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Benitec Biopharma Provides Overview of the BB-301 Phase 1b/2a Clinical Trial Design for 2022

HAYWARD, Calif., Sept. 8, 2021 /PRNewswire/ -- Benitec Biopharma Inc. (NASDAQ: BNTC), a development-stage biotechnology company focused on the advancement of novel genetic medicines, today provided an overview of the key elements of the BB-301 Phase 1b/2a clinical trial design. The clinical trial is planned for 2022.

BB-301 is a novel investigational gene therapy under development for the treatment of patients with Oculopharyngeal Muscular Dystrophy (OPMD). OPMD is a chronic, life-threatening genetic disorder affecting approximately 15,000 patients in the United States, Canada, Western Europe, and Israel. OPMD is caused by a mutation in the gene encoding poly(A) binding protein nuclear 1 (PABPN1). Patients with OPMD lose the ability to swallow liquids and solids, and the natural history of the disorder is characterized by chronic malnutrition, aspiration, and fatal episodes of aspiration pneumonia. Currently, no therapeutic agents are approved for the treatment of OPMD. Additionally, no surgical interventions capable of altering the long-term natural history of OPMD are available.

Goal of the BB-301 Phase 1b/2a Study:

- Benitec is focused on the accurate and reproducible characterization of the key physiological processes underlying the successful completion of the pharyngeal phase of swallowing
- In this regard, the core analytical tools and methods employed during the clinical study will focus on functional measures of swallowing efficiency for OPMD patients during the pharyngeal phase of swallowing

Summary and Background for the BB-301 Phase 1b/2a Study:

Study Title:

A Phase 1b/2a, Open-Label Dose Escalation Study to Evaluate the Safety and Clinical Activity of Intramuscular Doses of BB-301 Administered to Subjects with OPMD

Study Rationale:

The purpose of this clinical investigation is to evaluate the safety, tolerability, and clinical activity of ascending doses of BB-301 administered to subjects with OPMD via local intramuscular (IM) injection into the middle pharyngeal constrictor (MPC) muscles and the inferior pharyngeal constrictor (IPC) muscles following open surgical dissection of the pharyngeal region under general anesthesia.

Study Design:

This Phase 1b/2a, first-in-human (FIH) study is a single arm, open-label, sequential, dose escalation cohort study with a six-month pre-treatment observation period and a 52-week post injection follow-up period in up to 24 subjects diagnosed with OPMD.

BB-301 will be administered in three sequential escalating dose cohorts. After the initial three cohorts have been dosed, additional subjects may be added at the Maximally Effective Dose (MED), or at an alternate dose as determined by review of cumulative safety and efficacy data.

At 76 weeks all subjects will be enrolled into a long-term safety follow-up study.

Criteria for Study Subject Evaluation:

Primary Endpoint (assessed at screening and through end of treatment):

- To assess the safety and tolerability of ascending IM doses of BB-301 administered locally to the MPC muscles and the IPC muscles of subjects with OPMD following open surgical dissection of the pharyngeal region under general anesthesia

Secondary Endpoints (assessed at Day -180, Day -90, Day -2, Day 90, Day 180, Day 270, Day 360):

- To evaluate the impact of ascending IM doses of BB-301 on key functional elements of the pharyngeal phase of swallowing as measured by the following videofluoroscopic assessments:
    - Global swallowing function as measured by the Dynamic Imaging Swallowing Toxicity (DIGEST) scale
    - Pharyngeal constrictor muscle force generation as measured by the Pharyngeal Area at Maximum Constriction (PAMC)
    - Pharyngeal constrictor muscle force generation as measured by the Pharyngeal Constriction Ratio (PCR)
- To evaluate the impact of ascending IM doses of BB-301 on dysphagia severity as measured by the cold-water timed drinking test
- To evaluate the impact of ascending IM doses of BB-301 on patient reported dysphagia (Sydney Swallow Questionnaire)
- To evaluate the impact of ascending IM doses of BB-301 on functional oral intake (International Dysphagia Diet Standardization Initiative Functional Diet Scale)

Rationale for the Use of Videofluoroscopy to Assess Core Metrics of Pharyngeal Function and Pharyngeal Constrictor Muscle Strength:

- The key Secondary Endpoints outlined above will rely on the implementation of several videofluoroscopy-based methods
    - Videofluoroscopy (or modified barium swallow) is viewed as the gold standard for the assessment of swallowing function
- Recall that the core biological outcome of the BB-301 proof-of-concept studies in the A17 mouse model (Strings-Ufombah, V., et al., Molecular Therapy: Nucleic Acids, 2021; Malerba, A., et al. Nature Communications, 2017) was the increase in the cross-sectional area, and the increase in strength, of the skeletal muscles injected with BB-301
    - In this regard, Benitec's primary goal with respect to the functional assessment of OPMD patients enrolled onto the Phase 1b/2a study is to accurately and reproducibly document the impact of the administration of BB-301 on the strength and function of the injected pharyngeal constrictor muscles
- In the Phase 1b/2a study Benitec endeavors to use analytical methods that directly measure, or are robust surrogates for, pharyngeal constrictor muscle strength and swallowing efficiency for OPMD patients during the pharyngeal phase of swallowing
    - The videofluoroscopy-based methods outlined above (and further detailed below) have been demonstrated to measure the core biological and functional attributes that Benitec aims to address with the administration of BB-301 (i.e. improved efficiency of the pharyngeal phase of swallowing via increases in pharyngeal constrictor muscle strength)

