulatory standards or warrant continued development; the ability to enroll sufficient numbers of subjects in clinical trials; determinations made by the FDA and other governmental authorities; the Company's ability to protect and enforce its patents and other intellectual property rights; the Company's dependence on its

relationships with its collaboration partners and other third parties; the efficacy or safety of the Company's products and the products of the Company's collaboration partners; the acceptance of the Company's products and the products of the Company's collaboration partners in the marketplace; market competition; sales, marketing, manufacturing and distribution requirements; greater than expected expenses; expenses relating to litigation or strategic activities; the Company's ability to satisfy its capital needs through increasing its revenue and obtaining additional financing, given market conditions and other factors, including our capital structure; our ability to continue as a going concern; the length of time over which the Company expects its cash and cash equivalents to be sufficient to execute on its business plan; the impact of the COVID-19 pandemic, the disease caused by the SARS-CoV-2 virus and similar events, which may adversely impact the Company's business and pre-clinical and clinical trials; the impact of local, regional, and national and international economic conditions and events; and other risks detailed from time to time in the Company's reports filed with the Securities and Exchange Commission. The Company disclaims any intent or obligation to update these forward-looking statements.

Investor Relations Contact:
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Exhibit 99.2

Research and Development Day Presentation

April 2024

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Safe Harbor Statement

This presentation contains "forward-looking statements" within the meaning of section 27A of the US Securities Act of 1933 and section 21E of the US Securities Exchange Act of 1934. Benitec has tried to identify such forward-looking statements by use of such words as "expects," "intends," "hopes," "anticipates," "believes," "could," "may," "evidences" and "estimates," or the negative of these terms, and other similar expressions, but these words are not the exclusive means of identifying such statements. Such statements include, but are not limited to, any statements relating to Benitec's pipeline of ddRNAi-based therapeutics, the initiation, progress and outcomes of pre-clinical and clinical trials, the timing of the availability of data from our clinical trials, the timing and sufficiency of patient enrollment and dosing in clinical trials, the timing of expected regulatory filings, the clinical utility and potential attributes and benefits of ddRNAi and Benitec's product candidates, the intellectual property position and any other statements that are not historical facts. Such forward-looking statements involve risks and uncertainties, including, but not limited to, risks and uncertainties relating to the difficulties or delays in our plans to develop and potentially commercialize our product candidates, the timing of the initiation and completion of pre-clinical and clinical trials, the timing of patient enrollment and dosing in clinical trials, the timing of expected regulatory filings, the clinical utility and potential attributes and benefits of ddRNAi and our product candidates, potential future out-licenses and collaborations, our intellectual property position and duration of our patent portfolio, the ability to procure additional sources of financing, unanticipated delays, further research and development and the results of clinical trials possibly being unsuccessful or insufficient to meet applicable regulatory standards or warrant continued development, the ability to enroll sufficient numbers of subjects in clinical trials, determinations made by the US Food and Drug Administration and other governmental authorities, Benitec's ability to protect and enforce its patents and other intellectual property rights, Benitec's dependence on its relationships with its collaboration partners and other third parties, the efficacy or safety of Benitec's products and the products of Benitec's collaboration partners, the acceptance of Benitec's products and the products of Benitec's collaboration partners in the marketplace, market competition, sales, marketing, manufacturing and distribution requirements, greater than expected expenses, expenses relating to litigation or strategic activities, Benitec's ability to satisfy its capital needs through increasing its revenue and obtaining additional financing, the impact of the COVID-19 pandemic, the disease caused by the SARS-CoV-2 virus and similar events, which may adversely impact Benitec's business and pre-clinical and future clinical trials, the impact of local, regional, and national and international economic conditions and events, and other risks detailed from time to time in filings that Benitec makes with the US Securities and Exchange Commission, including our most recent annual report on Form 10-K and our reports on Form 8-K. Such statements are based on management's current expectations, but actual results may differ materially due to various factors, including those risks and uncertainties mentioned or referred to in this presentation. Accordingly, you should not rely on those forward-looking statements as a prediction of actual future results. Benitec disclaims any intent or obligation to update these forward-looking statements, except as required by law.

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Research and Development Day Agenda

01 Introduction to Speakers

02 Corporate Overview

03 OPMD Clinical and Pathophysiological Overview

04 BB-301: Mechanism of Action and Clinical Development Program

05 VFSS and Subject-Reported Outcome Measures

06 Preliminary BB-301 Phase 1b Clinical Data Summary

07 Upcoming Milestones

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Professional Biography:

Bernard Brais, MDCM, PhD

Professor, Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University Health Centre

Bernard Brais, MDCM, PhD, Professor, Department of Neurology and Neurosurgery at Montreal Neurological Institute (MNI), McGill University Health Centre (MGH, MNH) is Director of the Rare Neurological Diseases Group. He completed his MDCM, neurology residency and PhD at McGill. He is also trained as a historian of neurosciences and genetics. His research largely focuses on the genetic basis of neurogenetic disorders with founder effects in Quebec, with an increasing focus on disorders with ataxic manifestations such as Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS). Since 2007, he has headed a team of researchers on ARSACS. Dr. Brais has played important roles in identifying causal genes for Oculopharyngeal muscular dystrophy (OPMD), Hereditary Sensory and Autonomic Neuropathy type II (HSANII), Limb Girdle Muscular Dystrophy with Quadriceps atrophy (LGMD2L), Pol III-related leukodystrophies, and ZAK congenital myopathy.

Disclosures: Clinical advisor and consultant to Benitec Biopharma Inc

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Professional Biography:

Emily Plowman, PhD, CCC-SLP, FASHA, Professor, Department of Otolaryngology – Head and Neck Surgery, The Ohio State University College of Medicine is Director of the Aerodigestive Research Core across its two sites at the Ohio State University and University of Florida and Director of the Wexner Medical Center Dysphagia Program. She is an internationally recognized expert in the field of dysphagia who has held uninterrupted funding from the National Institutes of Health (NIH) since commencing her academic career in 2009. Her current research at OSU and UF are supported by the National Institute of Aging, National Institute of Nursing Research, National Institute of Cancer, Department of Defense, and the ALS Association. Dr. Plowman has authored over 85 peer-reviewed scientific manuscripts, given over 600 lectures worldwide, and obtained over 30 external research grants. In addition to her own research, Dr. Plowman is passionate about mentoring the future generation of clinician scientists and her mentorship efforts were recently recognized by the National Institutes of Health with the NINDS Story Landis Award for Outstanding Mentorship by a Neuroscientist (2022) and the University of Florida Doctoral Mentor of the Year award (2021). She was inducted into the American Speech and Hearing Association as a Fellow in 2022 and was elected to be the incoming President of the international Dysphagia Research Society for 2026.

Disclosures: Clinical advisor and consultant to Benitec Biopharma Inc

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Benitec Corporate Overview

Jerel A. Banks, MD, PhD

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Corporate Highlights

Novel Technology Platform

- Benitec's DNA-directed RNA interference (ddRNAi) platform combines gene therapy with RNA interference (RNAi) to simultaneously silence & replace disease-causing genes permanently, following a single administration
- Platform has application in diseases that cannot be treated with gene silencing or gene therapy alone

Lead Asset Entered Clinical Evaluation in Orphan Disease in November 2023

- BB-301 is being developed to treat dysphagia (difficulty swallowing) in subjects with Oculopharyngeal Muscular Dystrophy (OPMD). There are no therapies approved for the treatment of OPMD. The estimated prevalence in the US, Europe, Canada & Israel is 15k subjects.
- Compelling preclinical data demonstrated complete restoration of muscle function in vivo via a murine disease model
- The Investigational New Drug (IND) application for BB-301 was approved to proceed by the FDA in June 2023, and the first study subject was safely dosed in the BB-301 Phase 1b/2a clinical trial (NCT06185673) in November 2023

Significant Near-Term Milestones

- Preliminary clinical safety data and clinical efficacy data for the BB-301 Phase 1b/2a clinical trial are expected in 2024

Seasoned Management Team

- Benitec's management team has broad expertise in gene therapy development, biological manufacturing and capital allocation

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Experienced and Efficient Management

Jerel A. Banks, MD, PhD

CEO & Executive Chairman

Healthcare investment professional with over 15 years of experience

Former Vice president & co-portfolio manager at Franklin Templeton Investments

M.D., Ph.D. Brown University; A.B. Princeton University

Megan Boston

Executive Director

CEO & managing director of multiple ASX-listed entities

Chartered Accountant with over 20 years of experience

Held senior executive roles at various banking institutions in risk and compliance as well as PricewaterhouseCoopers

Claudia Kloth, PhD

SVP of Manufacturing

Over 20 years of cGMP manufacturing & process development experience in therapeutics

Led process development group at Lonza Viral Therapeutics

Developed, optimized, and transferred robust viral-based products (Ad5, AAV, lentivirus) to cGMP manufacturing

Guided process transfer & validation activities of Yervoy (BMY)

Oculopharyngeal Muscular Dystrophy: Clinical and Pathophysiological Overview

Bernard Brais, MDCM, PhD

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OPMD: A Chronic, Progressive Disease With No Approved Therapeutics

- Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant, chronic, myopathic disorder characterized by ptosis (drooping of the upper eyelid) and progressive dysphagia (loss of the ability to swallow) due to impairment of the muscles of the eyelids and throat.
- Typical age of onset in the 40s-50s, and affects approximately 15k adults in the US, Canada, Europe and Israel.
- Progressive dysphagia increases the risks of severe malnutrition and potentially life-threatening aspiration pneumonia.
- In OPMD, a genetic mutation results in trinucleotide repeat expansion within exon 1 of PABPN1 producing an expanded poly-alanine tract at the N-terminal end of the PABPN1 protein:

Wildtype: ATG $(GCG)_6$ ---------- $(GCA)_3$ GCG GGG GCT GCG…

OPMD Mutant: ATG $(GCG)_6$ **$(GCN)_{1-7}$** $(GCA)_3$ GCG GGG GCT GCG…

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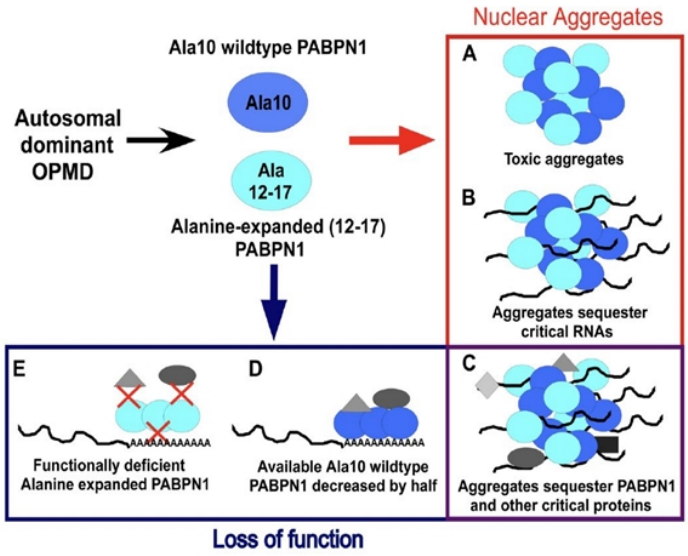
Models for OPMD Pathogenesis

- Currently two general models are used to explain how alanine-expanded PABPN1 confers muscle pathology in autosomal dominant OPMD where patients have one normal and one mutant allele of PABPN1
- One model suggests that nuclear aggregates cause disease (right column, outlined in red)
- A second model suggests that loss of PABPN1 function (bottom row, outlined in blue) underlies pathology



