Interim Results of IND-Enabling Large Animal Study for BB-301

February 2021

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Gene Silencing: *A Validated Approach to the Treatment of Some Genetic Diseases*

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- Mutation of a single gene can cause a chronic disease via the resulting intracellular production of a disease-causing protein (i.e. an abnormal form of the protein of interest)

- Genetic disorders of this type can often be treated exclusively by "silencing" the intracellular production of the disease-causing protein through well-validated biological approaches like RNA interference ("RNAi")

  – RNAi employs small nucleic acid molecules to activate an intracellular enzyme complex, and this biological pathway temporarily reduces the production of the disease-causing protein

  – In the absence of the disease-causing protein, normal cellular function is restored, and the chronic disease improves or resolves

- However, many genetic disorders are not amenable to gene silencing approaches, as the diseased cells produce a mixture of the normal protein of interest and the disease-causing variant of the protein, and the underlying genetic mutation does not allow for selective targeting of the disease-causing variant

  – In these cases it is impossible to exclusively silence the disease-causing protein without simultaneously silencing the normal intracellular protein of interest whose presence is vital to normal cellular functions

"Silence and Replace": *Permanent Gene Silencing and Tissue-Specific Restoration of Biological Function*

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- Our proprietary DNA-directed RNA interference (ddRNAi) platform combines RNAi with classical AAV-based gene therapy

- Through the use of the ddRNAi platform Benitec creates 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 this "Silence and Replace" approach for the treatment of Oculopharyngeal Muscular Dystrophy (OPMD)

Platform Enables Gene Therapy and Permanent Gene Silencing: *DNA-Directed RNA Interference (ddRNAi)*

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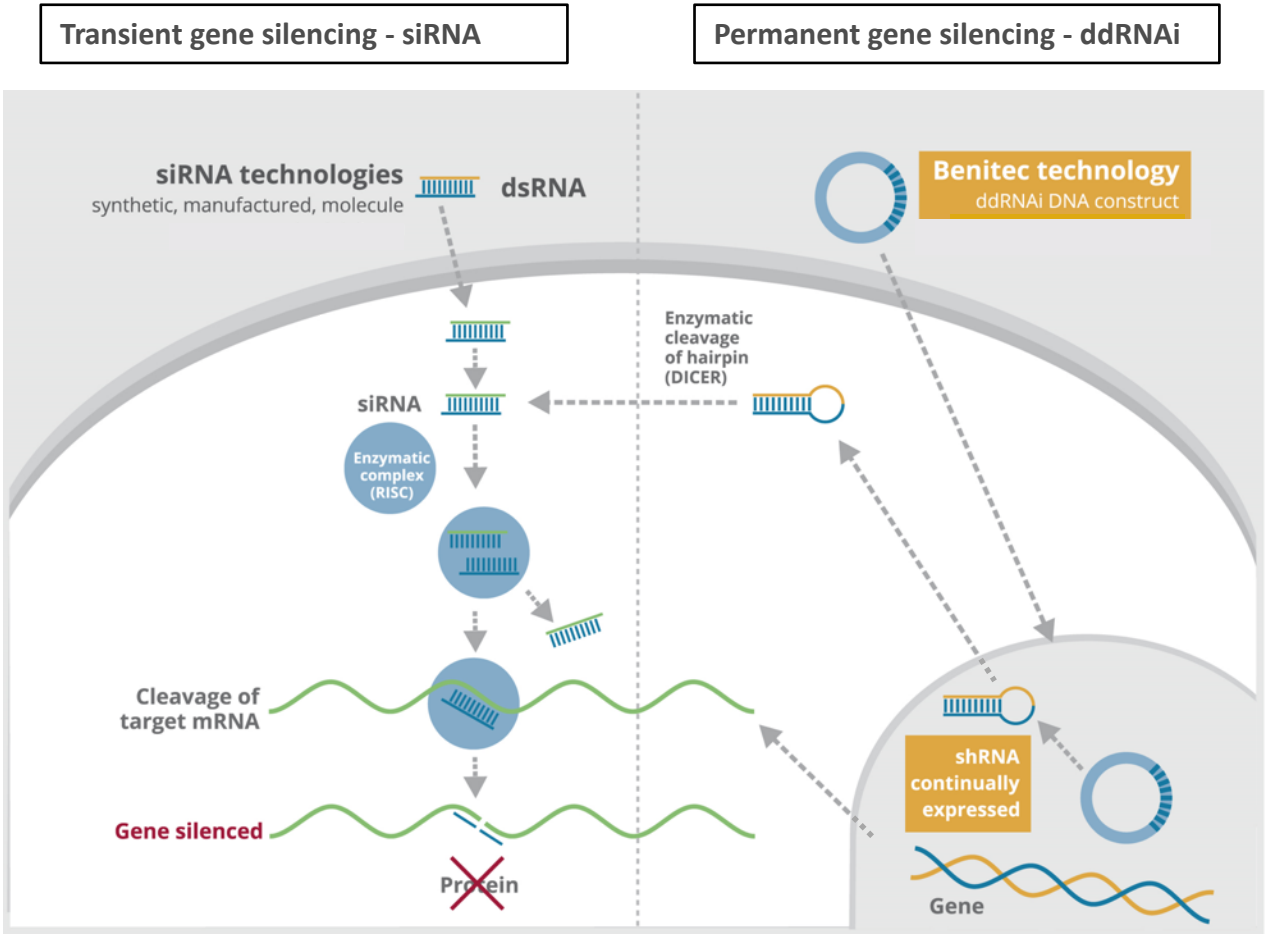
- Combines RNA interference with gene therapy delivery
- Long-term therapeutic potential from a single administration
- Constant, steady-state levels of shRNA expression
- Silence a single gene or target multiple genes simultaneously
- Simultaneous silencing of disease-causing genes and co-expression of normal genes to restore biological function



