

# Benitec Corporate Overview

**September 2019**

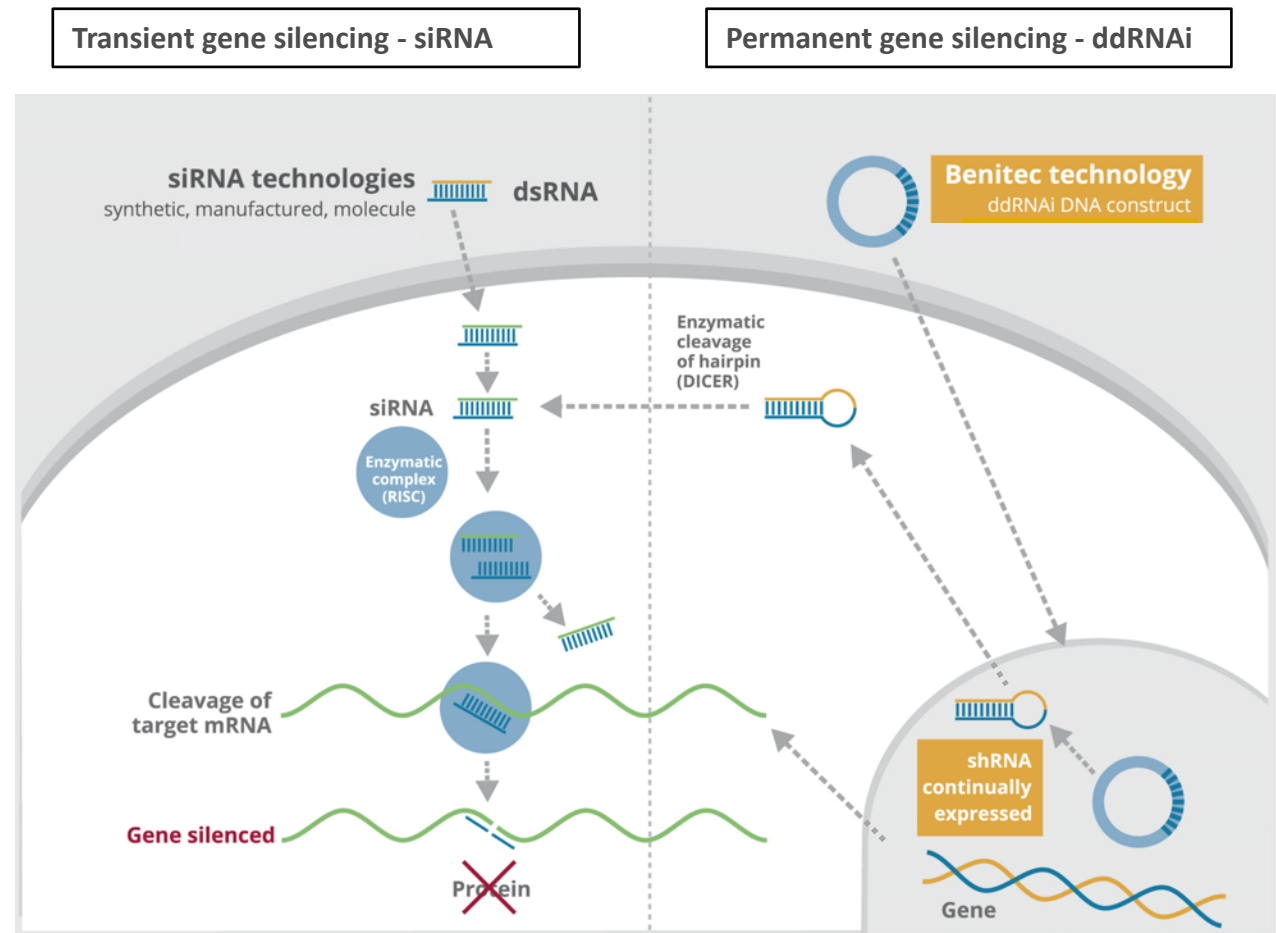
## **Safe Harbor Statement**

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," 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, including the initiation, progress and outcomes of clinical trials 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 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 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 and other risks detailed from time to time in filings that Benitec makes with US Securities and Exchange Commission, including our most recent annual report on Form 20-F and our reports on Form 6-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 Biopharma:** Gene therapy-focused biotechnology company developing novel genetic medicines derived from the proprietary DNA-directed RNA interference (“ddRNAi”) platform
- **Market Cap:** USD\$8.6 million
- **Net Cash** (*June 30, 2019*): USD\$15.5 million
- **Public Listing Exchanges:**
  - **NASDAQ** (*Listed in 2015*): *BNTC*
  - **ASX** (*Listed in 2002*): *BLT*

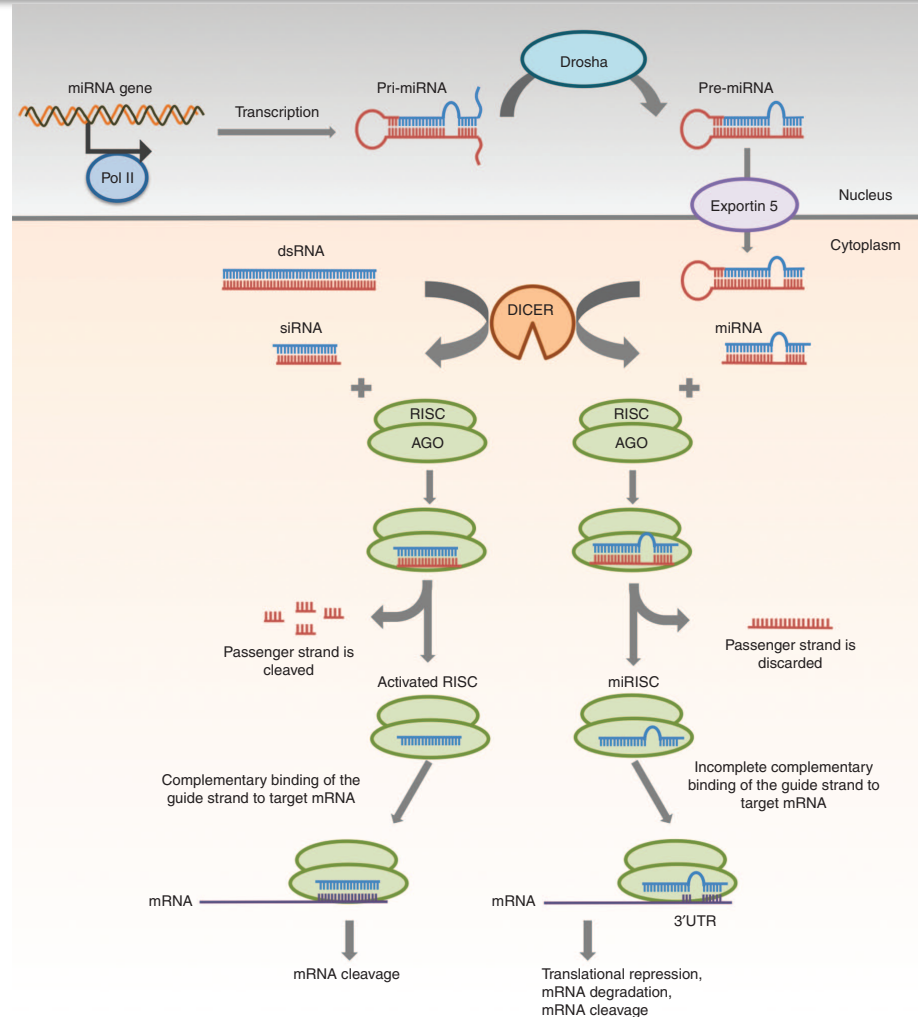
# Platform Enables Gene Therapy and Permanent Gene Silencing: *DNA-Directed RNA Interference (ddRNAi)*