Banerjee, A, FEBS J., 2013

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Key Epidemiological Estimates for OPMD:

At Least 15k adults in the United States, Canada, Europe and Israel

- OPMD has a global distribution and has been diagnosed in at least 33 countries
- The estimated prevalence in Western countries is 1:100,000
- Large patient cohorts exist in the United States (e.g., the University of New Mexico Patient Data-Base comprises several hundred subjects)
- Literature-based prevalence estimate for Europe is 1:100,000
- Literature-based prevalence estimate for the French-Canadian population is 1:1,000
- Literature-based prevalence estimates for Bukhara Jews in Israel is 1:600

Country/Province/Region	Estimated Population	OPMD Prevalence Estimate	Estimated OPMD Patient Population
United States	333,000,000	0.00001	**3,330**
Quebec	8,500,000	0.001	**8,500**
Europe	742,000,000	0.00001	**7,420**

Abu-Baker et al, 2007; Raz et al, 2014

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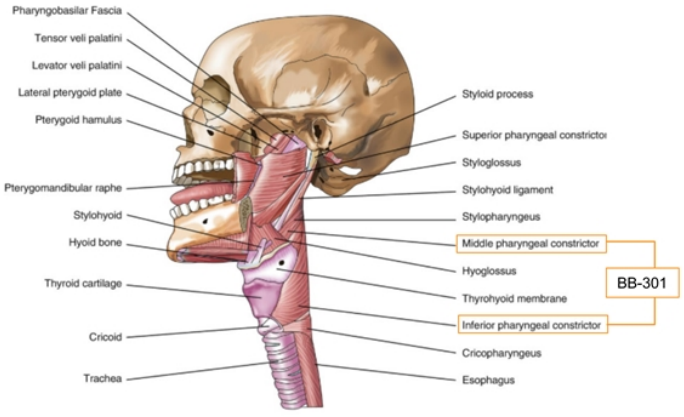
Swallowing Overview

Normal vs. Disordered Swallowing

- Under normal conditions, a food bolus leaves the oral cavity and is able to traverse the length of the pharynx, en route to the esophagus, via the propulsive activity of the coordinated constriction of the superior, middle, and inferior pharyngeal constrictor muscles
- As the food bolus nears the opening of the upper esophagus, the subsequent relaxation of the cricopharyngeal muscle allows the bolus to enter the esophagus and travel to the stomach
- In OPMD, the pharyngeal constrictor muscles are weakened and atrophic and, as a result, are unable to consistently exert the level of force required to support the propulsion of the food bolus that defines the normal swallowing process

Anatomical Structures of the Pharynx



Muscles Of Pharyngx: Lateral view

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OPMD: Onset and Progression

- More frequent choking
- Prolonged mealtime
- Avoidance of specific foods (e.g., rice, chicken, toast, etc.)
- Drooping eyelids that are often asymmetrical at disease onset
- Absence of limb weakness at disease onset

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OPMD: Clinical Presentation

- A retrospective chart review was conducted at the Saguenay Neuromuscular Clinic (Quebec, Canada)
- All health record of patients with an OPMD diagnosis were screened to identify patients who met inclusion criteria
- Patients were excluded if another neurological or musculoskeletal disorder was present that could impact the evolution of the disease
- **Dysphagia was present in 96.6% of subjects**
- **Pharyngeal pooling of thickened secretions was present in 74.1% of subjects**
- **Dysphagia worsens over time and, as a result, patients can develop malnutrition and aspiration pneumonia which can lead to death**

TABLE 1 Population characteristics (n = 333)

Characteristics	n (%)
Sex	
Male	166 (49.8)
Female	167 (50.2)
Transmission (n = 321)	
Paternal	167 (52.0)
Maternal	154 (48.0)
PABN1 test source	
Patient	254 (76.3)
Family member	80 (23.7)
First degree	56 (16.8)
Second degree	16 (4.8)
Third degree	5 (1.5)
Fourth degree	3 (0.9)
Ptosis (n = 332)	
Present	321 (96.7)
Absent	11 (3.3)
Dysphagia (n = 329)	
Present	318 (96.6)
Absent	11 (3.4)
Lower limb proximal weakness (n = 331)	
Present	287 (86.7)
Absent	44 (13.3)
Fatigue (n = 250)	
Present	220 (88.0)
Absent	30 (12.0)
Dysphonia	
Present	168 (50.5)
Absent	165 (49.5)
Pharyngeal pooling of thickened secretions (n = 220)	
Present	163 (74.1)
Absent	57 (25.9)

Brisson, JD, Muscle & Nerve, 2020

OPMD: Clinical Presentation (continued)

Median age at symptom onset as reported by the subject:

- Dysphagia onset at 54 years of age
- Pharyngeal pooling of thickened secretions onset at 66 years of age

Symptom	N[a]	Age at symptom onset (years)	
		Median	Range
Ptosis[b]	261	54	40–77
Dysphagia[b]	272	54	38-77
Lower limb proximal weakness[b]	199	58	41–77
Fatigue[c]	219	64	39-85
Dysphonia[c]	165	65	43-83
Pharyngeal pooling of thickened secretions[c]	161	66	51–85

[a]Number of data for each symptom.
[b]Age of symptom onset as reported by the patient.
[c]Age of the patient when symptom was first recorded in the medical record.

Brisson, JD, Muscle & Nerve, 2020

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OPMD: Clinical Presentation (continued)

Subjects may present with:

- Ptosis (drooping of the upper eyelid) and dysphagia (difficulty swallowing) together
- Ptosis, followed by dysphagia (median of 3.0 years following initial presentation of ptosis)
- Dysphagia, followed by ptosis (median of 5.0 years following initial presentation of dysphagia)

First symptom	Age, median (range), years	Latency before onset of a second symptom (ptosis or dysphagia), median (range), years	Latency before onset of proximal weakness, median (range), years
Ptosis	52.0 (40–71), n = 99	3.0 (1–19)	7.0 (0–21), n = 65
Dysphagia	50.0 (38–65), n = 81	5.0 (1–20)	6.0 (0–25), n = 50
Ptosis and dysphagia	53.5 (40–77), n = 46	—	4.0 (0–21), n = 28

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OPMD: Clinical Complications and Causes of Death

Approximately one third of subjects had respiratory diagnoses listed as the cause of death:

- Impaired swallowing (dysphagia) can lead to aspiration pneumonia
- Pneumonia can result from the aspiration of food and/or liquid
- Pneumonia can also result from the aspiration of thickened pharyngeal secretions

	n (%)
Diseases of the respiratory system	34 (31.5%)
Aspiration pneumonia	18 (16.7%)
Influenza or pneumonia of unspecified etiology	12 (11.1%)
Other respiratory disease	3 (2.8%)
Chronic lower respiratory disease	1 (0.9%)
Neoplasms	19 (17.6%)
Diseases of the circulatory system	9 (8.3%)
Heart failure	5 (4.6%)
Cardiac problem	3 (2.8%)
Cerebrovascular disease	1 (0.9%)
Others	9 (8.3%)
Hip fracture complications	3 (2.8%)
OPMD not otherwise specified	2 (1.9%)
Malnutrition	1 (0.9%)
Suicide	1 (0.9%)
Hepatic cirrhosis	1 (0.9%)
Urinary tract infection	1 (0.9%)
Unknown	37 (34.3%)
Total	108 (100%)

Brisson, JD, Muscle & Nerve, 2020

Clinical Management of Dysphagia

- Nutritional recommendations including adaptations
- Surgical Interventions for moderate to severe dysphagia:
  - Cricopharyngeal muscle paralysis with botulinum toxin injection (temporary effect in some patients, requires repeated administration)
  - Cricopharyngeal muscle dilation (temporary effect, requires repeated application)
  - Cricopharyngeal myotomy (clinical/subject-reported outcomes suggest temporary delay of disease progression)
- In all cases the pharyngeal constrictor muscles continue to atrophy, leading to progressive loss of pharyngeal propulsion/clearance of food and liquid into the esophagus

BB-301: Mechanism of Action and Clinical Development Program

Jerel A. Banks, MD, PhD

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BB-301 Construct Design and Mechanism of Action

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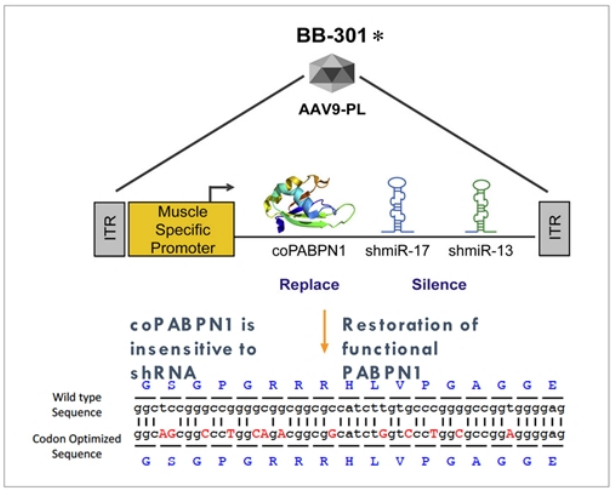
BB-301 Simultaneously Silences Mutant PABPN1 & Delivers Wildtype PABPN1 To Restore Normal Myocyte Function

PABPN1 in OPMD

- PABPN1 is a ubiquitous protein that controls the length of mRNA poly(A) tails, mRNA export from the nucleus & alternative poly(A) site usage
- The PABPN1 mutant protein underlying OPMD is aggregation prone due to an N-terminal expanded poly-alanine tract of up to 18 contiguous alanine residues, and drives the formation of intranuclear inclusions (INIs) in the myocytes
- INIs also sequester wildtype PABPN1 and may contribute to the "loss of function" phenotype associated with OPMD



* Strings-Ufombah, et al., Molecular Therapy: Nucleic Acids, Vol. 24, 67-78, June 2021

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ddRNAi Platform Enables Both Permanent Silencing AND Replacement of Mutated Genes in the Target Tissue

LIMITATIONS OF CURRENT siRNA TECHNOLOGIES:

Requires repeated administration

Enables only transient silencing of mutated gene

Silencing capacity restricted to a single gene

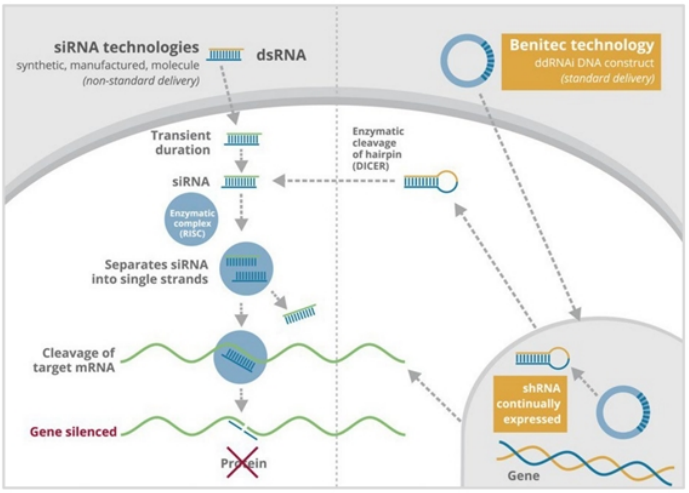
ADVANTAGES OF THE ddRNAi PLATFORM:

Long-term therapeutic potential from a single administration

Constant, steady-state levels of shRNA expression enables permanent silencing of mutated gene

Provides permanent expression of wildtype gene where activity is necessary for function or viability