BB-301 for Oculopharyngeal Muscular Dystrophy

- *LATE-STAGE NON-CLINICAL ASSET WITH CATEGORY-LEADING BIOLOGICAL EFFICACY*
- *GLOBAL PREVALENCE OF OPMD EXCEEDS 15,000 PATIENTS AND COMMERCIAL OPPORTUNITY EXCEEDS $1 BILLION OVER THE LIFE OF THE PRODUCT*

Oculopharyngeal Muscular Dystrophy
Lead Candidate BB-301: *Product Overview*

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Oculopharyngeal Muscular Dystrophy

- Rare, autosomal dominant, monogenic disease
- Estimated prevalence of 15,000 patients in Western countries
- Characterized by eyelid drooping, swallowing difficulties, proximal limb weakness, death due to aspiration pneumonia and malnutrition

BB-301 Product Profile/Milestones

- Designed to treat dysphagia associated with OPMD
- 'Silence and Replace' represents a unique gene therapy mechanism
- 'Silence': Inhibits mutant and wildtype PABPN1 gene expression
- 'Replace': Simultaneously reintroduces normal PABPN1 gene to restore function
- Clinical trial to begin enrollment over the next 18-to-22 months

Value / Commercial Opportunity

- Orphan Drug Designation received in the US and EU provides commercial exclusivity and expeditious development path
- Commercial scale manufacturing process has been optimized and reproducibly executed
- Commercial opportunity in excess of $1 billion over the life of the product

Genetic Basis of OPMD: *Expansion of the Poly-Alanine Tract Within PABPN1*

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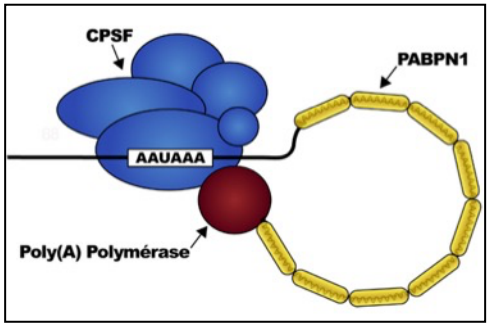
PABPN1:

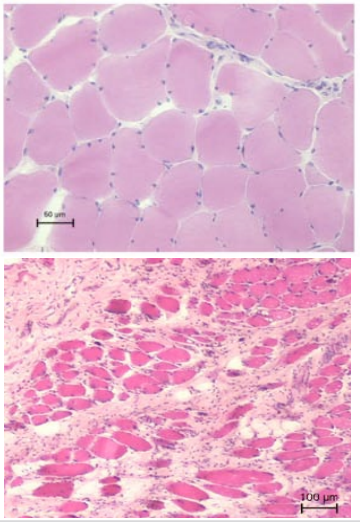
- Ubiquitous factor that promotes interaction between the poly(A) polymerase and CPSF (cleavage and polyadenylation specificity factor) and, thus, controls the length of mRNA poly(A) tails, mRNA export from the nucleus, and alternative poly(A) site usage



In OPMD:

- Genetic mutation results in trinucleotide repeat expansion within exon 1 of PABPN1 and results in an expanded poly-alanine tract at the N-terminal end of PABPN1
- Mutation generates a protein with an N-terminal expanded poly-alanine tract of up to 18 contiguous alanine residues prone to form aggregates called intranuclear inclusions (INIs)
- INIs that also sequester wild type PABPN1 could contribute to the "loss of function" phenotype associated with OPMD