- 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 with co-expression of normal genes to restore function



# Mechanism of RNA Interference Through the microRNA (miRNA) Pathway

- The use of shRNA/miRNA hybrids confers advantages with respect to expression, safety, and specificity
- Perfect complementary hairpins are processed by cellular RNase-III like enzymes at different positions, and a single “perfect” shRNA can be differentially processed into dozens of mature siRNA species (producing off-target effects and/or heterogenous pools with each siRNA species having differential inhibitory activity)
- Due to the intranuclear activity of Drosha, the use of a miRNA backbone allows for efficient processing of the shmiR into functional effector siRNAs with reduced heterogeneity
- Additionally, the expression of shRNA/miRNA hybrids is mediated by RNA II polymerase, which allows for the use of tissue specific promoters



- **Deep expertise in gene therapy**
- **Scientific operations in Hayward, California**
- **Internal manufacturing expertise**
  - Demonstrated capabilities for optimization of complex, scalable, AAV-based manufacturing processes
- **Management team with background in operations and capital allocation within the biopharmaceutical sector**

- **Jerel Banks, M.D., Ph.D.**

- *CEO and Executive Chairman*
- Healthcare investment professional with over 13 years of experience
- Former vice president and co-portfolio manager at Franklin Templeton Investments
- Earned an M.D. and Ph.D. at Brown University, and holds an A.B. in Chemistry from Princeton University

- **Megan Boston**

- *Executive Director, Head of Operations Australia*
- CEO and Managing Director of ASX listed entities
- Chartered Accountant with over 20 years of experience
- Held senior executive roles at various banking institutions in the area of risk and compliance, as well as PricewaterhouseCoopers



- **Claudia Kloth, Ph.D.**

- *SVP of Manufacturing*
- Over 20 years of cGMP manufacturing and 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 and process validation activities of Yervoy (Bristol-Myers Squibb)

- **Peter Roelvink, D.Sc.Ag.**

- *Senior Director Research*
- First to demonstrate delivery of a targeted vector from its native receptor to an artificial receptor
- Co-inventor on 19 issued US patents that cover RNAi vectors, targeted delivery of adenoviruses, and tissue specific expression using AAV

# Pipeline: *Oculopharyngeal Muscular Dystrophy (OPMD)* and *Chronic Hepatitis B Virus Infection*

| Program   | Delivery                | Discovery  | Preclinical | IND-Enabling | Early stage clinical (IND – Phase 2) | Late stage clinical (Phase 2 – Phase 3) | Commercial Rights |
|---|-------------------------|--|-------------|--------------|--------------------------------------|---|-------------------|
| Proprietary Pipeline Assets with Peer-Reviewed Proof-of-Concept |                         |  |             |              |                                      |   |                   |
| OPMD<br>BB-301  | ddRNAi<br>Intramuscular |  |             |              |                                      |   | Global            |
| HBV<br>BB-103   | ddRNAi<br>Systemic      |   |             |              |                                      |   | Global            |
|   |                         |  |             |              |                                      |   |                   |



# Broad Intellectual Property Portfolio for Lead Research Programs



- **OPMD-related intellectual property:**

- OPMD Family 4 anticipated expiry February 2040
- OPMD Family 3 anticipated expiry October 2039
- OPMD Family 2 anticipated expiry December 2037
- OPMD Family 1 anticipated expiry April 2037

- **AAV-related intellectual property:**

- AAV Family 1 anticipated expiry August 2038

- **HBV-related intellectual property:**

- HBV Family 3 anticipated expiry May 2037
- HBV Family 2 anticipated expiry May 2036

- **AAV-related intellectual property:**

- AAV Family 1 anticipated expiry August 2038

# BB-301 Program Overview

- BB-301 is an internally optimized, AAV-based gene therapy agent that can both silence the expression of the mutated, disease-causing PABPN1 gene (to slow, or halt, the underlying mechanism of disease progression in OPMD) and replace the mutant PABPN1 gene with a normal, “wild type” PABPN1 gene (to drive restoration of function in diseased cells)
- The biological efficacy and safety profiles observed for BB-301 in prior published non-clinical studies remain unchanged (BB-301 fully corrects the OPMD disease phenotype in the A17 mouse model), and upcoming publications will further outline the efficacy of BB-301 in this animal model
- The Benitec manufacturing team has optimized and reproduced the BB-301 commercial-scale manufacturing process, which removes key risks associated with production for clinical studies

- Over the preceding 12-months, an incomplete set of BB-301-focused non-clinical experiments were conducted in large animal subjects, the results of which were inconclusive
- As these non-clinical studies require repetition, Benitec will complete three non-clinical studies for BB-301 that will facilitate the filing of an Investigational New Drug (IND) application and the formal initiation of a Phase I clinical trial in patients suffering from OPMD
  - The three non-clinical BB-301 studies will be conducted in canine subjects and will support the optimization of the methods of administration, confirm the efficiency of vector transduction in the key tissue compartments underlying the disease phenotype, confirm the optimal drug doses in advance of initiation of human clinical studies, and finalize experiments designed to characterize any toxicological data-points

# BB-103 Program Overview: *Biological Activity of BB-102 and BB-103 Combinations with SOC on Key HBV Parameters (Seeking Strategic Investors)*

|  | Treatment                                     | Log Reduction of Serum HBV DNA | Log Reduction of HBsAg | Log Reduction of HBeAg |
|--|---|--------------------------------|------------------------|------------------------|
| Control groups                                       | entecavir (ETV)<br>6 mg/kg daily              | 2.63                           | 0.46                   | 0.37                   |
|  | pegylated interferon<br>30 mg/kg twice weekly | 2.41                           | 0.96                   | 1.09                   |
| Single administration of ddRNAi                      | BB-102<br>2e13 vg/kg                          | 1.87 max at Day 63             | 1.75 max at Day 70     | 1.17 max at Day 56     |
|  | BB-103<br>2e13 vg/kg                          | 2.17 max at Day 63             | 1.94 max at Day 70     | 1.61 max at Day 56     |
| Single administration of ddRNAi with daily entecavir | BB-102 + ETV                                  | * 3.72 +                       | 1.86                   | 1.42                   |
|  | BB-103 + ETV                                  | * 3.72 +                       | 2.14                   | 1.90                   |

## 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 USD\$1 BILLION*

# Oculopharyngeal Muscular Dystrophy

## Clinical Candidate BB-301: *Product Overview*



### 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 PABPN1 gene
- Replace: Simultaneously reintroduces normal PABPN1 gene to restore function
- Clinical trial to begin enrollment over the next 18-to-24 months

### Value / Commercial Opportunity

- US and EU Orphan status provides expeditious commercialization path
- Manufacturing process optimized at commercial scale
- Commercial opportunity in excess of \$1 billion

## Patterns of Inheritance, Epidemiology, and Age of Onset:

- Rare autosomal dominant inheritance
- Prevalence of 1:100,000 (Europe)
- Prevalence as high as 1:600 in specific populations
- Typical age of onset is in 40's-to-60's

## Natural History:

- Progressive eyelid drooping (ptosis)
- Progressive swallowing difficulties (dysphagia)
- Proximal limb weakness
- Chronic choking, regurgitation, aspiration pneumonia
- Death due to aspiration pneumonia and malnutrition

## Histopathology:

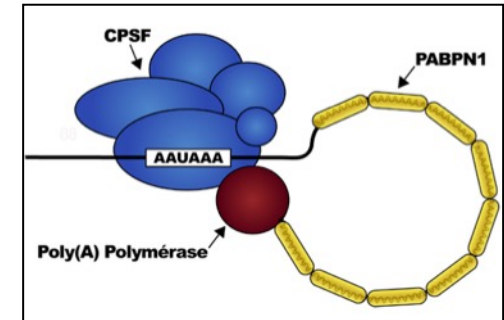
- Loss of muscle fibers in affected anatomical regions
- Variations in the size of muscle fibers
- Fibrosis (connective tissue)