Silence a single gene or multiple genes simultaneously



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BB-301 Silenced and Replaced PABPN1 Over a Broad Range of Doses in the A17 Mouse Model of OPMD

Varying levels of inhibition of PABPN1 expression, when coupled with partial replacement of wildtype PABPN1, significantly:

- Reduced INIs
- Increased muscle force generation
- Corrected disease phenotype

		"Silence"	"Replace"
BB-301 Dose (vg)		Inhibition of PABPN1	coPABPN1 Expression
7.50×10^{11}	Phase 1b Cohort 3 Analog	86%	63%
2.50×10^{11}	Phase 1b Cohort 2 Analog	75%	26%
5.00×10^{10}	Phase 1b Cohort 1 Analog	31%	2%
1.00×10^{10}		32%	1%
2.00×10^{9}		14%	0%
4.00×10^{8}		0%	0%

PABPN1 inhibition levels of ≥31% led to complete resolution of OPMD disease symptoms and correction of histological hallmarks

Data from Strings-Ufombah, et al, Molecular Therapy: Nucleic Acids, Vol. 24, 67-78, June 2021 VG = Viral Genomes

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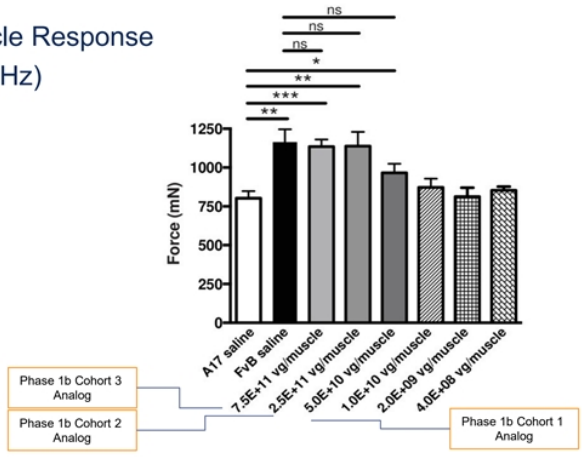
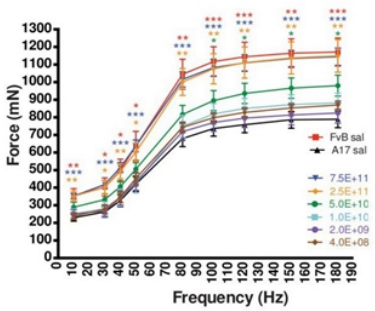
BB-301 Restored Muscle Strength to Wildtype Levels in A17 Model

At 14-weeks post intramuscular administration of BB-301, statistically significant improvements in muscle strength and complete phenotypic correction were achieved at doses ≥ 5.00 x 1010 vg

Muscle Response (150 Hz)



Muscle Response (10-190 Hz)



Data from Strings-Ufombah, et al, Molecular Therapy: Nucleic Acids, Vol. 24, 67-78, June 2021

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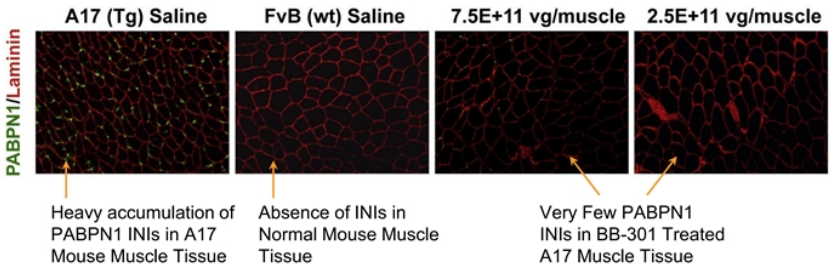
Dose-Dependent Resolution of INIs in Injected Muscles of A17 Mouse Model of OPMD

Immunofluorescence Staining of INIs in Mouse Muscle Tissue



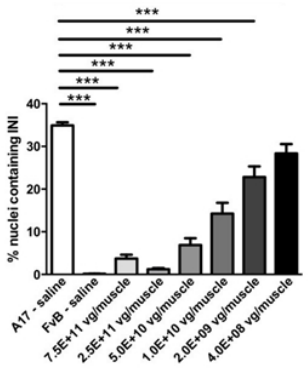
Heavy accumulation of PABPN1 INIs in A17 Mouse Muscle Tissue

Absence of INIs in Normal Mouse Muscle Tissue

Very Few PABPN1 INIs in BB-301 Treated A17 Muscle Tissue

At higher doses, BB-301 eliminated nearly all PABPN1 INIs in A17 Mouse Muscle Tissue 14 weeks after intramuscular administration

Quantitative Analysis of INIs in Mouse Muscle Tissue



Data from Strings-Ufombah, et al., Molecular Therapy: Nucleic Acids, Vol. 24, 67-78, June 2021

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The Rationale for BB-301 in OPMD

- In OPMD, the pharyngeal constrictor muscles are weakened and atrophic and, as a result, are unable to consistently exert the level of force required to support the propulsion of the food and liquid bolus
- In the preclinical efficacy studies for BB-301 carried out in the A17 mouse model, direct intramuscular injection of BB-301 facilitated increases in muscle cross-sectional area, increases in muscle mass, and increases in muscle force generating capacity relative to untreated A17 mice
- In the Beagle dog BB-301 dosing studies, intramuscular injections of BB-301 into the pharyngeal constrictor muscles supported dose-dependent tissue transduction, transgene expression, and target gene knockdown in the injected muscles
- Restoration of muscle fiber size and muscle force generating capacity in the weakened and atrophic pharyngeal constrictor muscles of OPMD patients following BB-301 administration would be expected to meaningfully enhance the ability of the pharyngeal constrictor muscles to support food bolus propulsion through the pharynx and towards the esophagus, reducing dysphagia in OPMD patients

BB-301 Clinical Development Program

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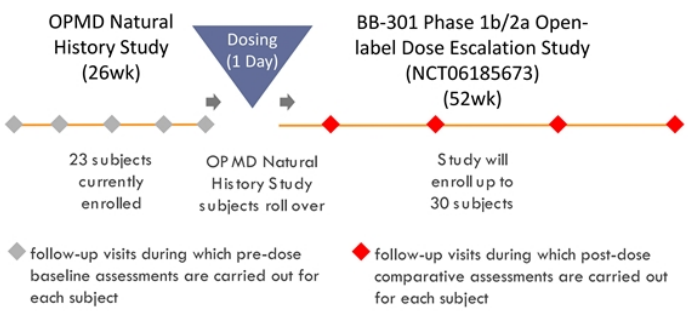
BB-301 Clinical Development Program and Key Efficacy Assessments

Characterization of OPMD subject disposition at baseline assessing:

- Rates of progression of dysphagia via quantitative radiographic measures of swallowing efficiency and pharyngeal constrictor muscle function (using Videofluoroscopic Swallowing Studies (VFSS)), and subject-reported oropharyngeal dysphagia
- 23 subjects enrolled as of January 2024



- First subject entered the Phase 1b/2a Clinical Trial (NCT06185673) in 4Q23, and the second subject was enrolled in February 2024
- Efficacy endpoints are defined statistically as the change from Baseline at Day 90, Day 180, Day 270, and Day 360 of the clinical and videofluoroscopic endpoints
- Baseline for each subject is defined as the mean of the respective assessments completed for each study endpoint during all clinical and videofluoroscopic assessments of the NH study prior to receiving BB-301 in the phase 1b/2a study

Endpoints

- **Primary:** Safety and tolerability
- **Secondary: VFSS** measures of pharyngeal constrictor muscle function, swallowing efficiency, and subject-reported oropharyngeal dysphagia as compared to analogous assessments completed during the OPMD Natural History Study
- 2 subjects enrolled as of February 2024

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Outcome Measures for the OPMD Natural History Study and the BB-301 Phase 1b/2a Clinical Study (NCT06185673)

Videofluoroscopic Swallowing Study Assessments

Global Swallowing Function

Dynamic Imaging Grade of Swallowing Toxicity Scale

Pharyngeal Constrictor Muscle Function

Pharyngeal Area at Maximum Constriction

Pharyngeal Constriction Ratio

Swallowing Efficiency

Total Pharyngeal Residue

Vallecular Residue

Pyriform Sinus Residue

Other Pharyngeal Residue

Normalized Residue Ratio Scale

Clinical Assessments

Other Assessments

Clinical measures of swallowing capacity & dysphagia (including timed-based and volume-based drinking tests)

Patient-reported measures of dysphagia

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Videofluoroscopic Swallowing Studies and Subject-Reported Outcome Measures: Clinical and Methodological Overview

Emily Plowman, PhD, CCC-SLP, FASHA

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Key Videofluoroscopic and Subject-Reported Endpoints

The primary and secondary outcome measures for the OPMD Natural History Study and the BB-301 Phase 1b/2a Clinical Study (NCT06185673) facilitate serial characterization of:

- Pharyngeal Constrictor Muscle Function
- Swallowing Efficiency
- Subject-Reported Oropharyngeal Dysphagia

Swallowing tasks employed during the conduct of the VFSS are effort independent

Videofluoroscopic swallowing studies are employed to complete several of the analyses outlined above, and the imaging results are reviewed and rated via a standardized, blinded process

- Blinded central review of the respective fluoroscopic images by multiple independent Speech Language Pathologists is used for all assessments
- Individual reviewers are assigned fluoroscopic studies to review and rate in a blinded manner (i.e., no knowledge of the other rater's scores, subject ID, task, consistency, volume, time point)
- The ratings are completed in full, and discrepancies are resolved during a consensus meeting

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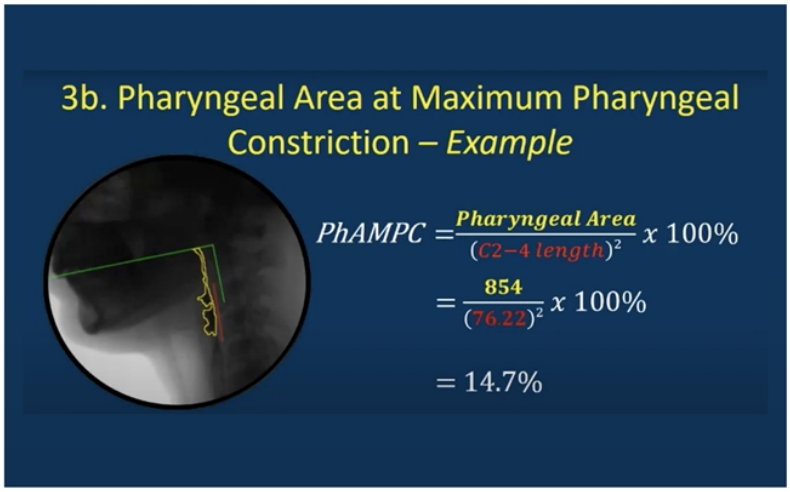
Pharyngeal Constrictor Muscle Function: PhAMPC

Pharyngeal constrictor muscle function as estimated by PhAMPC:



- C2-C4 length act as an anatomical scalar
- "Pharyngeal Area" measurement comprises the area of visible airspace or bolus at maximal constriction
- Measurement (yellow) occurs on the frame of tightest constriction of the pharyngeal lumen during the swallow
- Normal PhAMPC values span the range of 0% to 2.2% for the characteristic food and liquids that are evaluated in the swallowing tasks discussed in this presentation
- On the final follow-up visit prior to receiving BB-301, the first subject enrolled in the phase 1b study presented with PhAMPC values in the range of 15.8% to 24.2%

Steele, C., et al. ASHA 2019 Convention Session on the ASPEKT C Method of Videofluoroscopy Analysis