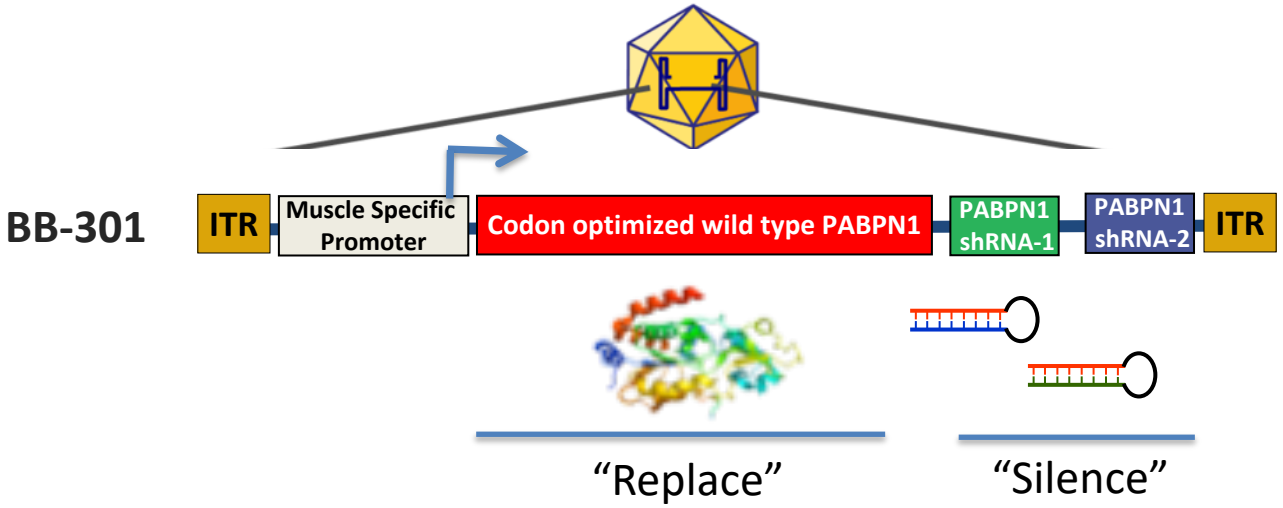
WT ATG $(GCG)_6$ ----------$(GCA)_3$ GCG GGG GCT GCG..
MUT ATG $(GCG)_6$ $(GCG)_{1\text{-}7}$ $(GCA)_3$ GCG GGG GCT GCG…--



Non-affected

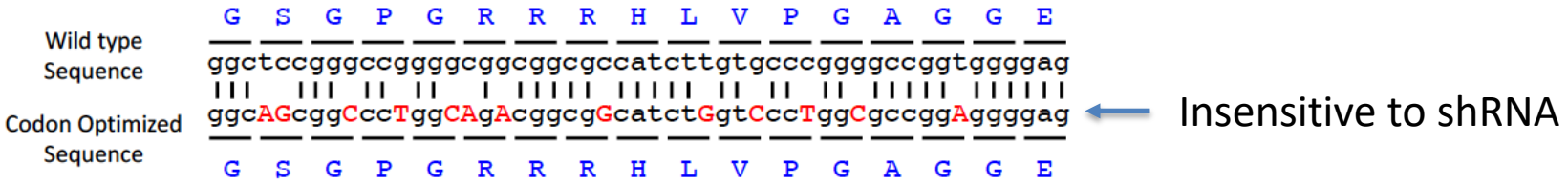
Affected

BB-301: *Single-Vector "Silence and Replace" Approach*



AAV

- Non-integrating, non-pathogenic viral delivery
- To date, AAV has been used in almost 200 clinical trials
- Sustained expression (years) following single injection



IND-Enabling Studies for BB-301 to be Completed Over the Next 12-to-18 Months

- The IND-enabling non-clinical studies outlined below are being carried out under the guidance of the scientific team at Benitec in close collaboration with a team of Thought Leaders in both medicine and surgery that have been deeply engaged in the treatment of OPMD patients for several decades

- **8-week Pilot Dosing study in Beagle dogs to confirm the transduction efficiency of BB-301 following direct intramuscular injection into the pharyngeal muscles via the use of an open surgical approach (*Beagle dog dosing has been completed in this study, and tissue analyses are currently ongoing*)**

  – Direct injection of BB-301 into the tibialis anterior muscle of A17 mice achieved robust transduction of the targeted skeletal muscle cells

  – This follow-up study in Beagle dogs is being conducted to optimize the proprietary dosing and surgical administration procedures for BB-301 injection into the pharyngeal muscle tissues that underlie the morbidity and mortality of OPMD and to refine the core analytical methods employed following the completion of dosing

- 12-week GLP Toxicology and Biodistribution study in Beagle dogs

8-Week BB-301 Pilot Dosing Study in Beagle Dogs: *Study Rationale and Background*

- BB-301 is directly injected into the pharyngeal muscles known to underlie the morbidity and mortality characterizing the natural history of OPMD, and large animals (e.g. canine subjects) possess anatomical architecture in the pharyngeal region similar to that of Human subjects with OPMD and were, therefore, identified by global regulatory agencies and our key collaborators as ideal subjects for the IND-enabling studies

- Against this backdrop, the BB-301 Pilot Dosing Study in Beagle dogs 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 (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

8-Week BB-301 Pilot Dosing Study in Beagle Dogs: *Study Design and Background*

- The 8-week 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
- Data analyses are ongoing for the canine subjects treated in BB-301 Pilot Dosing Study, and the interim data-points highlighted in this presentation are derived from the 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

Interim Results for the Pilot Dosing Study: *Summary of the Key Observations to Date*

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An interim analysis of the BB-301 Pilot Dosing Study in Beagle dogs revealed:

- 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 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

Interim Results for the Pilot Dosing Study: *Pharyngeal Muscle Tissue Transduction Levels for BB-301*

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- An interim analysis of the BB-301 pharyngeal muscle tissue transduction levels revealed 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)

- **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

Interim Results for the Pilot Dosing Study:
Pharyngeal Muscle Tissue Transduction Levels for BB-301