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

## PABPN1:

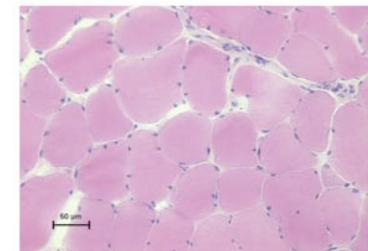
- Ubiquitous factor that promotes interaction between the poly(A) polymerase and CPSF (cleavage and polyadenylation specificity factor) and thus controls the length of mRNA poly(A) tails, mRNA export from the nucleus, and alternative poly(A) site usage



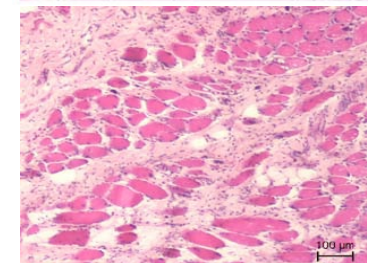
## In OPMD:

- 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) <sub>6</sub> | -----                | (GCA) <sub>3</sub> | GCG GGG GCT GCG..   |
| MUT | ATG (GCG) <sub>6</sub> | (GCG) <sub>1-7</sub> | (GCA) <sub>3</sub> | GCG GGG GCT GCG.... |



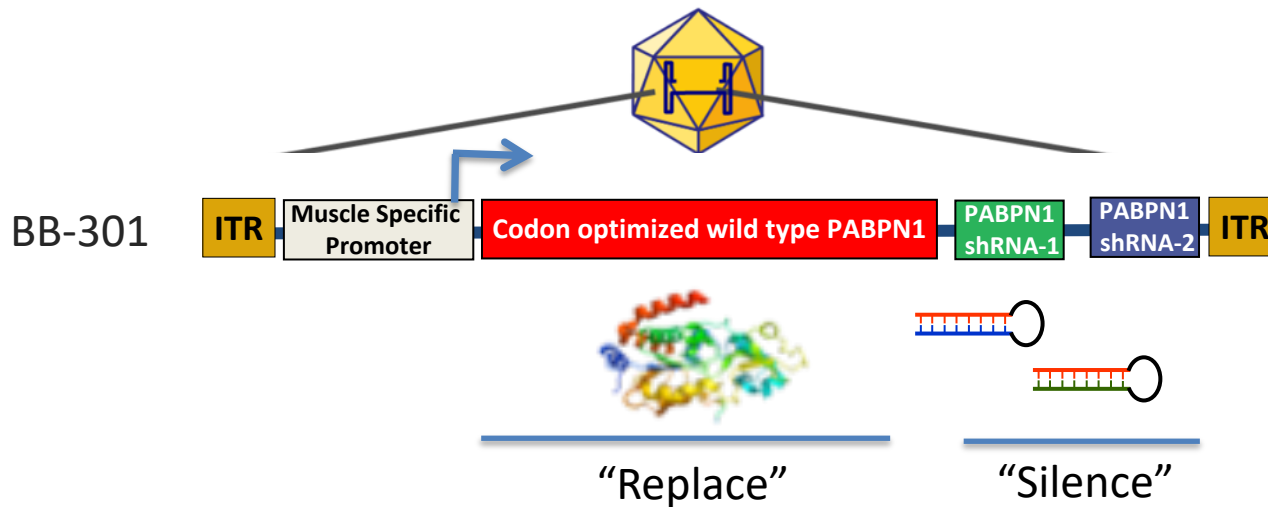
Non-affected



Affected



- Benitec has engineered a single-vector approach for the treatment of OPMD
- This proprietary approach combines the essential elements of a prior two-vector system (described in the supplementary slides) into a single recombinant AAV vector
- The construct (BB-301) is composed of a modified AAV serotype 9 (AAV9) capsid that expresses a single bifunctional construct under the control of a single muscle specific Spc5-12 promoter for the co-expression of both the codon-optimized PABPN1 protein and two shRNA molecules directed against wild type and mutant PABPN1 modeled into miRNA backbones
- Benitec demonstrated in a key non-clinical model (A17 mouse model) that a single intramuscular injection of BB-301 results in robust inhibition of mutant PABPN1 and concomitant replacement of the codon-optimized PABPN1 protein
  - In the A17 mouse model, the treatment restores muscle strength and muscle weight to wild type levels and improves other physiological hallmarks of the disease



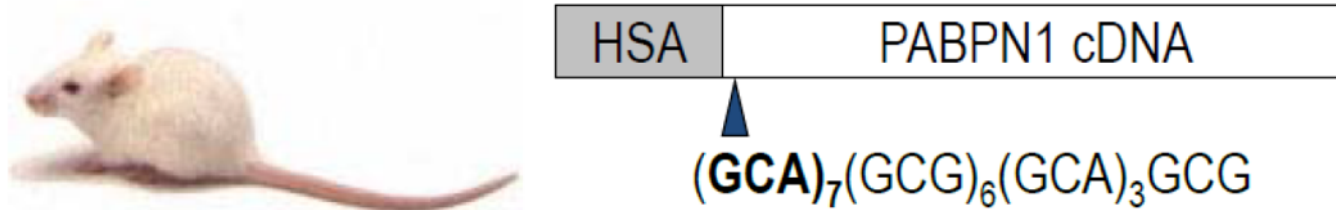
## AAV

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

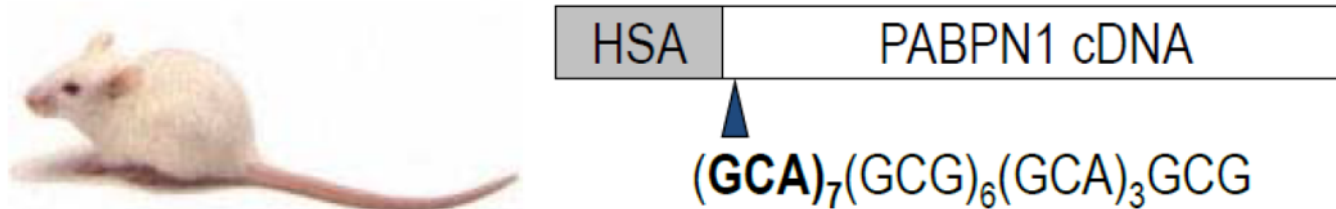
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|--------------------------|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|                          | G  | S | G | P | G | R | R | R | H | L | V | P | G | A | G | G | E |
| Wild type Sequence       | ggctccggggccggggcgggcgccatcttggtgcccggggccgggtggggag |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|                          |  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Codon Optimized Sequence | ggcAGcggCccTggCAGAcggcgGcatctGgtCccTggCgcccggAggggag |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|                          | G  | S | G | P | G | R | R | R | H | L | V | P | G | A | G | G | E |