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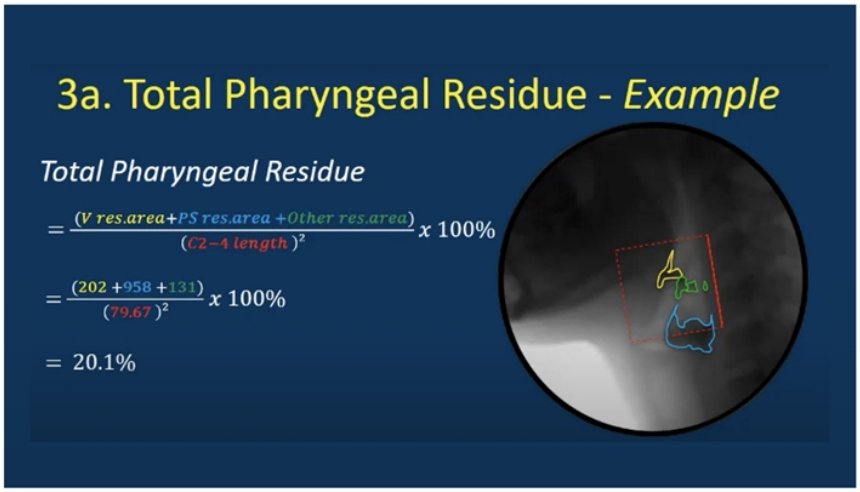
Swallowing Efficiency: Total Pharyngeal Residue

Swallowing Efficiency as measured by Total Pharyngeal Residue:



- C2-C4 length act as an anatomical scalar
- "Total Pharyngeal Residue" measurement comprises the amount of material remaining in the pharynx after the first swallow of the bolus
- Measurement (yellow, green, and blue) occurs on the first frame showing pyriform sinuses at lowest position
- Normal Total Pharyngeal Residue values should be close to zero
- On the final follow-up visit prior to receiving BB-301, the first subject enrolled in the phase 1b study presented with Total Pharyngeal Residue values in the range of 7.7% to 22.5%

Steele, C., et al. ASHA 2019 Convention Session on the ASPEKT C Method of Videofluoroscopy Analysis

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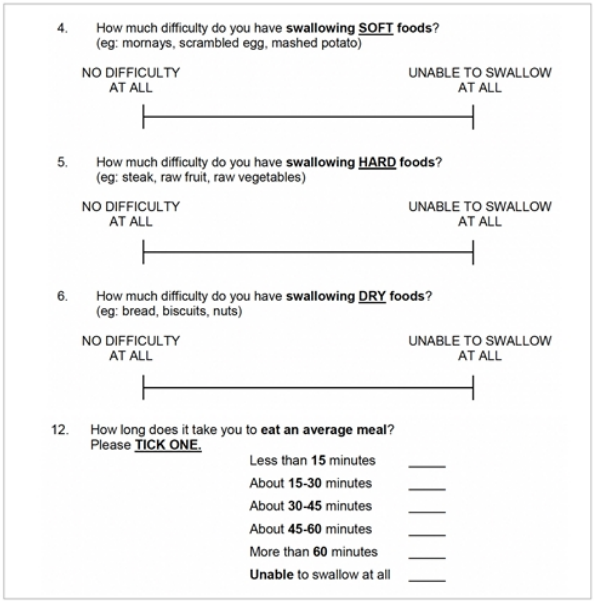
Subject-Reported Oropharyngeal Dysphagia: Sydney Swallow Questionnaire (SSQ)

Subject-reported oropharyngeal dysphagia as assessed by the SSQ:

- The SSQ is a self-report inventory assessing subjective symptoms of oropharyngeal dysphagia with strong content, construct, discriminant, and predictive validity and test-retest reliability in a range of patient populations
- The SSQ is a 17-item questionnaire which was developed to measure symptomatic severity of oral-pharyngeal dysphagia as reported by the affected subject
- The questionnaire uses a 100-mm long visual analogue scale for all but 1 question
- Possible scores range from 0 to 1700, with higher scores indicating greater swallowing difficulty
- Healthy Subjects without dysphagia present with a mean score of 59.0
- On the final follow-up visit prior to receiving BB-301, the first subject enrolled in the phase 1b study presented with an SSQ score of 1264



4. How much difficulty do you have **swallowing SOFT foods**?
(eg: mornays, scrambled egg, mashed potato)

NO DIFFICULTY AT ALL — UNABLE TO SWALLOW AT ALL

5. How much difficulty do you have **swallowing HARD foods**?
(eg: steak, raw fruit, raw vegetables)

NO DIFFICULTY AT ALL — UNABLE TO SWALLOW AT ALL

6. How much difficulty do you have **swallowing DRY foods**?
(eg: bread, biscuits, nuts)

NO DIFFICULTY AT ALL — UNABLE TO SWALLOW AT ALL

12. How long does it take you to **eat an average meal**?
Please **TICK ONE**.

- Less than **15** minutes ____
- About **15-30** minutes ____
- About **30-45** minutes ____
- About **45-60** minutes ____
- More than **60** minutes ____
- **Unable** to swallow at all ____

Szczesniak, M., et al, Dysphagia, 2014

Clinically Meaningful Improvements

Clinically meaningful improvement over the course of the BB-301 clinical development program will be defined by:

- Improvements in Subject-Reported Outcome assessments (i.e., reductions in the Sydney Swallow Questionnaire ["SSQ"] Scores) post BB-301 dose and Reductions in Total Pharyngeal Residue (i.e., reductions in the total food or liquid material remaining in the pharynx at the completion of swallowing) post BB-301 dose

Specific attention will be given to the following:

- Improvements in Subject-Reported Outcome assessments (i.e., SSQ Scores) post BB-301 dose that are accompanied by similar improvements in videofluoroscopic swallowing study assessments (i.e., reductions in PhAMPC% and/or reductions in Total Pharyngeal Residue across one or more consistencies of liquid and/or solid food)
- Improvements in the results of individual outcome measures post BB-301 dose as compared to the results of the analogous assessments conducted at Visit 1 of the OPMD Natural History Study (i.e., 6 to 12 months prior to the receipt of BB-301)

Preliminary BB-301 Phase 1b Clinical Data Summary for the First Subject (Day 90)

Jerel A. Banks, MD, PhD

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Key Questions for Subject 1 of the Phase 1b Study

Subject 1 experienced disease progression during their enrollment in the Natural History Study

In this regard, several critical questions emerged with respect to the potential impact of BB-301:

- Would BB-301 slow progression, halt, or improve dysphagia in this study subject?
- Would the current, low dose of BB-301 be sufficiently biologically active to facilitate a benefit in this study subject? Would this benefit be visible at the first follow-up assessments conducted at Day 90 post-dose?
- Would BB-301 cause any Serious Adverse Events?

VFSS: PhAMPC Results

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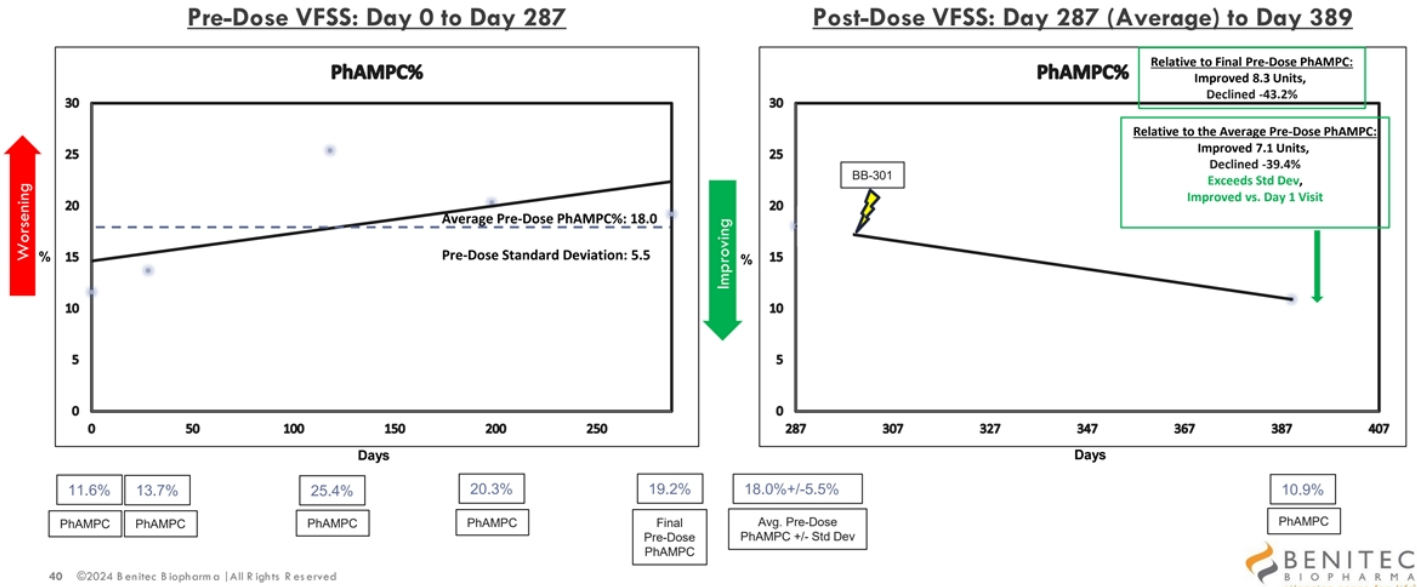
PhAMPC: Solid Food (*Declines Below SD and NH Study Screening Visit at Day 0*)

BB-301 administered on Day 296 (as designated by the yellow bolt)



11.6% PhAMPC | 13.7% PhAMPC | 25.4% PhAMPC | 20.3% PhAMPC | 19.2% Final Pre-Dose PhAMPC | 18.0%+/-5.5% Avg. Pre-Dose PhAMPC +/- Std Dev | 10.9% PhAMPC

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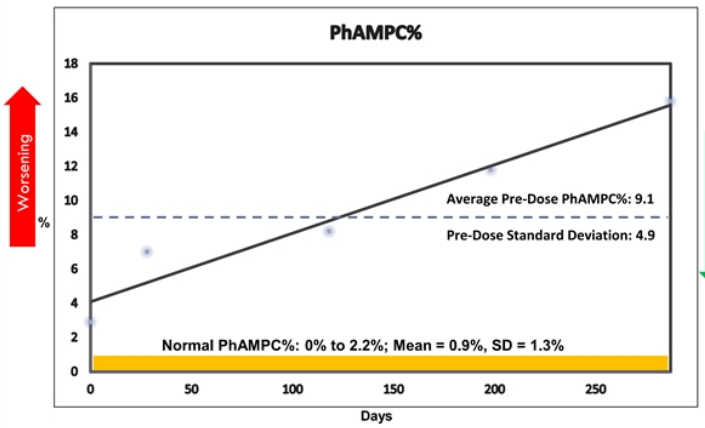
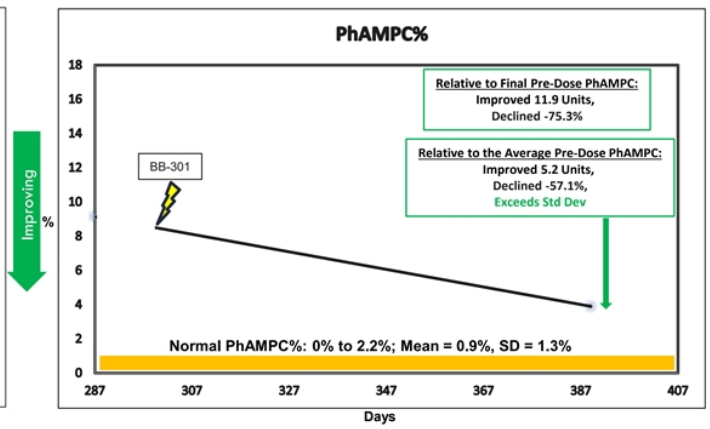
PhAMPC: Thin Liquid, 5 mL (*Declines Below SD Post-Dose*)

