February 24, 2021

Benitec Biopharma Announces Successful Results from the Interim Analysis of the BB-301 Pilot Dosing Study

HAYWARD, Calif., Feb. 24, 2021 /PRNewswire/ --

Highlights from the Interim Analysis:

- Biologically significant, highly-consistent, dose-dependent levels of BB-301 tissue transduction (i.e. delivery of the multi-functional genetic construct into the target pharyngeal muscle cells)
    - BB-301 copy numbers ranging from 1.7 copies per cell up to 8.6 copies per cell were achieved in the respective pharyngeal muscles after a single administration of increasing doses of BB-301
- Durable, broad-based, dose-dependent expression within the pharyngeal muscle cells of the three distinct genes comprising the BB-301 gene construct (i.e., siRNA13, siRNA17, and codon optimized PABPN1)
- Durable and biologically significant levels of target gene knock-down (i.e., inhibition of the expression of the gene of interest) within the pharyngeal muscle cells
    - Low-Dose, Intermediate-Dose, and High-Dose BB-301 administration achieved similar levels of inhibition, with an average of 74% inhibition of PABPN1 expression observed across all doses
    - BB-301 has been evaluated in prior non-clinical studies in animals that express mutant PABPN1 and manifest the key signs and symptoms of Oculopharyngeal Muscular Dystrophy (OPMD) and, in these animal models of OPMD, the achievement of PABPN1 silencing levels of 31% inhibition or higher led to complete resolution of OPMD disease symptoms and correction of the histological hallmarks of OPMD

- Finally, it is critical to highlight the key distinctions between the current BB-301 Pilot Dosing Study in Beagle dogs conducted by Benitec and the prior Beagle dog dosing study carried out independently by the previous BB-301 licensee of Benitec

    - The Benitec team optimized the route and method of administration for BB-301 and refined the core analytical methods employed following the completion of dosing

    - Following these methodological improvements, Benitec demonstrated a 248-fold improvement (+24,650%) and a 111-fold improvement (+11,027%) in BB-301 transduction of the two key pharyngeal muscles relative to the levels of BB-301 transduction observed in the analogous Beagle dog study conducted by the previous BB-301 licensee

- Benitec has scheduled a Scientific Advice Meeting in France in May 2021 to review the interim data and the Phase 1 clinical trial design, and the Company continues to plan for the initiation of the first-in-human clinical study of BB-301 in OPMD patients in 2022

- Robust validation of Benitec's proprietary "Silence-and-Replace" approach has been achieved

    - The data derived from the interim analysis validate the promise of the "Silence-and-Replace" approach to disease management, and Benitec plans to provide additional pipeline updates in 2H 2021

Benitec Biopharma Inc. (NASDAQ: BNTC), a development-stage biotechnology company focused on the advancement of novel genetic medicines, today announced the successful results of the interim analysis of the BB-301 Pilot Dosing Study. In addition to the data summarized below, please see the accompanying slide presentation available at www.benitec.com and accessible here.

The proprietary DNA-directed RNA interference (ddRNAi) platform combines RNA interference (RNAi) with classical AAV-based gene therapy. Through the use of the ddRNAi platform Benitec's goal is to create genetic medicines that, following a single administration, will enable target tissues to perpetually produce siRNA molecules which facilitate the sustained silencing of disease-causing genes. Importantly, the ddRNAi platform also allows for concomitant delivery of wild type replacement genes, and these distinct genetic elements work in concert to silence the expression of disease-causing mutant genes and to simultaneously replace the mutant genes with normal (wild type) genes to restore the natural underlying physiology of the diseased tissues. BB-301, the most advanced genetic medicine currently under development by Benitec, employs the proprietary platform, which allows for a "Silence and Replace" approach to the treatment of Oculopharyngeal Muscular Dystrophy (OPMD).

BB-301 is a first-in-class genetic medicine employing the "Silence and Replace" approach for the treatment of 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. BB-301 has received Orphan Drug Designation in the United States and the European Union which provides commercial exclusivity (independent of intellectual property protection) and opportunities for efficient pathways for regulatory review and approval. While OPMD is a rare (Orphan) disorder, the commercial opportunity for a safe and efficacious therapeutic agent in this indication exceeds $1 billion over the course of the commercial life of the product.