← Insensitive to shRNA

# Non-Clinical Model of OPMD: *The 'A17' Mouse*

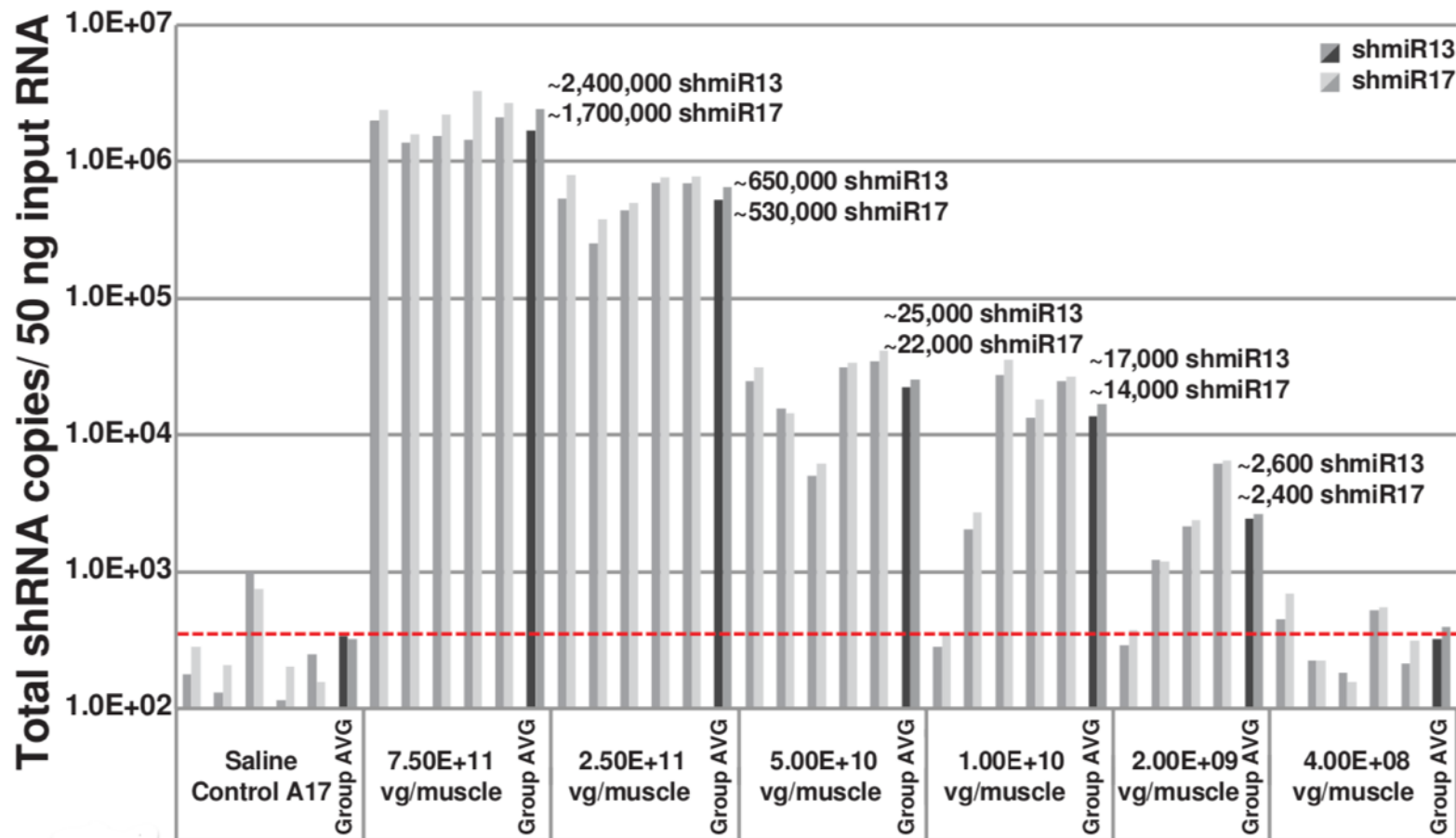


- **Transgenic A17 mouse:** expresses a mutated bovine PABPN1 driven by the human skeletal actin promoter in addition to the endogenous PABPN1
- **Reproduces the severe muscle atrophy found in the human phenotype**
- **Mimics other distinct pathological attributes of the human disorder:**
  - Progressive muscle weakness/atrophy
  - Fibrosis
  - Mitochondrial/Ubiquitin-Proteasome defects
  - Muscles contain intranuclear inclusions

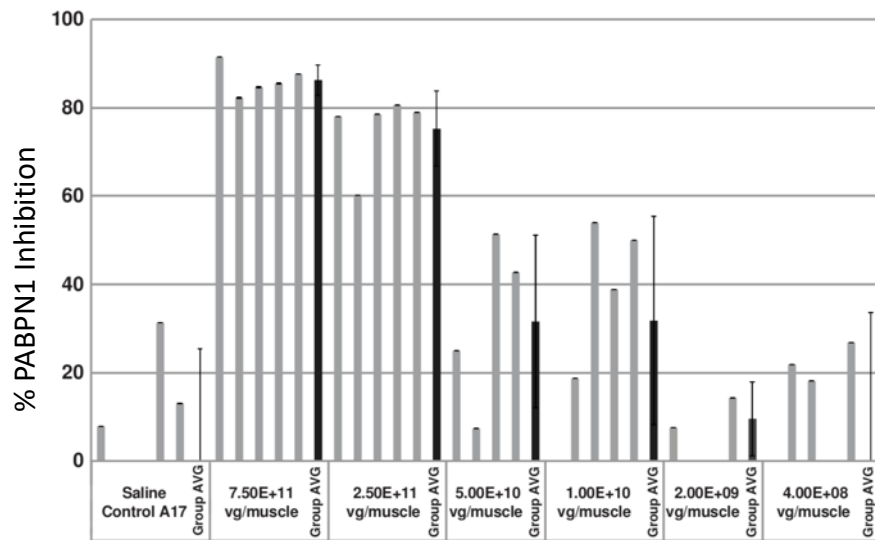


- The experiment was performed over 14-weeks to evaluate the activity of BB-301 as single doses administered at  $4 \times 10^8$  to  $7.5 \times 10^{11}$  vg/muscle
- A single dose of vector was injected into the Tibialis Anterior (TA) muscle of 10-12 week old A17 mice at concentrations ranging from  $4 \times 10^8$  to  $7.5 \times 10^{11}$  vg/muscle, and at 14-weeks post administration, mice were anesthetized and contractile properties of TA muscles were analyzed by in-situ muscle electrophysiology
- Mid-range doses of BB-301 resulted in 75% inhibition of mutant PABPN1 and 26% restoration of wild type PABPN1 activity, leading to full restoration of muscle strength, clearance of INIs, and a reduction of fibrosis
- An additional experiment conducted over the course of 20-weeks demonstrated that a suboptimal dose of BB-301 that achieves only partial resolution of the phenotype at week-14 is also able to facilitate significant benefit at 20-weeks, as evidenced by full restoration of all parameters relating to muscle strength, weight and INI formation associated with disease pathology in the A17 model

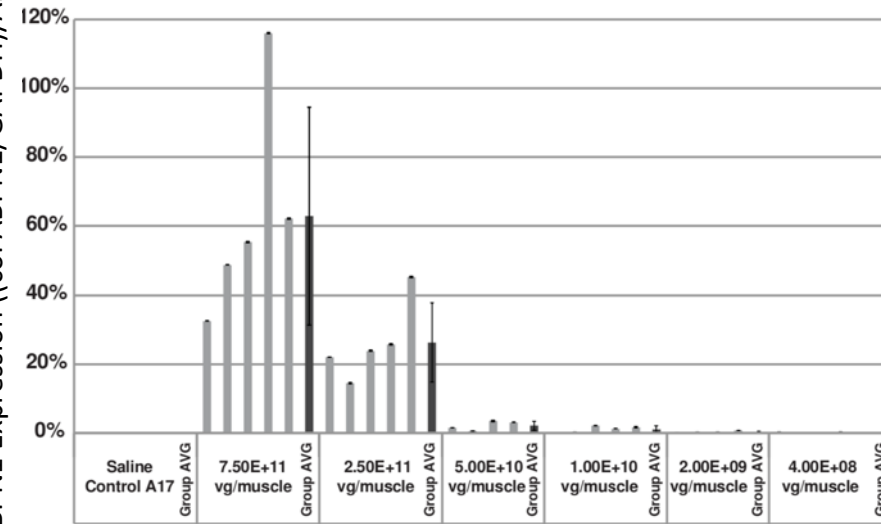
# BB-301 Drove Dose-Dependent shRNA Expression (Analysis Performed 14-weeks after Administration)