BB-301 administered on Day 296 (as designated by the yellow bolt)

Pre-Dose VFSS: Day 0 to Day 287



Post-Dose VFSS: Day 287 (Average) to Day 389



2.9% PhAMPC | 7.0% PhAMPC | 8.2% PhAMPC | 11.8% PhAMPC | 15.8% Final Pre-Dose PhAMPC | 9.1%+/-4.9% Avg. Pre-Dose PhAMPC +/- Std Dev | 3.9% PhAMPC

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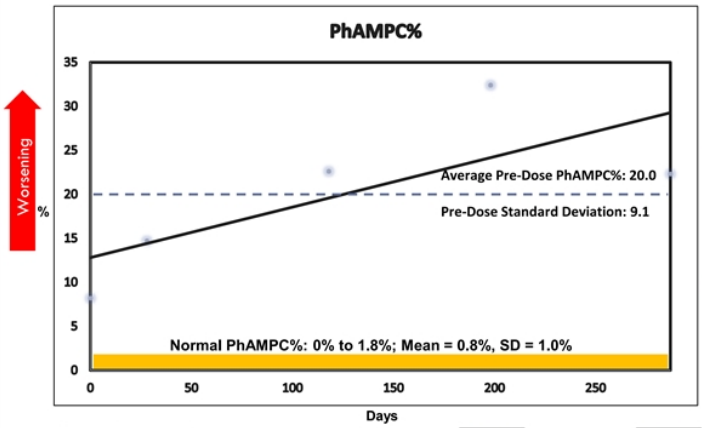
PhAMPC: Moderately Thick Liquid

BB-301 administered on Day 296 (as designated by the yellow bolt)

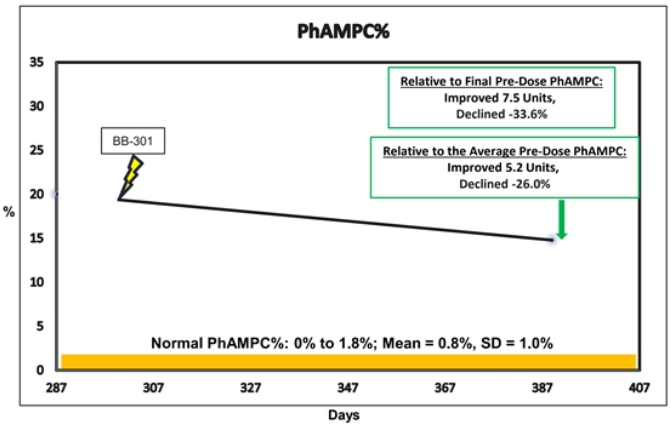
Pre-Dose VFSS: Day 0 to Day 287



8.2% PhAMPC | 14.7% PhAMPC | 22.6% PhAMPC | 32.4% PhAMPC | 22.3% Final Pre-Dose PhAMPC

Improving

Post-Dose VFSS: Day 287 (Average) to Day 389



20.0%+/-9.1% Avg. Pre-Dose PhAMPC +/- Std Dev

14.8% PhAMPC

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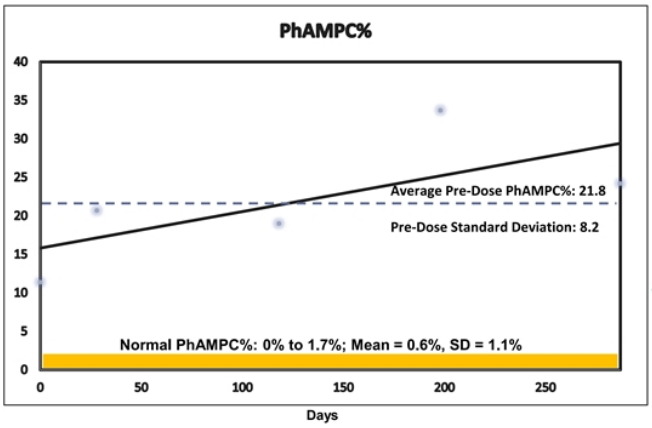
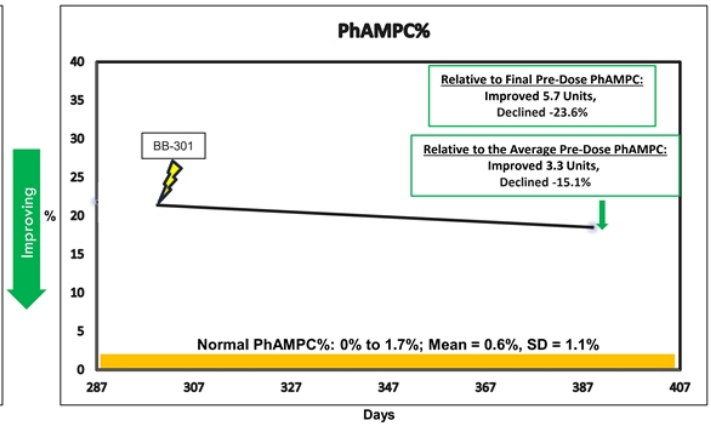
PhAMPC: Extremely Thick Liquid

BB-301 administered on Day 296 (as designated by the yellow bolt)

Pre-Dose VFSS: Day 0 to Day 287



Post-Dose VFSS: Day 287 (Average) to Day 389



11.3%	20.7%	19.0%	33.7%	24.2%	21.8%+/-8.2%	18.5%
PhAMPC	PhAMPC	PhAMPC	PhAMPC	Final Pre-Dose PhAMPC	Avg. Pre-Dose PhAMPC +/- Std Dev	PhAMPC

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Improvement was Observed Across all PhAMPC Assessments

Average Pre-Dose PhAMPC Values vs. Day 90 PhAMPC Values

Radiographic Assessments of Pharyngeal Area at Maximum Constriction to Determine Pharyngeal Constrictor Muscle Function During Swallowing

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Average PhAMPC During Swallowing	Day 90 PhAMPC During Swallowing	Improvement in Pharyngeal Closure During Swallowing After BB-301 Dose
Thin Liquid	9.1	3.9	5.2 Units (-57.1%)
Moderately Thick Liquid	20.0	14.8	5.2 Units (-26.0%)
Extremely Thick Liquid	21.8	18.5	3.3 Units (-15.1%)
Solid Food	18.0	10.9	7.1 Units (-39.4%)

Final Pre-Dose PhAMPC Values vs. Day 90 PhAMPC Values

Radiographic Assessments of Pharyngeal Area at Maximum Constriction to Determine Pharyngeal Constrictor Muscle Function During Swallowing

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Final Pre-Dose PhAMPC During Swallowing	Day 90 PhAMPC During Swallowing	Improvement in Pharyngeal Closure During Swallowing After BB-301 Dose
Thin Liquid	15.8	3.9	11.9 Units (-75.3%)
Moderately Thick Liquid	22.3	14.8	7.5 Units (-33.6%)
Extremely Thick Liquid	24.2	18.5	5.7 Units (-23.6%)
Solid Food	19.2	10.9	8.3 Units (-43.2%)

VFSS:
Total Pharyngeal Residue Results

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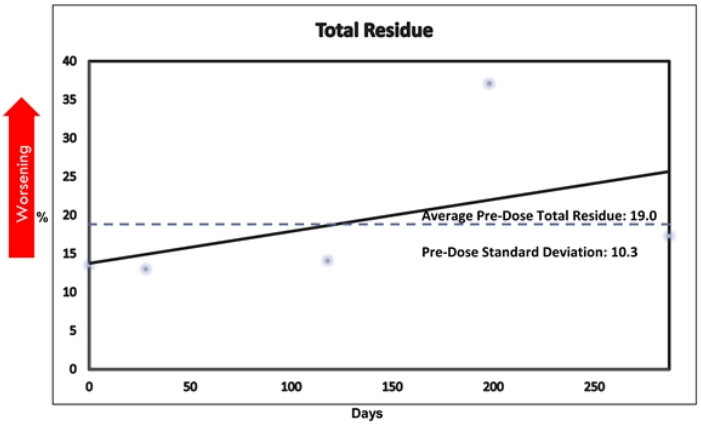
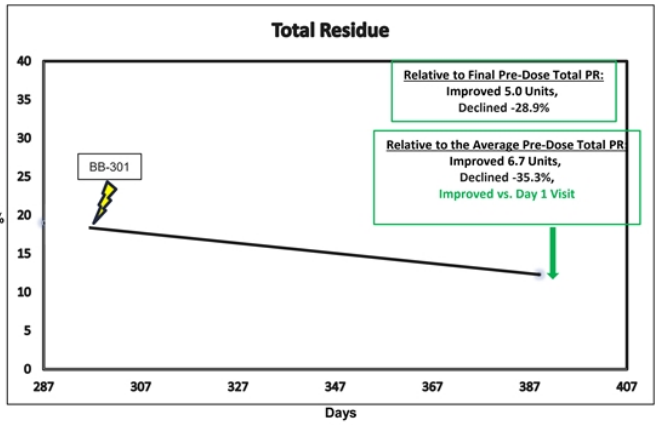
Total Pharyngeal Residue: Solid Food (*Declines Below NH Study Screening Visit at Day 0*)

BB-301 administered on Day 296 (as designated by the yellow bolt)

Pre-Dose VFSS: Day 0 to Day 287



Post-Dose VFSS: Day 287 (Average) to Day 389



13.5% Total PR	13.0% Total PR	14.1% Total PR	37.1% Total PR	17.3% Final Pre-Dose Total PR	19.0%+/-10.3% Avg. Pre-Dose Total PR +/- Std Dev	12.3% Total PR

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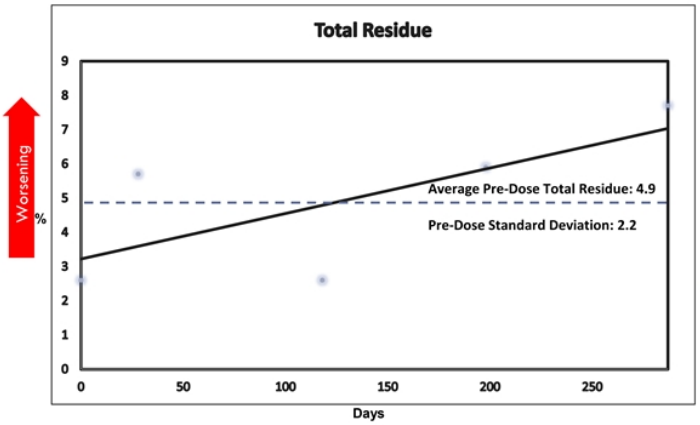
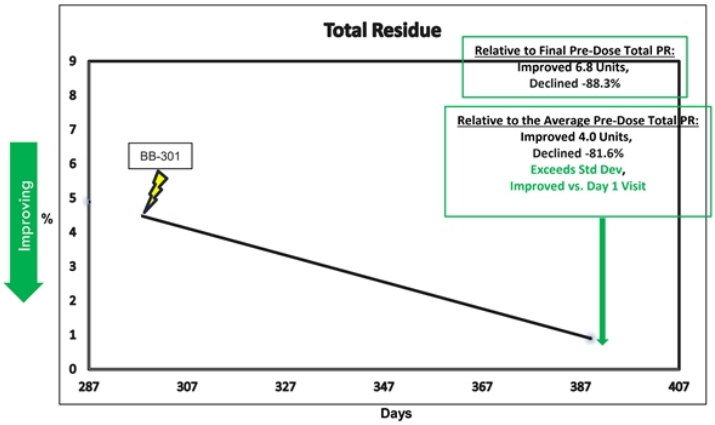
Total Pharyngeal Residue: Thin Liquid, 5 mL (*Declines Below SD and NH Study Screening Visit at Day 0*)