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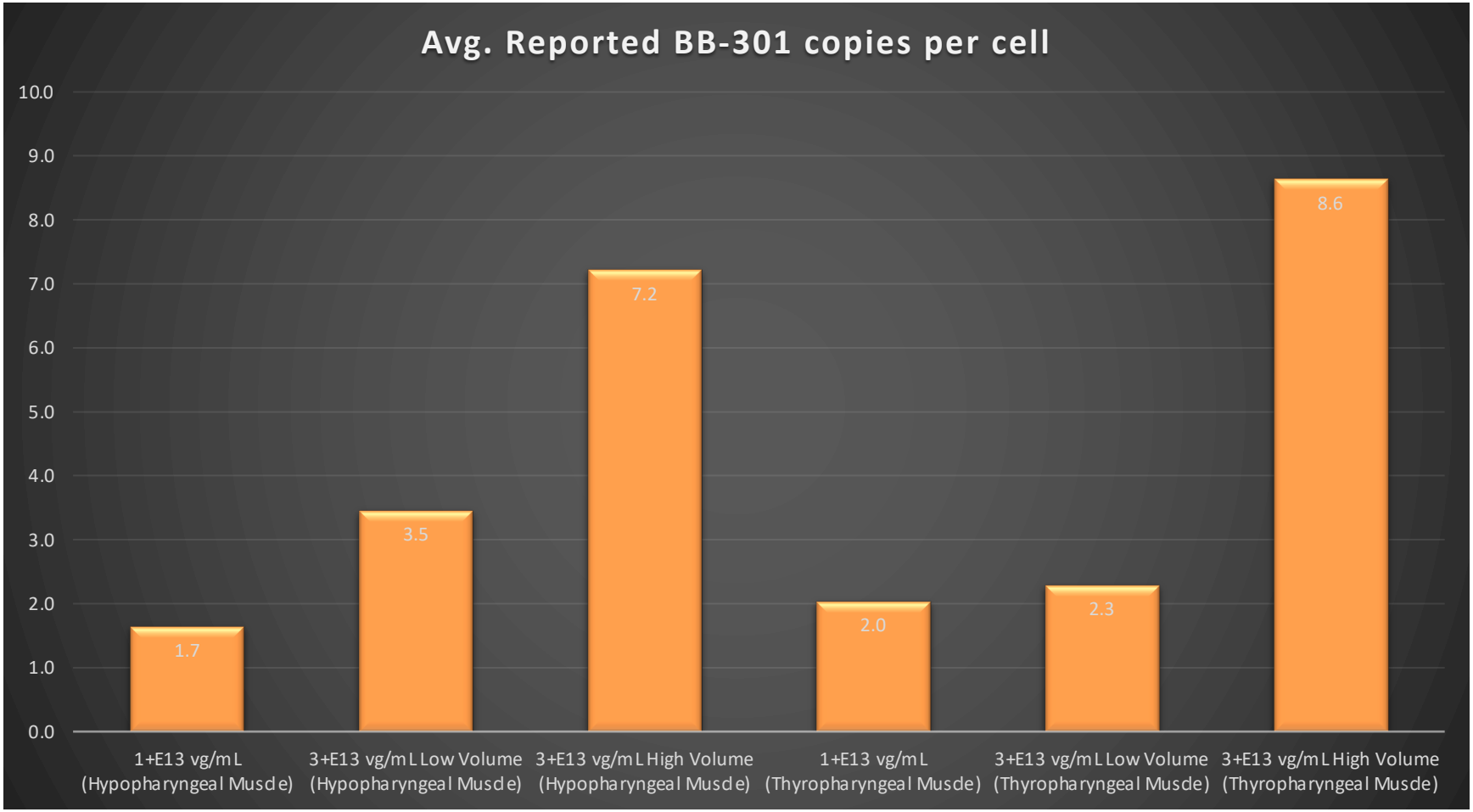

Interim Results for the Pilot Dosing Study: *Gene Expression Levels for BB-301 within Pharyngeal Muscles*

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- BB-301 encodes two distinct siRNA species:
  - siRNA13
  - siRNA17
- 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

Interim Results for the Pilot Dosing Study: *Gene Expression Levels for BB-301 within Pharyngeal Muscles*