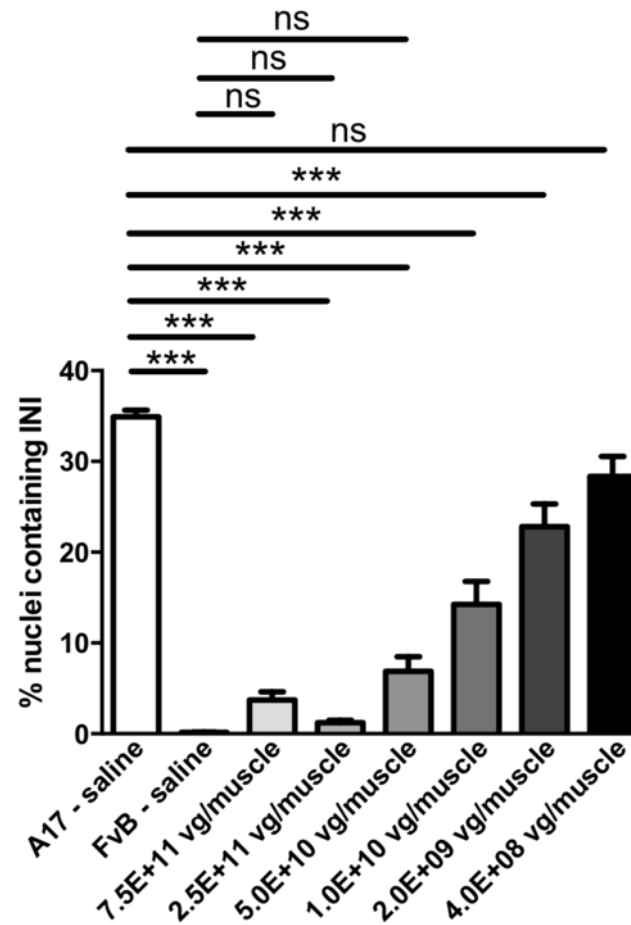
# BB-301 Inhibits Mutant PABPN1 Expression and Restores Near Wild Type Levels of coPABPN1 (Analysis Performed 14-weeks after Administration)



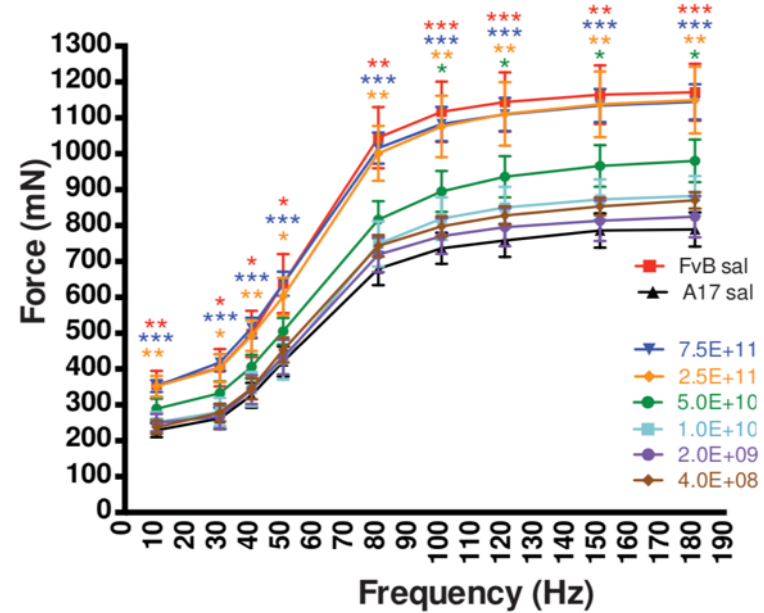
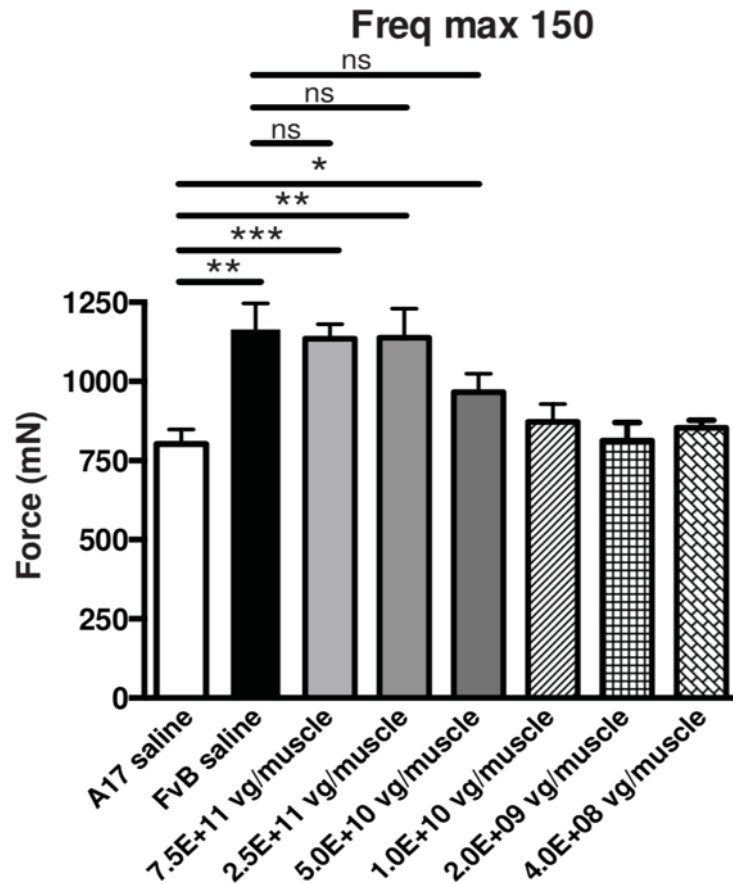
Relative coPABPN1 Expression ((coPABPN1/GAPDH)/A17 Saline)



# BB-301 Drives Dose-Dependent Resolution of Intranuclear Inclusions in the Injected Muscles



# BB-301 Restores Muscle Force to Wild Type Levels (Analysis Performed 14-weeks after Administration)



Restoration of muscle strength was assessed by muscle contractility measurements in response to a series of induced impulses that ranged from 10 to 180 Hz