BB-301 administered on Day 296 (as designated by the yellow bolt)

Pre-Dose VFSS: Day 0 to Day 287



Post-Dose VFSS: Day 287 (Average) to Day 389



2.6% Total PR	5.7% Total PR	2.6% Total PR	5.9% Total PR	7.7% Final Pre-Dose Total PR	4.9%+/-2.2% Avg. Pre-Dose Total PR +/- Std Dev	0.9% Total PR

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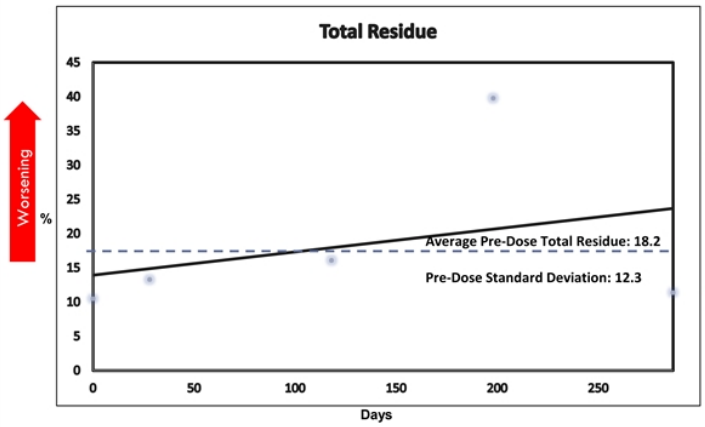
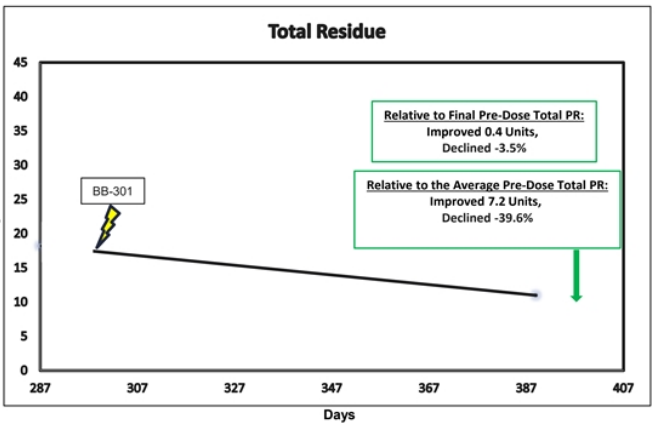
Total Pharyngeal Residue: Moderately Thick Liquid

BB-301 administered on Day 296 (as designated by the yellow bolt)

Pre-Dose VFSS: Day 0 to Day 287



Post-Dose VFSS: Day 287 (Average) to Day 389



10.5%	13.3%	16.1%	39.8%	11.4%	18.2%+/-12.3%	11.0%
Total PR	Total PR	Total PR	Total PR	Final Pre-Dose Total PR	Avg. Pre-Dose Total PR +/- Std Dev	Total PR

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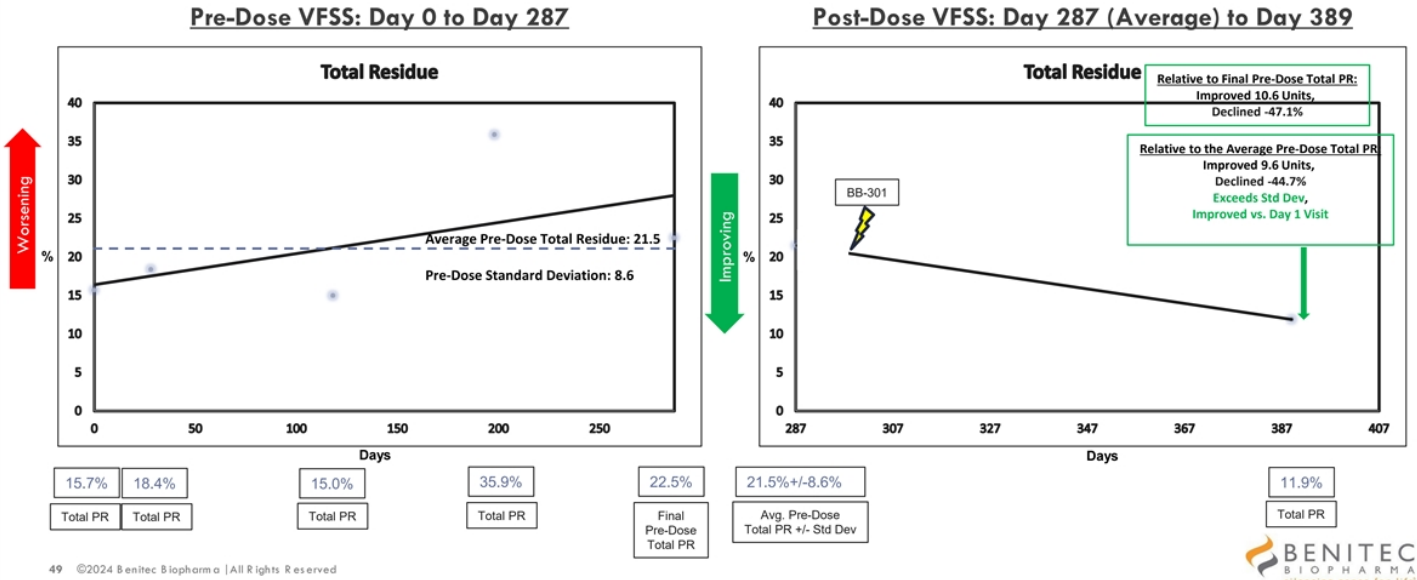
Total Pharyngeal Residue: Extremely Thick Liquid (*Declines Below SD and NH Study Screening Visit at Day 0*)

BB-301 administered on Day 296 (as designated by the yellow bolt)



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Improvement was Observed Across all Total Pharyngeal Residue Assessments

Average Pre-Dose Total Pharyngeal Residue Values vs. Day 90 Total Pharyngeal Residue Values

Radiographic Assessments of Pharyngeal Residue (i.e., food or liquid material) Remaining Post-Swallow to Determine Swallowing Efficiency

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Average Pharyngeal Residue Remaining Post-Swallow	Day 90 Pharyngeal Residue Remaining Post-Swallow	Reduction in Post-Swallow Pharyngeal Residue After BB-301 Dose
Thin Liquid	4.9	0.9	4.0 Units (-81.6%)
Moderately Thick Liquid	18.2	11.0	7.2 Units (-39.6%)
Extremely Thick Liquid	21.5	11.9	9.6 Units (-44.7%)
Solid Food	19.0	12.3	6.7 Units (-35.3%)

Final Pre-Dose Total Pharyngeal Residue Values vs. Day 90 Total Pharyngeal Residue Values

Radiographic Assessments of Pharyngeal Residue (i.e., food or liquid material) Remaining Post-Swallow to Determine Swallowing Efficiency

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Final Pre-Dose Pharyngeal Residue Remaining Post-Swallow	Day 90 Pharyngeal Residue Remaining Post-Swallow	Reduction in Post-Swallow Pharyngeal Residue After BB-301 Dose
Thin Liquid	7.7	0.9	6.8 Units (-88.3%)
Moderately Thick Liquid	11.4	11.0	0.4 Units (-3.5%)
Extremely Thick Liquid	22.5	11.9	10.6 Units (-47.1%)
Solid Food	17.3	12.3	5.0 Units (-28.9%)

Cold Water Timed Drinking Test (CWDT) Results

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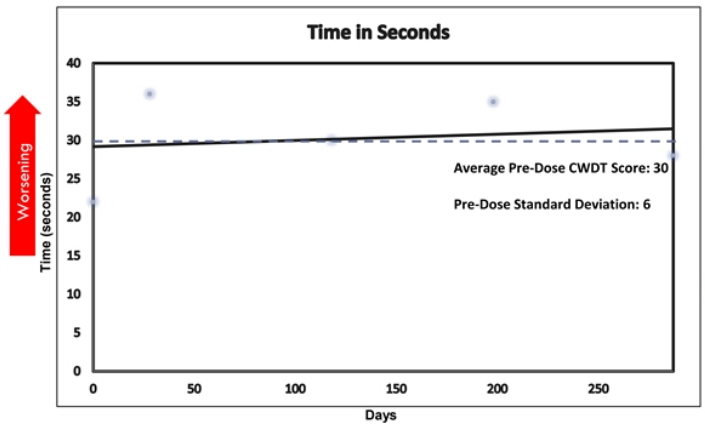
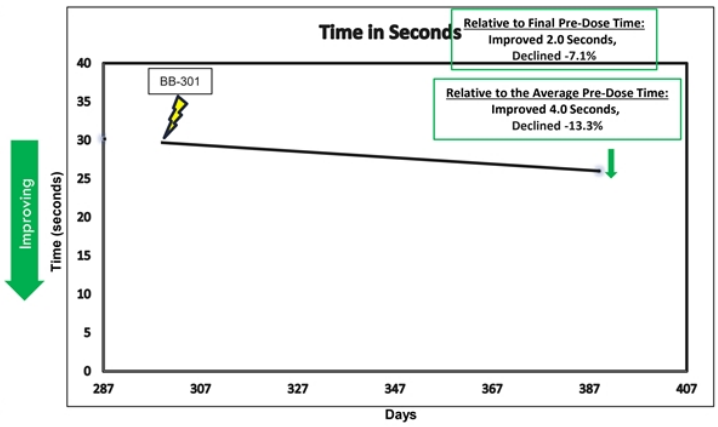
Timed Drinking Test: CWDT

BB-301 administered on Day 296 (as designated by the yellow bolt)

Pre-Dose Results: Day 0 to Day 287



Post-Dose VFSS: Day 287 (Average) to Day 389



22	36	30	35	28	30+/-6	26
Time	Time	Time	Time	Final Pre-Dose Time	Avg. Pre-Dose Time +/- Std Dev	Time

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Improvement was Observed for the CWDT Assessment

Average Pre-Dose CWDT Values vs. Day 90 CWDT Values

Cold Water Timed Drinking Test: Time in Seconds the Subject Requires to Consume 80 mL of Cold Water

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Average Time (sec) Recorded for the Study Subject	Day 90 Time (sec) Recorded for the Study Subject	Reduction in Total Drinking Time (sec) After BB-301 Dose
Thin Liquid	30	26	4.0 Seconds (-13.3%)

Final Pre-Dose CWDT Values vs. Day 90 CWDT Values

Cold Water Timed Drinking Test: Time in Seconds the Subject Requires to Consume 80 mL of Cold Water

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Final Pre-Dose Time (sec) Recorded for the Study Subject	Day 90 Time (sec) Recorded for the Study Subject	Reduction in Total Drinking Time (sec) After BB-301 Dose
Thin Liquid	28	26	2.0 Seconds (-7.1%)