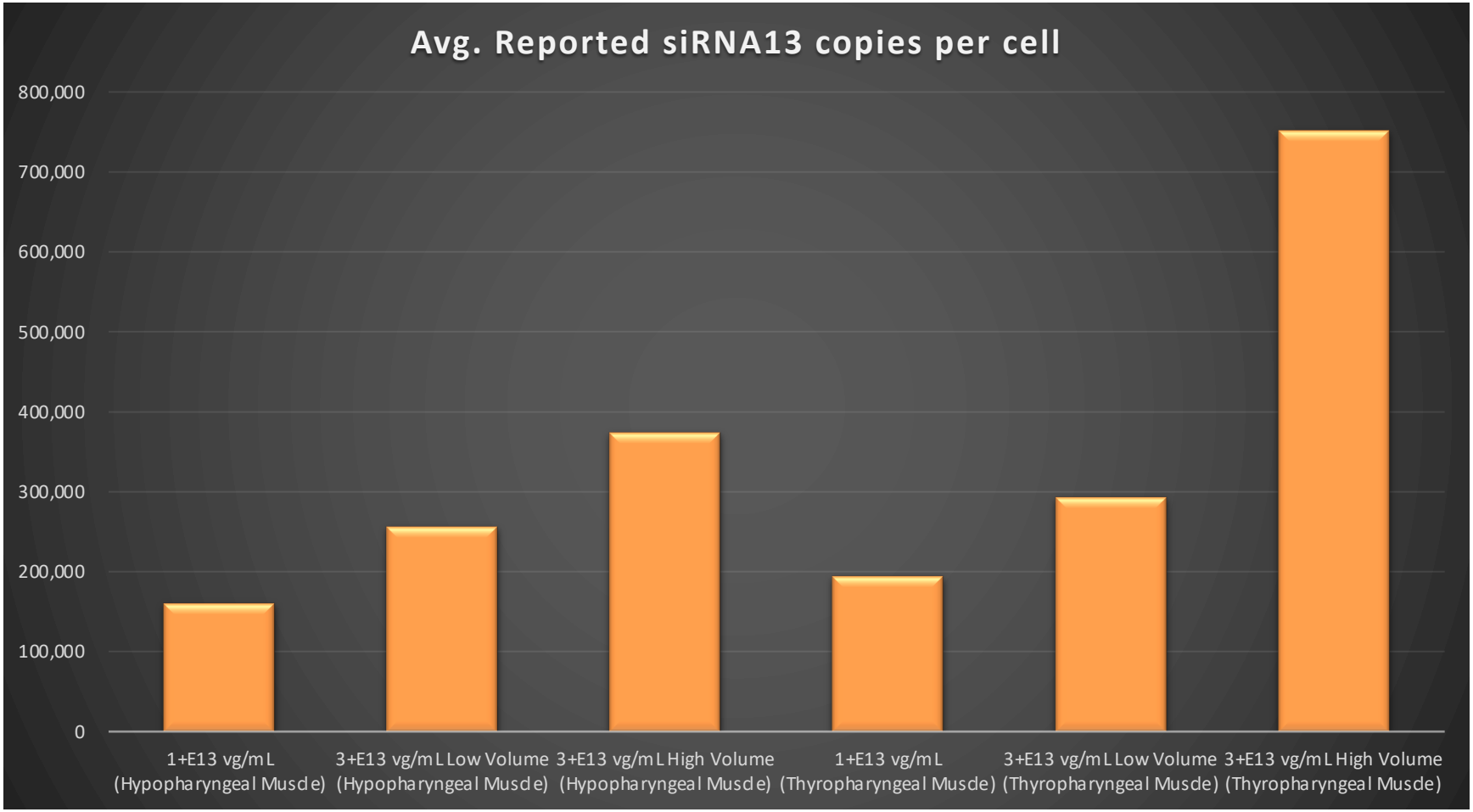
- An interim analysis of the BB-301 expression levels within the target pharyngeal muscle tissues revealed biologically significant, highly-consistent, dose-dependent levels of gene expression

- **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

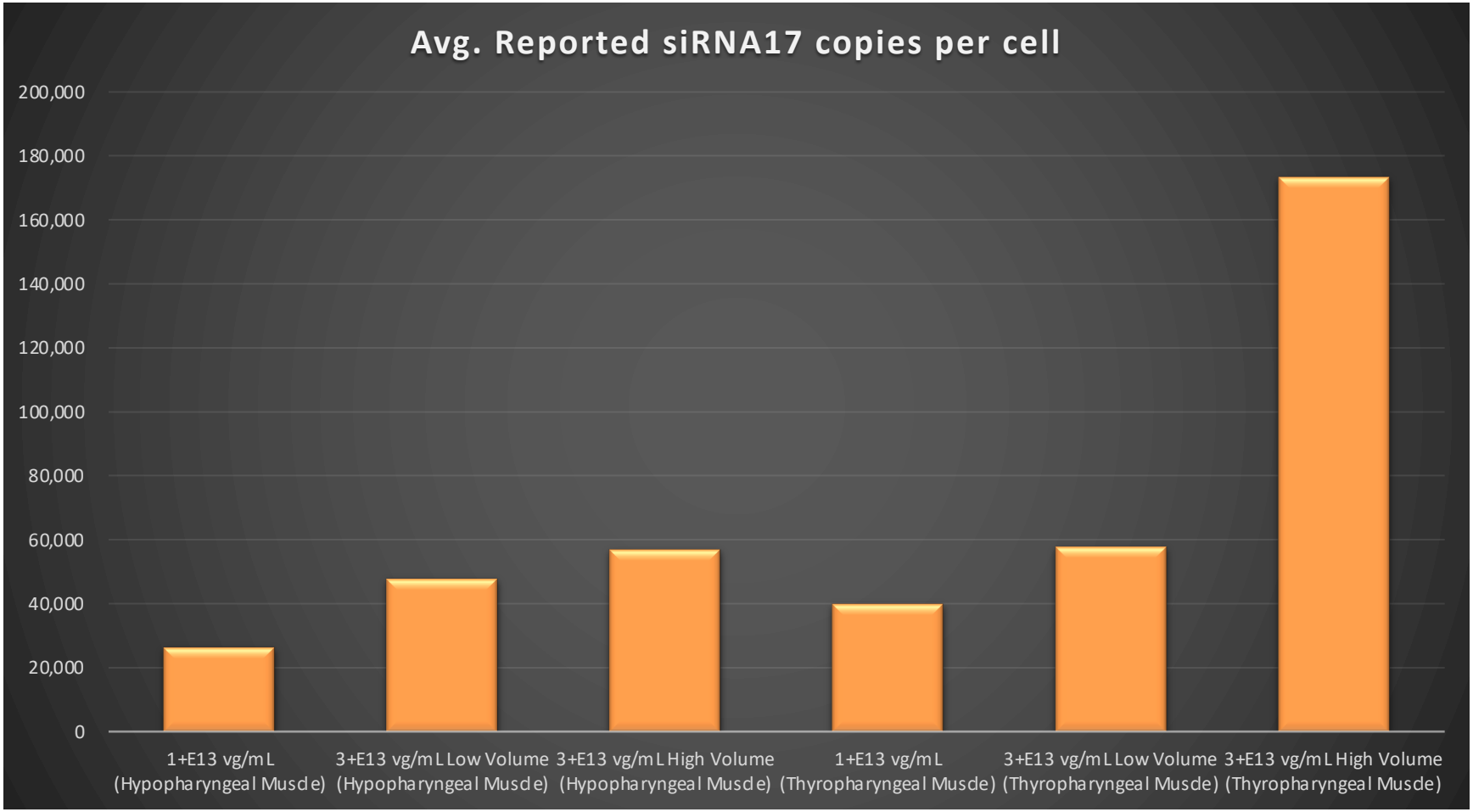
Interim Results for the Pilot Dosing Study: *siRNA13*