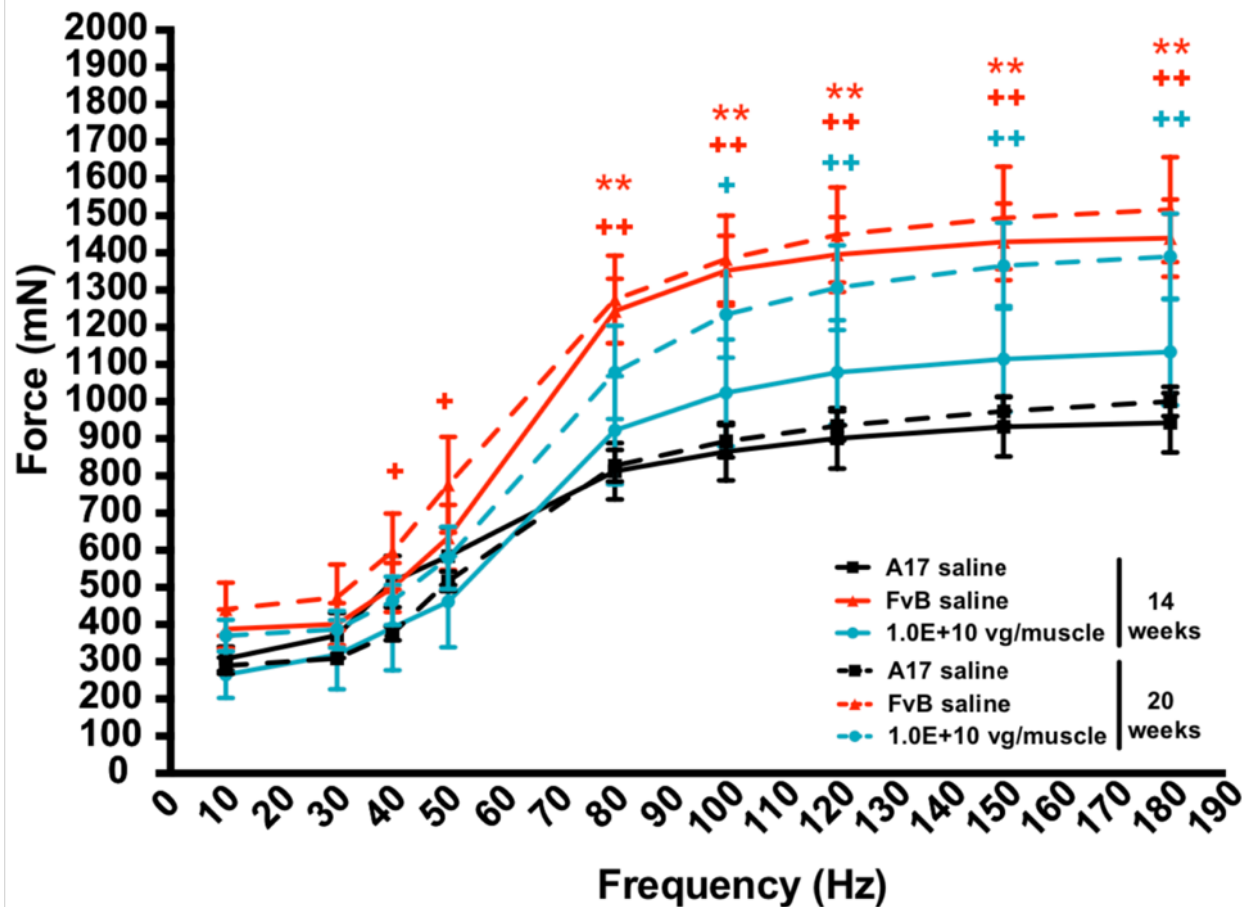
# BB-301 Drives Robust Phenotype Rescue over a Broad Range of Doses

- Data suggest that modest restoration of strength (at the  $5 \times 10^{10}$  vg/muscle dose) occurs at 31% PABPN1 inhibition when coupled with wildtype protein expression at 2% of normal levels
- $2.5 \times 10^{11}$  vg/muscle resulted in complete maximal force restoration despite modest levels of inhibition (75%) and codon-optimized protein expression (26%)
- These data suggest that partial knockdown of mutant BB-301, when coupled with partial replacement, is sufficient to significantly reduce INIs, increase muscle function, and improve disease phenotype, supporting biological efficacy over a broad range of doses

|                  | "Silence"         | "Replace"           |
|------------------|-------------------|---------------------|
| BB-301 Dose (vg) | Inhibition PABPN1 | coPABPN1 Expression |
| 7.50E+11         | 86%               | 63%                 |
| 2.50E+11         | 75%               | 26%                 |
| 5.00E+10         | 31%               | 2%                  |
| 1.00E+10         | 32%               | 1%                  |
| 2.00E+09         | 14%               | 0%                  |
| 4.00E+08         | 0%                | 0%                  |

# BB-301 Injected at “Suboptimal” Doses Restores Muscle Force to Wild Type Levels

(Analysis Performed at 14-weeks and 20-weeks after Administration)



# Non-Clinical Experiments Conducted During the Past 12-months in Canines Employed Inconsistent Dosing Methods and Tissue-Processing Techniques



- An endoscopic procedure was employed, without the aid of fluoroscopy or electromyography, to directly inject BB-301 into the muscles of interest in canines
  - This method of administration led to significant variability with respect to the vector genomes of BB-301 delivered to the targeted anatomical sites (e.g. contralateral sides of the same target muscle contained vector copy numbers that could vary by 3-fold to 8-fold)
- Additionally, a chemical dye-based tissue marking procedure was employed to facilitate analyses of the tissues near the BB-301 injection sites in the muscles of each animal, however, as the dye was not present at the time of necropsy, this method did not support accurate characterization of the vector copy numbers achieved following BB-301 administration (i.e. BB-301 tissue transduction)
  - Several concentrations and volumes of dye were injected with BB-301 or adjacent to the dosing site, however, at necropsy, no dye was found in the target muscles

# New BB-301 Non-Clinical Studies Will be Conducted Over the Next 12-to-18 Months



- The IND-enabling non-clinical studies will be 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
- 6-week study in Beagle dogs to confirm the transduction efficiency of BB-301 upon administration via direct intramuscular injection into the pharyngeal muscles following an open surgical approach
  - Direct injection of BB-301 into the tibialis anterior muscle of A17 mice demonstrated that AAV9PL achieved robust transduction of the targeted skeletal muscle cells
  - This follow-up study will be conducted to optimize the dosing and surgical administration procedures for BB-301 injection into the pharyngeal muscle tissues of interest in Beagle dogs and, ultimately, in human subjects
- 20-week dose-range finding study in Beagle dogs
  - This study will be conducted to further bolster our understanding of the transduction efficiency of BB-301 in addition to providing a more fulsome characterization of the level of shRNA and codon-optimized PABPN1 expression observed across distinct drug doses administered into the targeted pharyngeal muscles (and will facilitate BB-301 dose selection for the Phase I/II clinical trial)
- 12-week regulatory toxicology study in Beagle dogs

# Conclusions

**Bolstered by robust non-clinical proof-of-concept data for BB-301, Benitec will advance BB-301 through IND-enabling studies and subsequent clinical testing in OPMD patients**



**Continued demonstration of positive non-clinical data and early-stage clinical trial data in an orphan Muscular Dystrophy indication is anticipated to support improved patient outcomes and enhanced shareholder value**



**Additionally, non-clinical data and early-stage clinical trial data supportive of biological and clinical efficacy will serve as validation for the broader research and discovery platform**



**In infectious disease indications (e.g. Chronic Hepatitis B Virus infection), strategic partnerships for genetic medicine assets have been executed that are valued at more than USD\$3 billion with significant up-front cash payments**

September 2019

# **SUPPLEMENTARY SLIDES**

## 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 USD\$1 BILLION*

# Two-Vector “Silence-and-Replace” Approach for the Treatment of OPMD



- Benitec previously designed a two-vector gene therapy strategy that significantly ameliorated the OPMD-derived pathology in the A17 mouse model of the disease (the A17 mouse model is described on Slide 20)
- This initial approach was based on the intramuscular injection of two recombinant AAVs, one expressing three short hairpin RNAs (shRNAs) to silence both mutant and wildtype PABPN1 and one expressing a codon-optimized, shRNA-insensitive version of PABPN1
  - The two recombinant AAV vectors were comprised of (1) a recombinant AAV8 producing short hairpin RNA (shRNAs) to silence endogenous (mutant and wildtype) PABPN1 and (2) an AAV9 vector expressing a codon-optimized version of wildtype PABPN1 (coPABPN1) that takes advantage of amino acid codon degeneracy to produce the wildtype PABPN1 protein from a mRNA that is not targeted by the anti-PABPN1 shRNAs
- Single administration of either of the two vectors resulted only in partial improvement of the mutant phenotype, however, simultaneous administration of both vectors led to restoration of muscle strength to wildtype levels
- A two-vector approach for human therapeutic applications is, however, undesirable, as it would require two independent manufacturing processes, which can significantly increase costs, technical risk and introduce potential regulatory challenges as well