SSQ Results

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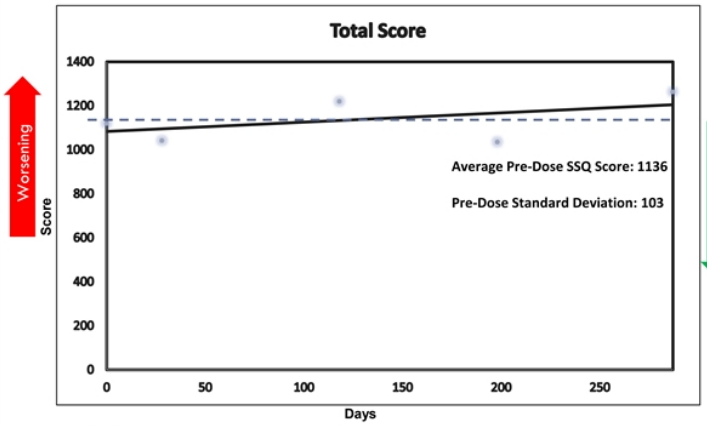
Subject Reported Outcomes: SSQ (*Declines Below SD and NH Study Screening Visit at Day 0*)

BB-301 administered on Day 296 (as designated by the yellow bolt)

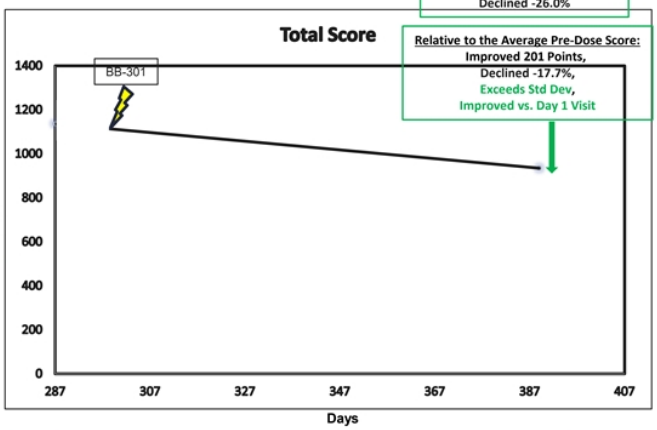
Pre-Dose Scores: Day 0 to Day 287



1120 | 1042 | 1220 | 1036 | 1264

Score | Score | Score | Score | Final Pre-Dose Score

Post-Dose VFSS: Day 287 (Average) to Day 389



Relative to Final Pre-Dose Score:
Improved 329 Points,
Declined -26.0%

Relative to the Average Pre-Dose Score:
Improved 201 Points,
Declined -17.7%,
Exceeds Std Dev,
Improved vs. Day 1 Visit

1136+/-103

Avg. Pre-Dose Score +/- Std Dev

935

Score

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Improvement was Observed for the SSQ Assessment

Average Pre-Dose SSQ Scores vs. Day 90 SSQ Scores

Subject Reported Outome Measure: Sydney Swallow Questionnaire or "SSQ" (17-Question Self-Report Inventory Assessing Subjective Symptoms of Oropharyngeal Dysphagia)

OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
Pre-Dose Period	Post-Dose Period	
Average SSQ Score for the Study Subject	Day 90 SSQ Score for the Study Subject	Reduction in SSQ Score After BB-301 Dose
1,136	935	201 Points (-17.7%)

Final Pre-Dose SSQ Scores vs. Day 90 SSQ Scores

Subject Reported Outome Measure: SSQ (17-Question Self-Report Inventory Assessing Subjective Symptoms of Oropharyngeal Dysphagia)

OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
Pre-Dose Period	Post-Dose Period	
Final Pre-Dose SSQ Score for the Study Subject	Day 90 SSQ Score for the Study Subject	Reduction in SSQ Score After BB-301 Dose
1,264	935	329 Points (-26.0%)

Clinically Meaningful Improvements

Clinically meaningful improvement over the course of the BB-301 clinical development program will be defined by:

- Improvements in Subject-Reported Outcome assessments (i.e., reductions in the Sydney Swallow Questionnaire ["SSQ"] Scores) post BB-301 dose and Reductions in Total Pharyngeal Residue (i.e., reductions in the total food or liquid material remaining in the pharynx at the completion of swallowing) post BB-301 dose

Specific attention will be given to the following:

- Improvements in Subject-Reported Outcome assessments (i.e., SSQ Scores) post BB-301 dose that are accompanied by similar improvements in videofluoroscopic swallowing study assessments (i.e., reductions in PhAMPC% and/or reductions in Total Pharyngeal Residue across one or more consistencies of liquid and/or solid food)
- Improvements in the results of individual outcome measures post BB-301 dose as compared to the results of the analogous assessments conducted at Visit 1 of the OPMD Natural History Study (i.e., 6 to 12 months prior to the receipt of BB-301)

Our Learnings for Subject 1 of the Phase 1b Study

Subject 1 experienced disease progression during their enrollment in the Natural History Study

After dosing:

- BB-301 slowed improved dysphagia in this study subject
- The current, low dose of BB-301 was sufficiently biologically active to facilitate a benefit in this study subject and these benefits were visible at the first follow-up assessments conducted at Day 90 post-dose
- BB-301 did not cause any Serious Adverse Events

Improvement was Observed Across All Assessments

Radiographic Assessments of Pharyngeal Area at Maximum Constriction to Determine Pharyngeal Constrictor Muscle Function During Swallowing

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Average PhAMPC During Swallowing	Day 90 PhAMPC During Swallowing	Improvement in Pharyngeal Closure During Swallowing After BB-301 Dose
Thin Liquid	9.1	3.9	5.2 Units (-57.1%)
Moderately Thick Liquid	20.0	14.8	5.2 Units (-26.0%)
Extremely Thick Liquid	21.8	18.5	3.3 Units (-15.1%)
Solid Food	18.0	10.9	7.1 Units (-39.4%)

Radiographic Assessments of Pharyngeal Residue (i.e., food or liquid material) Remaining Post-Swallow to Determine Swallowing Efficiency

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Average Pharyngeal Residue Remaining Post-Swallow	Day 90 Pharyngeal Residue Remaining Post-Swallow	Reduction in Post-Swallow Pharyngeal Residue After BB-301 Dose
Thin Liquid	4.9	0.9	4.0 Units (-81.6%)
Moderately Thick Liquid	18.2	11.0	7.2 Units (-39.6%)
Extremely Thick Liquid	21.5	11.9	9.6 Units (-44.7%)
Solid Food	19.0	12.3	6.7 Units (-35.3%)

Subject Reported Outome Measure: Sydney Swallow Questionnaire or "SSQ" (17-Question Self-Report Inventory Assessing Subjective Symptoms of Oropharyngeal Dysphagia)

OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
Pre-Dose Period	Post-Dose Period	
Average SSQ Score for the Study Subject	Day 90 SSQ Score for the Study Subject	Reduction in SSQ Score After BB-301 Dose
1,136	935	201 Points (-17.7%)

Cold Water Timed Drinking Test: Time in Seconds the Subject Requires to Consume 80 mL of Cold Water

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Average Time (sec) Recorded for the Study Subject	Day 90 Time (sec) Recorded for the Study Subject	Reduction in Total Drinking Time (sec) After BB-301 Dose
Thin Liquid	30	26	4.0 Seconds (-13.3%)

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Improvement was Observed Across all Assessments

Radiographic Assessments of Pharyngeal Area at Maximum Constriction to Determine Pharyngeal Constrictor Muscle Function During Swallowing

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Final Pre-Dose PhAMPC During Swallowing	Day 90 PhAMPC During Swallowing	Improvement in Pharyngeal Closure During Swallowing After BB-301 Dose
Thin Liquid	15.8	3.9	11.9 Units (-75.3%)
Moderately Thick Liquid	22.3	14.8	7.5 Units (-33.6%)
Extremely Thick Liquid	24.2	18.5	5.7 Units (-23.6%)
Solid Food	19.2	10.9	8.3 Units (-43.2%)

Radiographic Assessments of Pharyngeal Residue (i.e., food or liquid material) Remaining Post-Swallow to Determine Swallowing Efficiency

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Final Pre-Dose Pharyngeal Residue Remaining Post-Swallow	Day 90 Pharyngeal Residue Remaining Post-Swallow	Reduction in Post-Swallow Pharyngeal Residue After BB-301 Dose
Thin Liquid	7.7	0.9	6.8 Units (-88.3%)
Moderately Thick Liquid	11.4	11.0	0.4 Units (-3.5%)
Extremely Thick Liquid	22.5	11.9	10.6 Units (-47.1%)
Solid Food	17.3	12.3	5.0 Units (-28.9%)

Subject Reported Outome Measure: SSQ (17-Question Self-Report Inventory Assessing Subjective Symptoms of Oropharyngeal Dysphagia)

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
	Final Pre-Dose SSQ Score for the Study Subject	Day 90 SSQ Score for the Study Subject	Reduction in SSQ Score After BB-301 Dose
	1,264	935	329 Points (-26.0%)

Cold Water Timed Drinking Test: Time in Seconds the Subject Requires to Consume 80 mL of Cold Water

	OPMD Natural History Study	Phase 1b/2a BB-301 Dosing Study	
	Pre-Dose Period	Post-Dose Period	
Barium-Containing Food Items	Final Pre-Dose Time (sec) Recorded for the Study Subject	Day 90 Time (sec) Recorded for the Study Subject	Reduction in Total Drinking Time (sec) After BB-301 Dose
Thin Liquid	28	26	2.0 Seconds (-7.1%)

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Preliminary Observations and Conclusions for Subject 1

- Subject 1 experienced progressive worsening of dysphagia during the pre-dose period as demonstrated by the videofluoroscopic swallowing study (VFSS) results, the cold water timed drink test results, and the subject-reported outcome results
- Following the administration of BB-301, at the Day 90 time-point, Subject 1 demonstrated improvements in key clinical and videofluoroscopic assessments as compared to the average pre-dose assessments
- The most significant VFSS improvements at Day 90 were observed for swallowing tasks centered on the evaluation of pharyngeal constrictor muscle function and swallowing efficiency in the context of the consumption of:
  - Solid foods (e.g., crackers)
  - Thick, non-solid foods (e.g., yogurt or pudding)
  - Thin liquids
- The VFSS improvements observed for pharyngeal constrictor muscle function and swallowing efficiency in the context of the consumption of thin liquids, solid foods (e.g., crackers) and thick, non-solid foods (e.g., yogurt or pudding) correlated with a significant improvement in the key subject-reported outcome measure (i.e., Sydney Swallow Questionnaire) indicating an improvement in swallowing function as reported by Subject 1

Clinical Safety Update for the BB-301 Phase 1b/2a Clinical Study (NCT06185673)

- The benign safety profile for Subject 1 (the first Study Subject dosed with BB-301) remains unchanged from that which has been reviewed by the Data Safety Monitoring Board
- During the first week following the administration of BB-301, Subject 1 experienced heartburn
- The heartburn was attributed to the prophylactic corticosteroids that are administered per Protocol to each Study Subject for Day -1 (the day preceding BB-301 dosing), Day 1 (the day of BB-301 dosing), and the 56 days following dosing
- The heartburn was managed with a short course of prescription medication, and the heartburn resolved over the following three days
- The use of a prescription medication to alleviate the heartburn renders the heartburn a Grade 2 Adverse Event

Clinical Safety Update for the BB-301 Phase 1b/2a Clinical Study (NCT06185673), Continued