Expression Levels for BB-301 within Pharyngeal Muscles



Interim Results for the Pilot Dosing Study: *siRNA17*

Expression Levels for BB-301 within Pharyngeal Muscles



Interim Results for the Pilot Dosing Study: *coPABPN1 Expression Levels for BB-301 within Pharyngeal Muscles*

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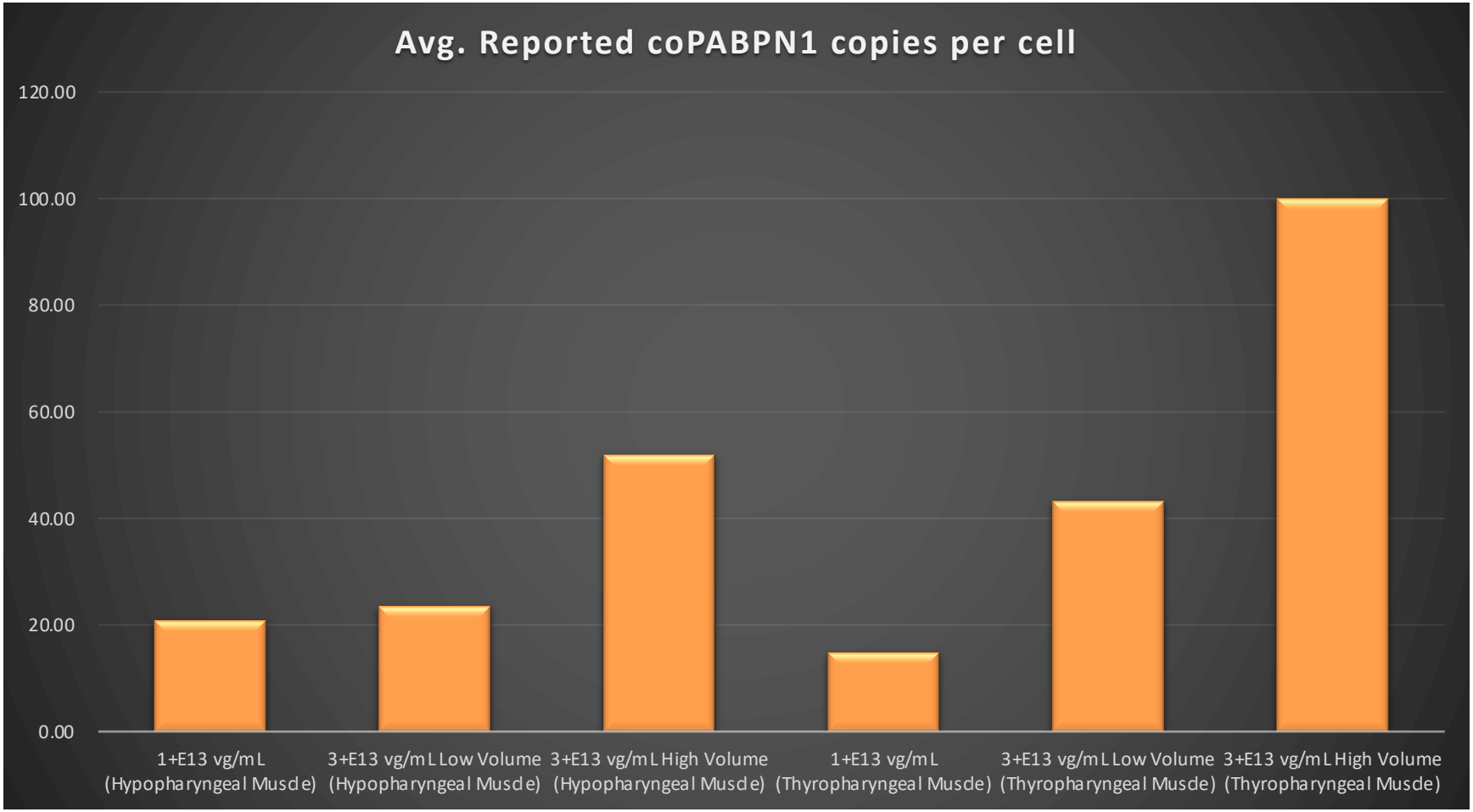