## BB-103 for Chronic Hepatitis B Virus Infection

- *LATE-STAGE NON-CLINICAL ASSET FOR LICENSURE TO POTENTIAL PARTNERS*
- *CATEGORY-LEADING BIOLOGICAL EFFICACY ACHIEVED IN VALIDATED ANIMAL MODEL*

# Chronic Hepatitis B Virus Infection

## Clinical Candidate BB-103: *Product Overview*



### Chronic Hepatitis B Virus Infection

- Global prevalence estimated at 257 million people
- Need for safe and effective therapies that promote the restoration of a host immune response through targeted HBsAg knockdown

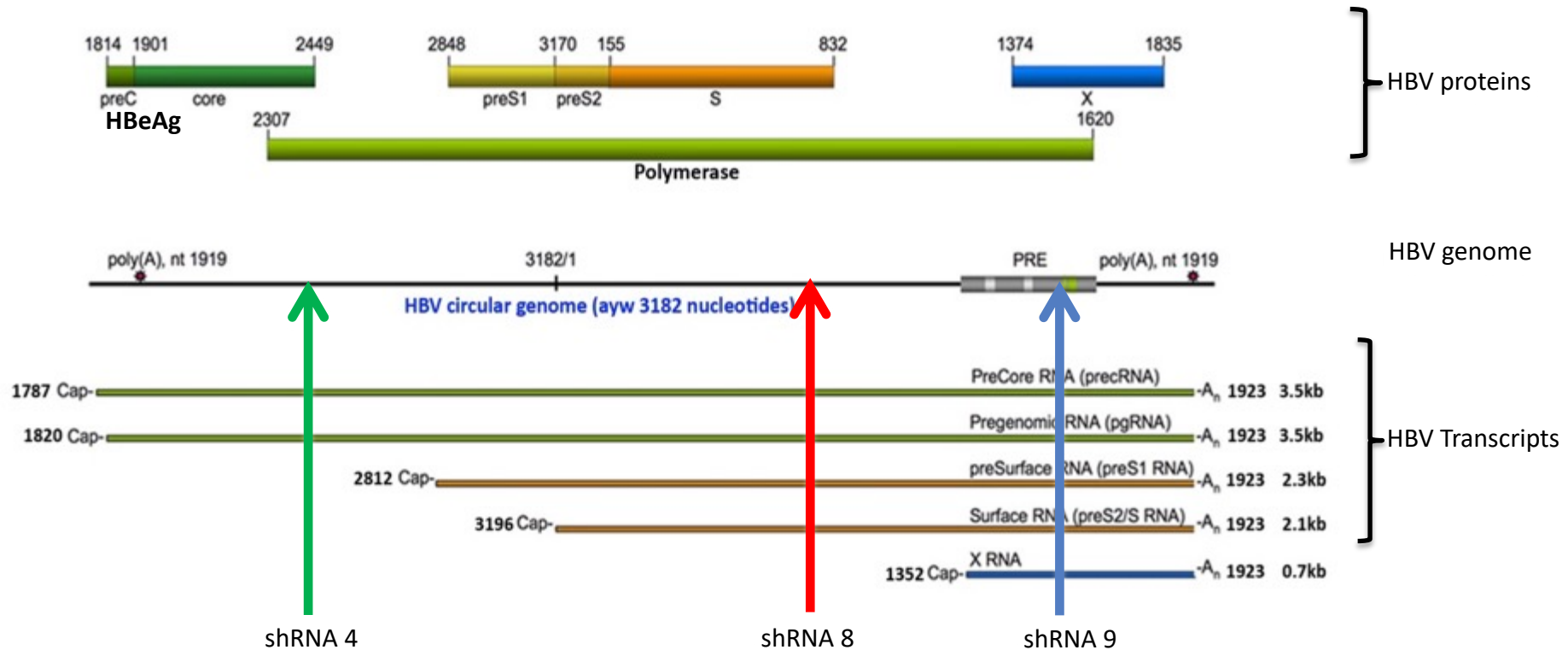
### BB-103 Product Profile/Milestones

- Designed as a single-dose treatment to be paired with existing standard of care
- Combined with a daily NUC, a single dose of BB-103 results in a > 4 log drop in HBV DNA and > 2 log drop in HBsAg in human chimeric liver mouse model
- Clinical trial could begin enrollment over the next 18-to-24 months
- Pre-IND FDA meeting informed a clear and expeditious path to the clinic

### Value / Commercial Opportunity

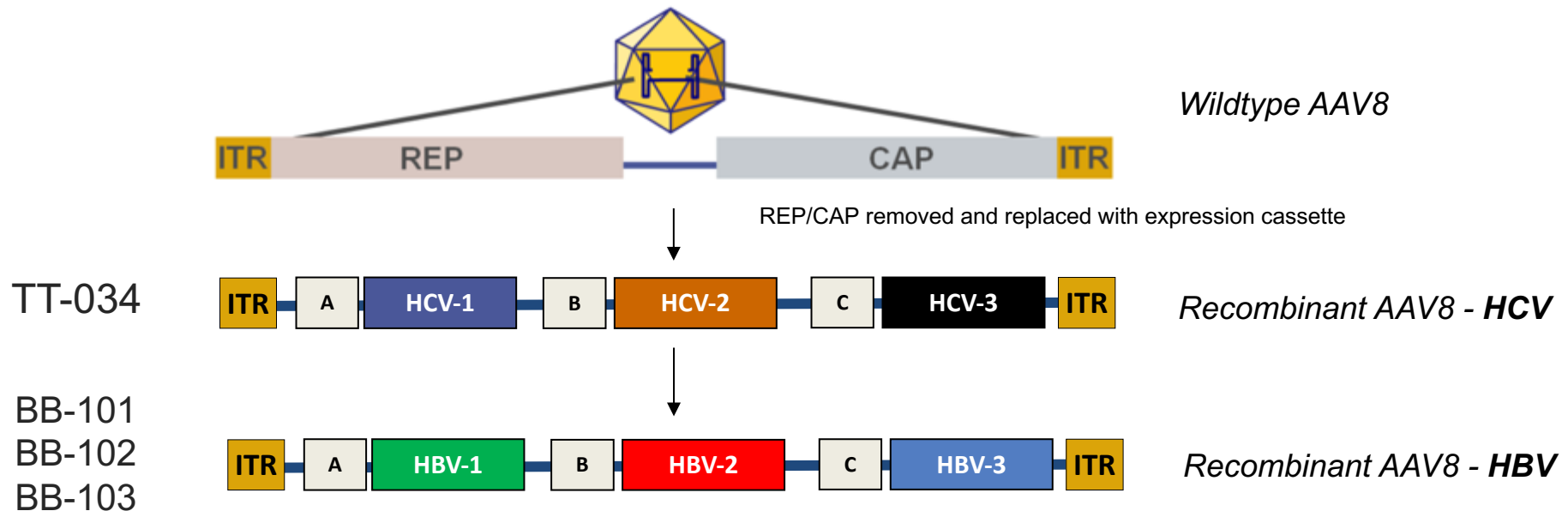
- BB-103 is the only gene silencing agent that guarantees perfect compliance, providing the opportunity to reduce the development of drug resistance
- Recent Janssen licensure of Arrowhead HBV gene silencing program for \$250 million up-front and \$3.7 billion of milestones executed on the basis of interim 3-month follow-up data for 8 patients (without evidence of seroconversion)
- Commercial opportunity in excess of \$1 billion