- During the first week following the administration of BB-301, Subject 2 (the second Study Subject dosed with BB-301) experienced heartburn
- The heartburn was attributed to the prophylactic corticosteroids that are administered per Protocol to each Study Subject for Day -1 (the day preceding BB-301 dosing), Day 1 (the day of BB-301 dosing), and the 56 days following dosing
- The heartburn was managed prophylactically with a prescription medication over a 14-day period
- The use of a prescription medication to alleviate the heartburn renders the heartburn a Grade 2 Adverse Event (see **Figure 1**)

The clinical severity of an AE will be graded using the NCI CTCAE v5.0.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL).
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Figure 1

Clinical Safety Update for the BB-301 Phase 1b/2a Clinical Study (NCT06185673), Continued

- According to the Phase 1b/2a Study Protocol, any Grade 2 Adverse Event not resolving within 14 days, assessed to be possibly related to the investigational product (see **Figure 2**) is characterized as a Dose Limiting Toxicity (DLT) and requires the expansion of the size of a Cohort from 3 Subjects to 6 Subjects
- In this regard, the 14-day prophylactic management of the subject's heartburn with a prescription medication triggers the expansion of the size of the Cohort 1 from 3 Subjects to 6 Subjects

Not related	An AE with sufficient evidence to accept that there is no causal relationship to study drug administration and/or study procedure (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven.)
Unlikely related	An AE, including laboratory test abnormality, with a temporal relationship to study drug administration and/or study procedure that makes a causal relationship improbable, and in which other drugs, events, or underlying disease provide plausible explanations.
Potentially related	An AE with a reasonable time sequence to administration of the study drug and/or study procedure, but that could also be explained by concurrent disease or other drugs or events.
Probably related	An AE with evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study drug or study procedure, is unlikely to be attributed to concurrent disease, other drugs or chemicals, or other event.
Definitely related	An AE occurring in a plausible time relationship to study drug administration and that cannot be explained by a concurrent disease or other drugs or events.

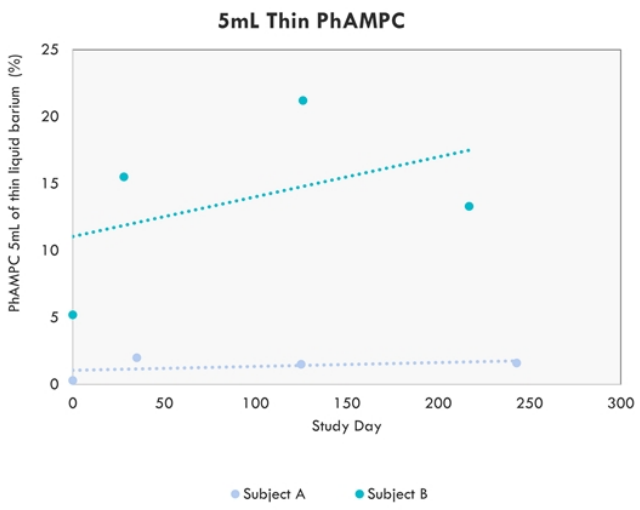
Figure 2

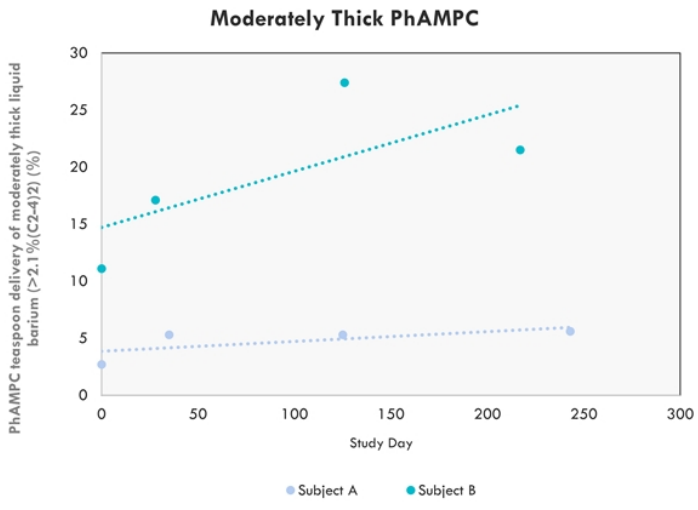
Upcoming Milestones

- Updates on additional subjects are anticipated later in 2024
- Updates on additional subjects at higher doses, and with longer durations of follow-up, are anticipated in 2025
- By year-end 2025, Benitec would potentially have clinical follow-up data for multiple study subjects for up to 12 months in Dose Cohort 1 and up to 9 months in Dose Cohort 2
- If clinical safety and efficacy data continue to evolve favorably over the first two dose cohorts, then, by early 2026 Benitec would plan to review the clinical data set with the FDA and inquire about plans for a pivotal study

Appendix

PhAMPC Natural History Assessments for Other Enrolled Subjects





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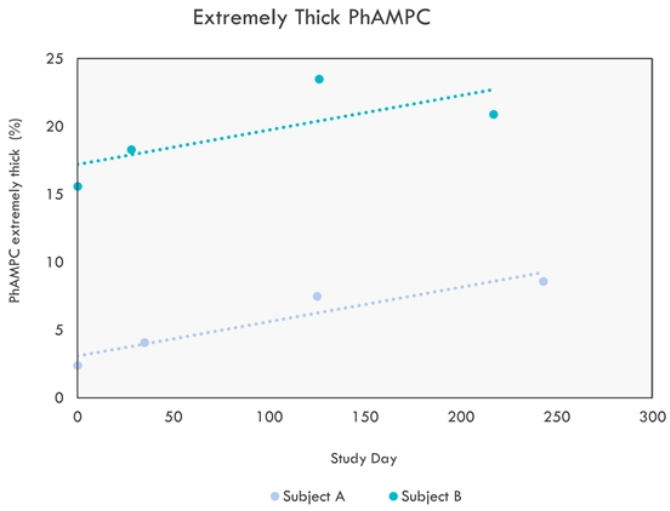
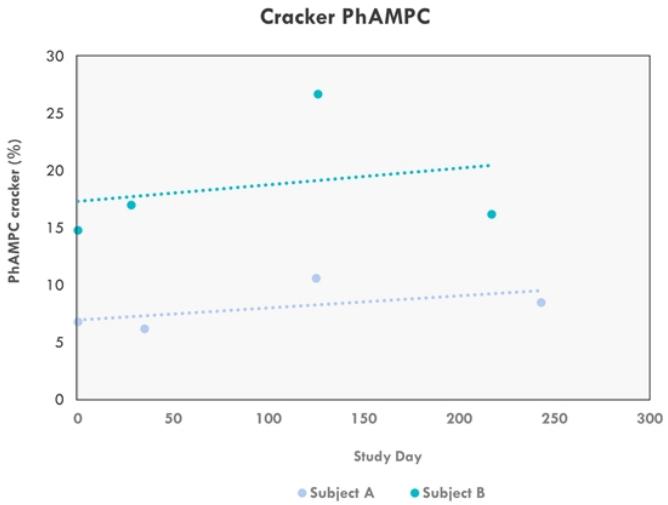
PhAMPC Natural History Assessments for Other Enrolled Subjects





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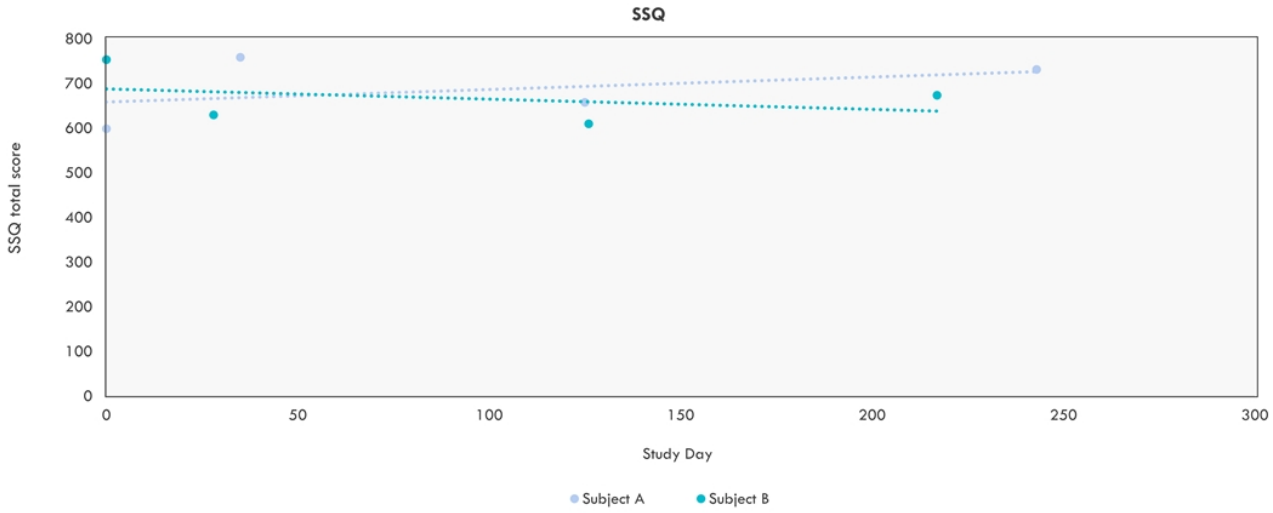
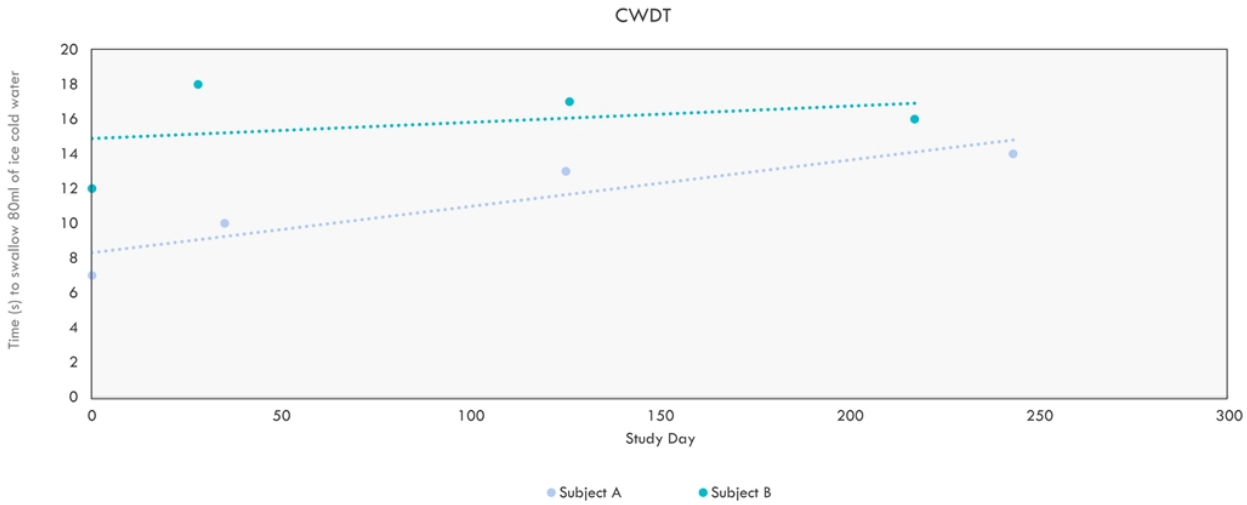
Sydney Swallow Questionnaire Natural History Assessments for Other Enrolled Subjects



Cold Water Timed Drinking Test Natural History Assessments for Other Enrolled Subjects



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