Interim Results for the Pilot Dosing Study: *PABPN1 Silencing (i.e. target "knock-down") within Pharyngeal Muscles*

- 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**

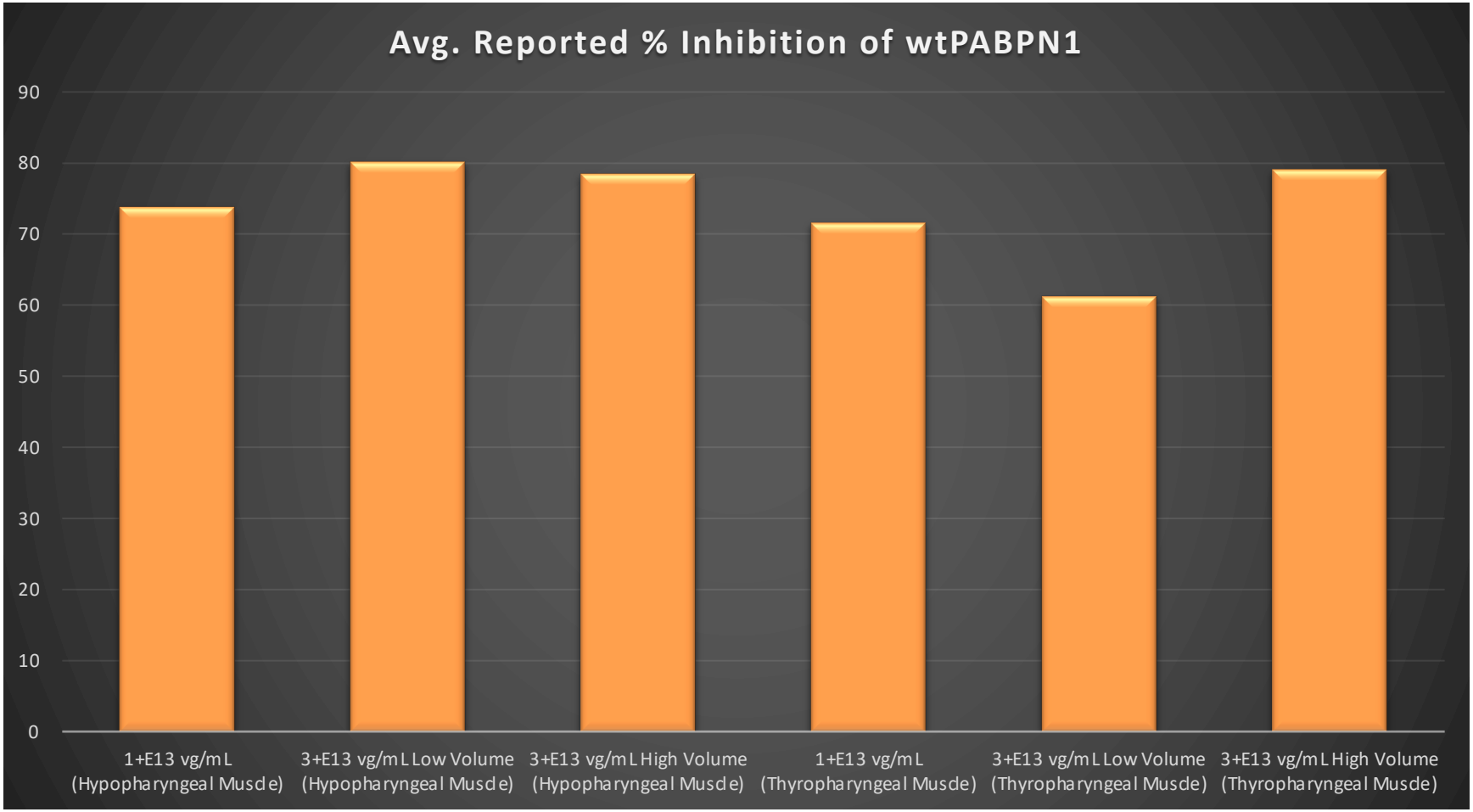
Interim Results for the Pilot Dosing Study: *PABPN1 Silencing (i.e. target "knock-down") within Pharyngeal Muscles*

- An interim analysis of the level of PABPN1 silencing achieved at 8-weeks revealed 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

- **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

Interim Results for the Pilot Dosing Study: *PABPN1 Silencing (i.e. target "knock-down") within Pharyngeal Muscles*



BB-301 Pilot Dosing Study: *Key Methodological Improvements to the Study Design and Analytical Procedures*