# shRNAs Employed in BB-301 Construct Ensure Cleavage of Multiple HBV Transcripts



\* Sequences selected for shRNA are well conserved across HBV genotypes A-H

# BB-103: Anti-HBV Agent Builds on Key Lessons from First-in-Man TT-034 Trial in HCV



- Replacement of three anti-HBV shRNA into anti-HCV shRNA positions
- Maintains AAV8 capsid – biodistribution identical to TT-034 (can use other capsids)
- Employs optimal aspects of the recombinant expression cassette
- TT-034 clinical data guides HBV Protocol development and provides simpler regulatory path

## TT-034 for HCV

- **Mutant promoters led to suboptimal expression of shRNA hairpins and modest suppression of HCV replication**
  - **Drove expression of 3-to-191 shRNA copies per cell**
- **Wild type shRNA constructs drove variable expression of biologically active hairpins**
  - **Led to expression of a mosaic of RNA molecules and diluted biological activity**

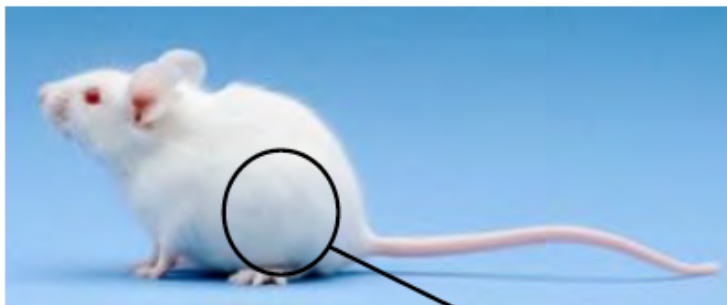
## BB-103 for HBV

- **Wild type Pol III promoters increased expression of shRNA hairpins by several orders of magnitude**
  - **Drove expression of 903-to-129,670 shRNA copies per cell**
- **shRNA constructs were embedded into an artificial miRNA backbone**
  - **Significant reduction of unprocessed precursor shRNA species and improved production of core biologically active species**

# Humanized Animal Model: *PhoenixBio PXB*

## *Human Liver Chimeric Mouse*

A chimeric mouse with a liver highly replaced by human hepatocytes



1. Human hepatocytes proliferating under physiologically relevant conditions
2. Histologically normal liver constitution
3. Human specific metabolism and excretion pathways
4. Infectable with HBV and HCV



cDNA-uPA/SCID  
Liver weight: 0.7 – 1 g

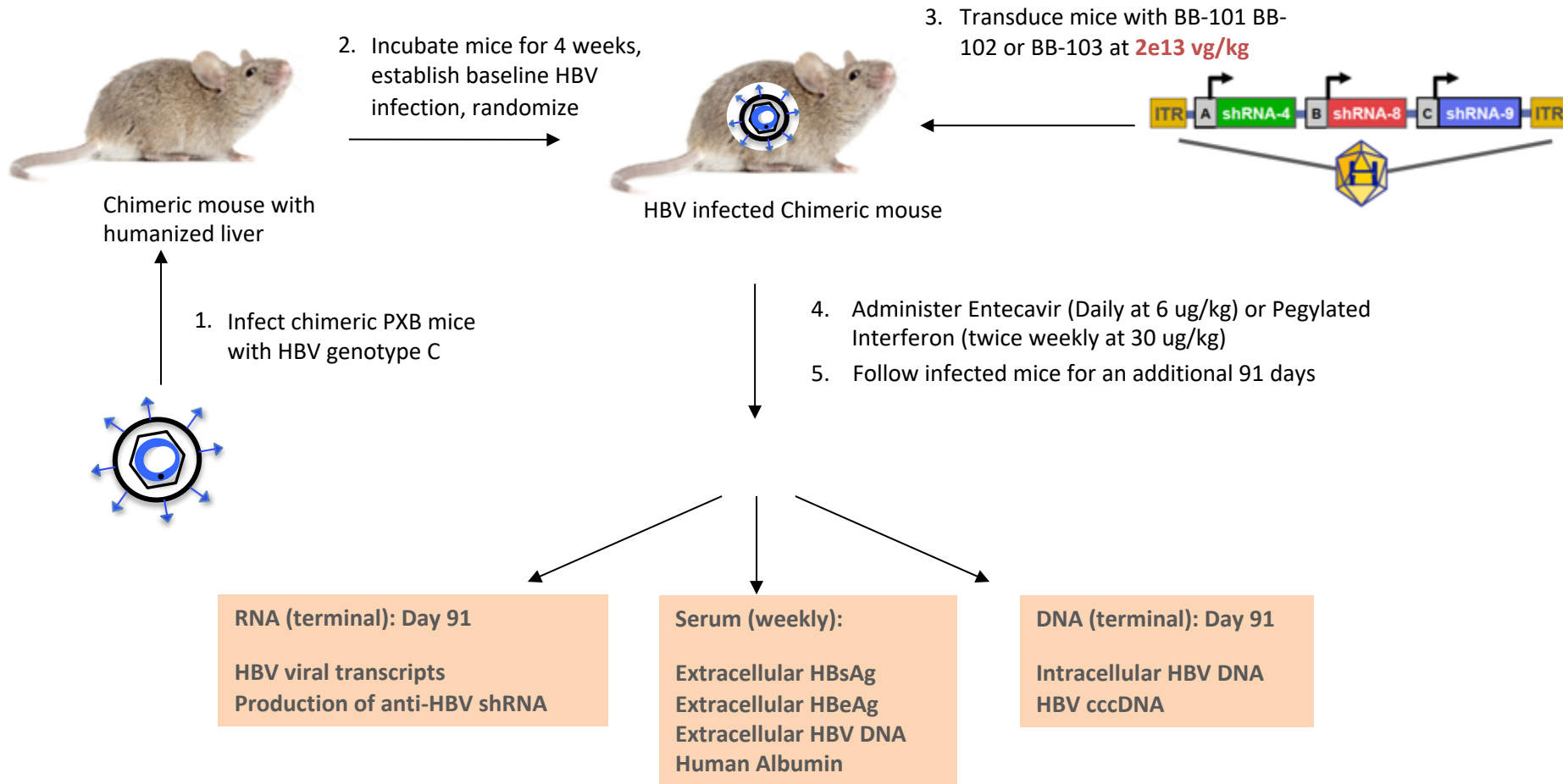
**Transplantation**  
3-week old mice



PXB-Mouse®  
Liver weight: 2 – 2.5 g  
(RI: 98 %)

10-week old mice

# In Vivo HBV Studies Using PXB Mice



# Biological Activity of BB-102 and BB-103

## Combinations with SOC on Key HBV Parameters

|  | Treatment                                     | Log Reduction of Serum HBV DNA | Log Reduction of HBsAg | Log Reduction of HBeAg |
|--|---|--------------------------------|------------------------|------------------------|
| Control groups                                       | entecavir (ETV)<br>6 mg/kg daily              | 2.63                           | 0.46                   | 0.37                   |
|  | pegylated interferon<br>30 mg/kg twice weekly | 2.41                           | 0.96                   | 1.09                   |
| Single administration of ddRNAi                      | BB-102<br>2e13 vg/kg                          | 1.87 max at Day 63             | 1.75 max at Day 70     | 1.17 max at Day 56     |
|  | BB-103<br>2e13 vg/kg                          | 2.17 max at Day 63             | 1.94 max at Day 70     | 1.61 max at Day 56     |
| Single administration of ddRNAi with daily entecavir | BB-102 + ETV                                  | * 3.72 +                       | 1.86                   | 1.42                   |
|  | BB-103 + ETV                                  | * 3.72 +                       | 2.14                   | 1.90                   |