Benitec has previously outlined the core IND-enabling studies required by global regulatory agencies to support the initiation of BB-301 clinical trials in OPMD patients, and these IND-enabling studies include a BB-301 Pilot Dosing Study in large animals and a classical 12-week GLP Toxicology and Biodistribution Study. BB-301 is directly injected into the pharyngeal muscles known to underlie the morbidity and mortality characterizing the natural history of OPMD. Against this backdrop, the BB-301 Pilot Dosing Study in large animal subjects was conducted to demonstrate that direct intramuscular injection of BB-301 via the use of a proprietary dosing device in an open surgical procedure could safely achieve the following goals:

- Biologically significant, highly-consistent, dose-dependent levels of BB-301 tissue transduction (i.e., delivery of the multi-functional genetic construct into the target pharyngeal muscle cells)

- Durable, broad-based, dose-dependent expression within the pharyngeal muscle cells of the three distinct genes comprising the BB-301 gene construct

- Durable and biologically significant levels of target gene knock-down (i.e., inhibition of the expression of the gene of interest) within the pharyngeal muscle cells

The Pilot Dosing Study evaluated the safety and biological activity of two concentrations of BB-301 (1.0+E13 vg/mL and 3.0+E13 vg/mL) across three distinct doses (1.0+E13 vg/mL, 3.0+E13 vg/mL with a low injection volume, and 3.0+E13 vg/mL with a high injection volume) following direct intramuscular injection into the Hypopharyngeus (HP) muscles and the Thyropharyngeus (TP) muscles of Beagle dogs via the use of a proprietary delivery device employed in an open surgical procedure. The HP muscle in Beagle dogs corresponds to the Middle Pharyngeal Constrictor muscle in Human subjects, and the TP muscle in Beagle dogs corresponds to the Inferior Pharyngeal Constrictor muscle in Human subjects. BB-301 was injected only on Day 1 of the Pilot Dosing Study, and the corresponding canine pharyngeal muscles were harvested for analysis after 8 weeks on study. BB-301 dosing was carried out by both a veterinary surgeon and a practicing Otolaryngologist who has extensive experience with the provision of palliative surgical care for OPMD patients.

Further data analyses are ongoing for the canine subjects treated in the BB-301 Pilot Dosing Study, and the interim data-points highlighted today are derived from completed analyses of pharyngeal muscle tissues isolated from the 6 Beagle dog subjects to date (of the 24-subject study population). The data-set and the initial conclusions will be updated as additional subjects are analyzed. The key preliminary results are summarized at the end of this announcement.

Finally, it is critical to highlight the key methodological distinctions between the current BB-301 Pilot Dosing Study in Beagle dogs conducted by Benitec and the prior Beagle dog dosing study carried out independently by the previous BB-301 licensee of Benitec. The BB-301 dosing study conducted by the prior BB-301 licensee employed non-ideal routes and methods of BB-301 administration to the target pharyngeal muscle tissues and employed similarly limited analytical methods at the completion of the dosing phase of the study. The Benitec team worked to optimize the route and method of administration of BB-301 and to refine the core analytical methods employed following the completion of dosing.

Following these methodological improvements, Benitec demonstrated a 248-fold improvement (+24,650%) in BB-301 transduction of the HP muscle and a 111-fold improvement (+11,027%) in BB-301 transduction of the TP muscle relative to the levels of BB-301 transduction observed by the previous BB-301 licensee.

Benitec has scheduled a Scientific Advice Meeting in France in May 2021 to review the interim data and the Phase 1 clinical trial design, and the Company continues to plan for the initiation of the first-in-human clinical study of BB-301 in OPMD patients in 2022. The interim data validate the promise of the "Silence and Replace" approach to disease management, and Benitec plans to provide additional pipeline updates in 2H2021.

Preliminary Results of the Pilot Dosing Study:

Regarding Pharyngeal Muscle Tissue Transduction Levels Observed for BB-301:

In the HP muscle:

- Low-Dose BB-301 (1.0E+13 vg/mL) achieved a vector copy number of 1.7 copies per cell
- Intermediate-Dose BB-301 (3.0E+13 vg/mL, low volume) achieved a vector copy number of 3.5 copies per cell
- High-Dose BB-301 (3.0E+13 vg/mL, high volume) achieved a vector copy number of 7.2 copies per cell

In the TP muscle:

- Low-Dose BB-301 (1.0E+13 vg/mL) achieved a vector copy number of 2.0 copies per cell
- Intermediate-Dose BB-301 (3.0E+13 vg/mL, low volume) achieved a vector copy number of 2.3 copies per cell
- High-Dose BB-301 (3.0E+13 vg/mL, high volume) achieved a vector copy number of 8.6 copies per cell

Regarding Gene Expression Levels Observed for BB-301 Within the Pharyngeal Muscle Tissues:

BB-301 encodes 2 distinct siRNA species (i.e. siRNA13 and siRNA17) which are each, independently, capable of inhibiting (i.e. "silencing") the expression of the mutant form of the

PABPN1 protein and the wild type (i.e. endogenous) form of the PABPN1 protein (importantly, the mutant form of the PABPN1 protein underlies the development and progression of OPMD)