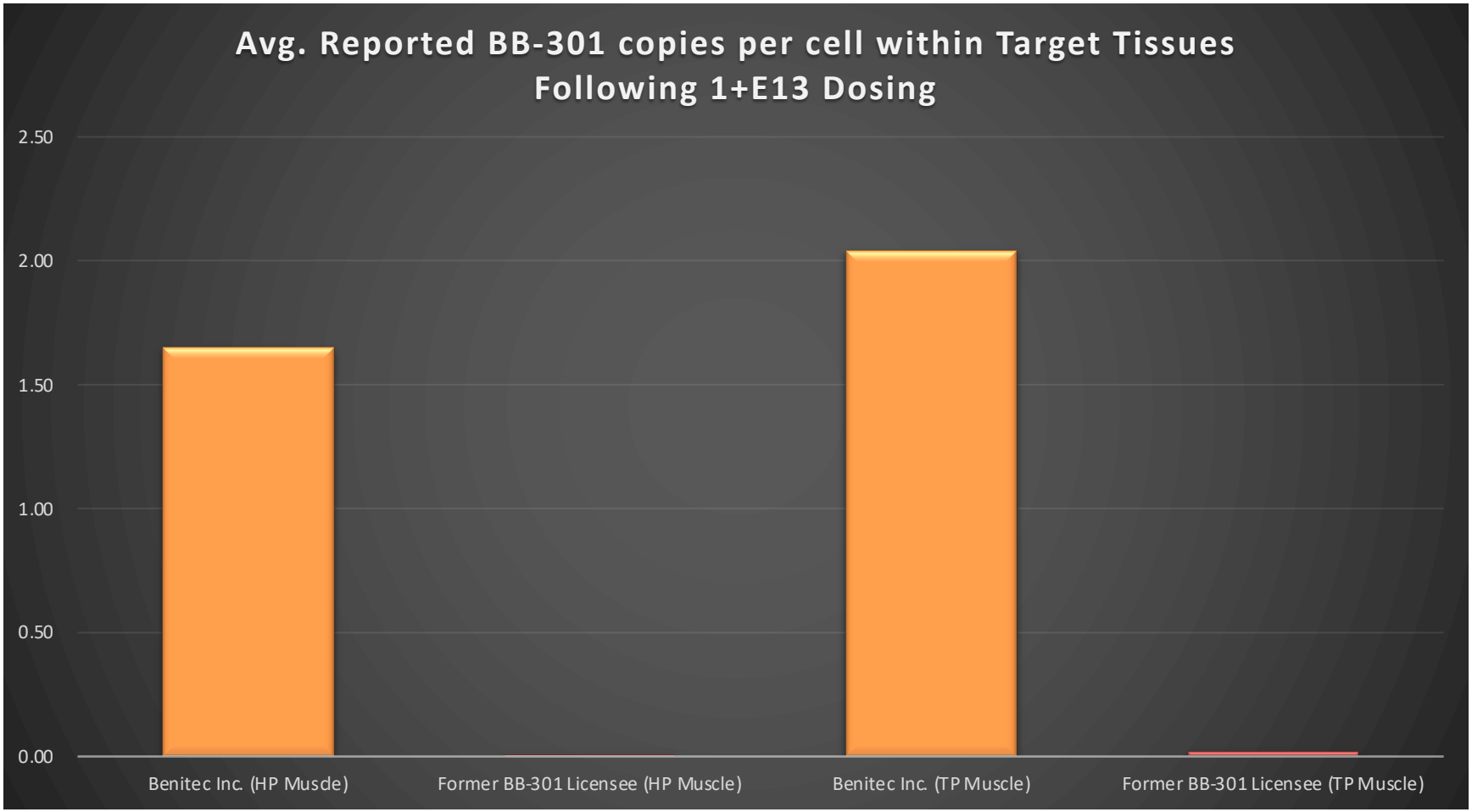
- It is critical to highlight the key methodological distinctions between the current BB-301 Pilot Dosing Study in Beagle dogs conducted by Benitec and the prior Beagle dog dosing study carried out independently by the previous BB-301 Licensee of Benitec

- 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 +24,650% improvement in BB-301 transduction of the HP muscle and a +11,027% improvement in BB-301 transduction of the TP muscle relative to the levels of BB-301 transduction observed by the previous BB-301 Licensee**

BB-301 Pilot Dosing Study: *Key Methodological Improvements to the Study Design and Analytical Procedures*



Interim Results for the Pilot Dosing Study: *Summary of the Key Conclusions*

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An interim analysis of the BB-301 Pilot Dosing Study in Beagle dogs revealed:

- Biologically significant, highly-consistent, dose-dependent levels of BB-301 tissue transduction
  - 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
- Durable and biologically significant levels of target gene knock-down 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
- Robust validation of Benitec's proprietary "Silence and Replace" approach has been achieved

BB-301 Development Program and Benitec Pipeline Updates: *Key Upcoming Milestones*

- Benitec has scheduled a Scientific Advice Meeting in France in May 2021 to review the interim data and the Phase 1 clinical trial design

- Benitec continues to plan for the initiation of the first-in-human clinical study of BB-301 in OPMD patients in 2022

- The interim data for the BB-301 Pilot Dosing Study validate the promise of the "Silence and Replace" approach to disease management, and Benitec plans to provide additional pipeline updates in 2H2021