Key Standardization Measures:

The following measures will be put into place to minimize variability in the study:

- Guidelines will be produced for videofluoroscopic swallowing studies to ensure standardization across all sites
- A central blinded reader will receive the videofluoroscopy data and will be responsible for calculating the DIGEST score, Pharyngeal Area at Maximum Constriction (PAMC), and Pharyngeal Constriction Ratio (PCR)

The BB-301 Phase 1b/2a study is designed in a manner that could, potentially, demonstrate clinical benefit for OPMD patients via three distinct scenarios:

- Stabilization of the rate of the loss of function for the pharyngeal phase of swallowing relative to the baseline rate of disease progression observed over the course of the 6-month pre-treatment observation period
- Slowing of the rate of the loss of function for the pharyngeal phase of swallowing relative to the baseline rate of disease progression observed over the course of the 6-month pre-treatment observation period
- Improvement in function for the pharyngeal phase of swallowing relative to the baseline rate of disease progression observed over the course of the 6-month pre-treatment observation period

<u>Methodological Background for the Key Analytical Tools and Methods:</u>

Summary:

- Prior studies employing high resolution manometry and videofluoroscopy have

demonstrated that OPMD patients exhibit significant dysfunction with respect to the pharyngeal phase of swallowing
    - Studies employing high resolution manometry have illustrated significantly lower pharyngeal pressures during swallowing in OPMD patients (Castell, J. *et al.*, Dysphagia, 1995)
    - Additionally, videofluoroscopy studies have demonstrated significant pharyngeal residue post-swallow (references detailed below)
- As a consequence, in the BB-301 Phase 1b/2a study, Benitec will focus on imaging modalities and diagnostic protocols that accurately and reproducibly characterize the efficiency of the pharyngeal phase of swallowing

Overview of the Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) Scale:

- DIGEST is a 5-point scale that allows clinical researchers to grade pharyngeal dysphagia in a uniform manner in clinical studies (0 = no dysphagia; 1 = mild dysphagia; 2 = moderate dysphagia; 3 = severe dysphagia; 4 = life threatening dysphagia)
- The DIGEST scale is a validated tool developed by the NCI to assess dysphagia related to the pharyngeal phase of swallowing (Hutcheson, K., *et al.*, Cancer, 2017)
- DIGEST was developed to allow clinical researchers that study Head and Neck Cancer to grade the dysphagia that may result from the common surgical and radiological treatment interventions
- Video fluoroscopy (or modified barium swallow) is viewed as the gold standard for the assessment of swallowing function
    - In this regard, the NCI sought to develop and validate a video fluoroscopy-based scale that could be used by Head and Neck Cancer clinical researchers to monitor and report dysphagia-related toxicity (and in Head and Neck Cancer, the pharyngeal phase of swallowing is most often disturbed)
- DIGEST focuses on two elements of the pharyngeal phase of swallowing: 1. swallowing efficiency, and 2. swallowing safety; swallowing inefficiency leads to weight loss and malnutrition and problems with swallowing safety can lead to aspiration
- Grades for swallowing efficiency are combined with grades for swallowing safety to calculate the final DIGEST score

Overview of DIGEST Scale Use for the Evaluation of OPMD Patients:

- OPMD patients experience dysphagia, and, primarily, it is the pharyngeal phase of swallowing that is disturbed
- Videofluoroscopy examinations have been conducted by investigators in 22 patients with OPMD, and the results were employed to grade the levels of dysphagia for these patients with the DIGEST method (Tabor, L., *et al.*, Neurogastroenterology & Motility, 2017)
- Based on the DIGEST method, 96% of these 22 OPMD patients had dysphagia (i.e. a DIGEST score of 1 or greater), and, therefore, DIGEST accurately identified patients with dysphagia
- 50% of the patients had Mild dysphagia (DIGEST = 1), 15% had Moderate dysphagia (DIGEST = 2), and 31% had Severe dysphagia (DIGEST = 3)

Overview of the Pharyngeal Constriction Ratio:

- The Pharyngeal Constriction Ratio (PCR) was created to quantify the efficiency of the pharyngeal phase of swallowing via videofluoroscopy
- The PCR was demonstrated to be a surrogate for pharyngeal muscle strength (Leonard, R. *et al.*, Dysphagia, 2011)
- The PCR compares the amount of free air-space visible in the pharynx at the point of maximal pharyngeal constriction during swallowing to the amount of free air-space visible in the pharynx in its resting state (i.e. the area of the free air-space during maximal constriction is the numerator and the area of the free air-space at rest is the denominator)
- Ideally, the pharynx should close completely during swallowing (as it does in young, healthy individuals) and this would result in a very low PCR (i.e. 1% or 0%)
- If a patient experiences difficulty while attempting to close the pharynx (i.e. patients that have difficulty swallowing due to pharyngeal-focused dysphagia), then the PCR will be much higher than that observed for young, healthy individuals (i.e. the PCR can be 25% or higher in patients with dysphagia)
- Leonard, *et al.* validated the correlation between PCR and pharyngeal pressure generated during swallowing as measured via high resolution manometry

Overview of the Pharyngeal Area at Maximum Constriction:

- Videofluoroscopy was employed to evaluate the pharyngeal phase of swallowing in 11 OPMD patients to characterize abnormalities in the key elements underlying the successful completion of the pharyngeal phase of swallowing (Waito, A., *et al.*, Dysphagia, 2018)
- In this study, pharyngeal constriction was found to be the most significant abnormality in this OPMD patient population as illustrated by the abnormal Pharyngeal Area at Maximum Constriction (PAMC) values obtained in 91% of the swallows during the study
- PAMC uses the pixelated area of the pharynx at the point of maximum constriction during swallowing as the numerator and the C2-C4 length squared (i.e. $C2\text{-}C4^2$) is used as the denominator
    - Healthy individuals without dysphagia do not have PAMC values above 3% (Steele, C. *et al.*, Journal of Speech, Language, and Hearing Research, 2019)
- In the Waito, et al. study, 91% of the swallows exhibited PAMC values above 4%

Overview of the Sydney Swallow Questionnaire:

- The Sydney Swallow Questionnaire is a 17-question self-report inventory that is used by a patient to describe the severity of dysphagia
- This tool was developed and validated as a self-report inventory

Overview of the International Dysphagia Diet Standardization Initiative (IDDSI) Functional Diet Scale:

- IDDSI is a newly developed functional outcome scale intended to capture the severity of oropharyngeal dysphagia as represented by the degree of diet texture restriction recommended for the patient

About Benitec Biopharma, Inc.

Benitec Biopharma, Inc. ("Benitec" or the "Company") is a development-stage biotechnology company focused on the advancement of novel genetic medicines with its headquarters in Hayward, California. The proprietary platform, called DNA-directed RNA interference, or ddRNAi, combines RNA interference, or RNAi, with gene therapy to create medicines that facilitate sustained silencing of disease-causing genes following a single administration. The Company is developing ddRNAi-based therapeutics for chronic and life-threatening human conditions including Oculopharyngeal Muscular Dystrophy (OPMD), and Chronic Hepatitis B. 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 represent forward-looking statements, including statements regarding BB-301, Benitec's plans to develop and commercialize its product candidates, the timing of the initiation and completion of preclinical and clinical trials, the timing of patient enrolment 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, potential future out-licenses and collaborations, the intellectual property position and the ability to procure additional sources of financing, and other forward-looking statements. In addition, preliminary results or other preliminary analyses do not in any way ensure that later or final results in a clinical trial or in similar clinical trials will replicate those interim results.

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 Some of the risks and uncertainties that may cause our actual results, performance or achievements to differ materially from those expressed or implied by forward-looking statements include the following:

- the success of our plans to develop and potentially commercialize our product candidates; the timing of the initiation and completion of preclinical studies and clinical trials;
- the timing and sufficiency of patient enrollment and dosing in any future clinical trials;
- the timing of the availability of data from clinical trials;
- the timing and outcome of regulatory filings and approvals;
- unanticipated delays;
- sales, marketing, manufacturing and distribution requirements;
- market competition and the acceptance of our products in the marketplace;
- regulatory developments in the United States;
- the development of novel AAV vectors;
- the plans of licensees of our technology;
- the clinical utility and potential attributes and benefits of ddRNAi and our product candidates;
- including the potential duration of treatment effects and the potential for a "one shot" cure;
- our dependence on our relationships with collaborators and other third parties;
- expenses, ongoing losses, future revenue, capital needs and needs for additional financing;
- the length of time over which we expect our cash and cash equivalents to be sufficient

to execute on our business plan;
- our intellectual property position and the duration of our patent portfolio;
- the impact of local, regional, and national and international economic conditions and events; and
- the impact of the current COVID-19 pandemic, the disease caused by the SARS-CoV-2 virus, which may adversely impact our business and preclinical and future clinical trials;

as well as other risks detailed under the caption "Risk Factors" in our reports filed with the SEC from time to time. Any forward-looking statements in this release speak only as of the date on which it was made. We undertake no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise.

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