BB-301 also codes for a wild type version of the PABPN1 protein whose intracellular expression is unaffected by the inhibitory activities of siRNA13 and siRNA17, and this codon optimized PABPN1 protein (i.e. coPABPN1) serves to replenish the endogenous form of the PABPN1 protein and to replace the mutant form of PABPN1 that underlies the development and progression of OPMD in diseased tissues

For comparative purposes, is should be noted that the average level of expression for wild type PABPN1 within the pharyngeal muscle cells of Beagle dogs is 4.5 copies per cell to 7.8 copies per cell

In the HP muscle:

- Low-Dose BB-301 (1.0E+13 vg/mL) achieved siRNA13, siRNA17, and coPABPN1 copy numbers of 161,358 copies per cell, 26,652 copies per cell, and 21 copies per cell, respectively

- Intermediate-Dose BB-301 (3.0E+13 vg/mL, low volume) achieved siRNA13, siRNA17, and coPABPN1 copy numbers of 256,928 copies per cell, 47,944 copies per cell, and 24 copies per cell, respectively

- High-Dose BB-301 (3.0E+13 vg/mL, high volume) achieved siRNA13, siRNA17, and coPABPN1 copy numbers of 374,324 copies per cell, 57,126 copies per cell, and 52 copies per cell, respectively

In the TP muscle:

- Low-Dose BB-301 (1.0E+13 vg/mL) achieved siRNA13, siRNA17, and coPABPN1 copy numbers of 195,182 copies per cell, 40,106 copies per cell, and 15 copies per cell, respectively

- Intermediate-Dose BB-301 (3.0E+13 vg/mL, low volume) achieved siRNA13, siRNA17, and coPABPN1 copy numbers of 293,597 copies per cell, 57,969 copies per cell, and 43 copies per cell, respectively

- High-Dose BB-301 (3.0E+13 vg/mL, high volume) achieved siRNA13, siRNA17, and coPABPN1 copy numbers of 751,484 copies per cell, 173,211 copies per cell, and 100 copies per cell, respectively

Regarding Wild Type PABPN1 Silencing (i.e. target "knock-down") Observed for BB-301 Within the Pharyngeal Muscle Tissues:

As noted above, BB-301 encodes 2 distinct siRNA species (i.e. siRNA13 and siRNA17) which are each, independently, capable of inhibiting (i.e. "silencing") the expression of all forms of the PABPN1 protein (siRNA13 and siRNA17 silence the expression of both wild type PABPN1 [wtPABPN1] and mutant PABPN1)

While the Beagle dog subjects treated in the current BB-301 Pilot Dosing Study do not

express mutant PABPN1, the level of BB-301-driven gene silencing for the PABPN1 target can be accurately assessed due to the equivalent inhibitory effects of siRNA13 and siRNA17 on both wtPABPN1 and mutant PABPN1

Thus, the wtPABPN1 silencing activity observed in the current BB-301 Pilot Dosing Study serves as a surrogate for the activity that would be anticipated in the presence of mutant PABPN1

BB-301 has been evaluated in prior non-clinical studies in animals that express mutant PABPN1 and manifest the key signs and symptoms of OPMD and, in these animal models of OPMD, the achievement of PABPN1 silencing levels of 31% inhibition or higher led to complete resolution of OPMD disease symptoms and correction of the histological hallmarks of OPMD

In the HP muscle:

- Low-Dose BB-301 (1.0E+13 vg/mL) achieved 74% inhibition of wtPABPN1 expression
- Intermediate-Dose BB-301 (3.0E+13 vg/mL, low volume) achieved 80% inhibition of wtPABPN1 expression
- High-Dose BB-301 (3.0E+13 vg/mL, high volume) achieved 78% inhibition of wtPABPN1 expression

In the TP muscle:

- Low-Dose BB-301 (1.0E+13 vg/mL) achieved 72% inhibition of wtPABPN1 expression
- Intermediate-Dose BB-301 (3.0E+13 vg/mL, low volume) achieved 61% inhibition of wtPABPN1 expression
- High-Dose BB-301 (3.0E+13 vg/mL, high volume) achieved 79% inhibition of wtPABPN1 expression

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 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;
- the timing and sufficiency of patient enrollment and dosing in any future clinical trials;
- 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.

Media & Investor Relations Contact:

Jay A. Morakis
CEO of M Group Strategic Communications (for Benitec Biopharma, Inc.)
Phone: 646-859-5951
Email: jmorakis@mgroupsc.com

View original content to download multimedia: http://www.prnewswire.com/news-releases/benitec-biopharma-announces-successful-results-from-the-interim-analysis-of-the-bb-301-pilot-dosing-study-301234604.html

SOURCE Benitec Biopharma Inc.