

# PATHWAY TO VALUE CREATION

BIO Corporate Presentation 28 May 2018

**Greg West, Chief Executive Officer** 

# SAFE HARBOR STATEMENT

This presentation contains "forward-looking statements" within the meaning of section 27A of the US Securities Act of 1934 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 outlicenses 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.



### **BUSINESS OVERVIEW**



### Proven Technology

First company into human clinical studies under a US IND with systemically delivered nonwithdrawable RNAi (TT-034)



### **Robust Pipeline**

Assets in oncology (Phase 2 entry, 1Q18), orphan genetic disorders (Phase 1/2a entry, 1Q19), retinal disease, and infectious disease.



#### Valuable Products

Human therapeutic products for commercialization, partnering, and collaborations

Benitec has created a novel combination of gene therapy and gene silencing to change treatment paradigms of human disease



### HIGHLIGHTS



**Programs** advancing to clinic

EGFR-targeted gene silencing therapy confirmatory Phase 2 trial initiated in Q1 2018

Unique 'silence and replace' therapeutic designed to treat OPMD with IND filing in Q1 2019 Other programs could be clinic-ready in late 2019



Capital markets access

Listed on ASX (2002, BLT) and NASDAQ (2015, BNTC)

US\$50M capital raised since 2014

US shelf registration statement filed June 2017



Strong in-house capabilities

19 staff with scientific operations in Hayward CA, including 9 PhDs with deep gene therapy expertise

In-house manufacturing expertise for process optimization and scalability

Extensive commercial and drug development expertise



# **CORPORATE SNAPSHOT**

KEY SHAREHOLDER DETAILS	AUSTRALIA Listed ASX 2002: BLT	US Listed NASDAQ 2015: BNTC/BNTCW
Share Price as of 31st March, 2018: (ADS ratio 20:1)	A\$0.20	US\$3.18
52 week high/low as of 31st March, 2018	A\$0.33/A\$0.11	US\$5.48 / US\$1.85 (ADS)
Average daily volume (6 months to 31st March, 2018)	272,504 shares	56,763
Market Capitalization as of 31st March, 2018 (all shares)	A\$41M	US\$32M
Issued ordinary shares as of 31st March, 2018	205,142,734	
Total options and warrants on issue as of 31st March, 2018	42,528,203	
Insider holdings – Nant Capital LLC	29%	
Cash balance as of 31st March, 2018	A\$10.5M	
Net assets as of 31st March, 2018	A\$14.4M	
Net loss as of 31st March, 2018	A\$8.6M	
Capital raised to 31st March, 2018*	US\$50m since 2014	
US SEC shelf registration	June 2017	
Facilities	Corporate	Scientific Operations
	Sydney, Australia	Hayward, California

<sup>\*</sup>Entitlements issue is due for completion on 28 May, 2018



### EXPERIENCED EXECUTIVE TEAM



**Greg West Chief Executive Officer** 

- Former CFO of Benitec Biopharma
- Prior roles as NED, CEO, CFO at a number of public companies
- Background at PriceWaterhouse, Bankers Trust, Deutsche Bank



**Bryan Dulhunty Chief Financial Officer** 

- Chairman of ASX listed Cryosite Ltd
- Former Executive Chairman, Viralytics
- Prior roles as NED, MD, CFO and Company Secretary of a number of listed and non-listed biotech companies



**Dr. David Suhy Chief Scientific Officer** 

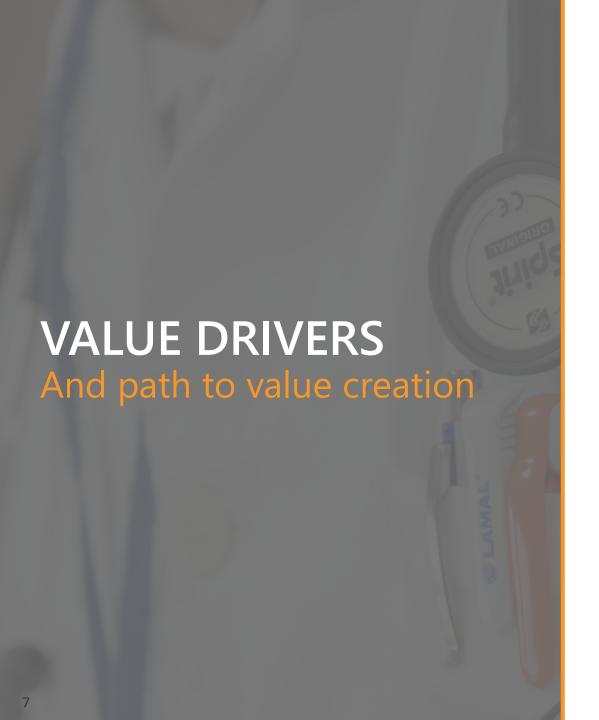
- Former SVP of Research & Development, Benitec Biopharma
- Prior roles at Tacere Therapeutics, Antara Biosciences and PPD Discovery



**Georgina Kilfoil Chief Development Officer** 

- Former VP of Clinical Operations, Benitec Biopharma
- Prior roles at Anthera Pharmaceuticals, InClin and Peninsula Pharmaceuticals





### Value Drivers



One year major value inflection points include initial data readout from Phase 2 oncology study and entry into the clinic with OPMD asset (BB-301)



Additional programs could be clinic-ready in late 2019



Flexibility of ddRNAi platform can potentially accelerate clinical and shareholder value with the ability to move proven ddRNAi therapeutics into additional rare diseases



# RECENT **ACHIEVEMENTS** And path to value creation

#### Achievements



Nant Capital makes strategic investment in Benitec to bring in Phase 2 oncology asset (BB-401)



Phase 2 clinical study of BB-401 in head & neck squamous cell carcinoma (HNSCC)



US and EU orphan drug designation for oculopharyngeal muscular dystrophy (OPMD)



Nature Communications publication of initial 'silence and replace' preclinical data (OPMD)



Pre-IND meeting with US FDA, Health Canada and several EU agencies informs a clear path to the clinic for OPMD asset (BB-301)

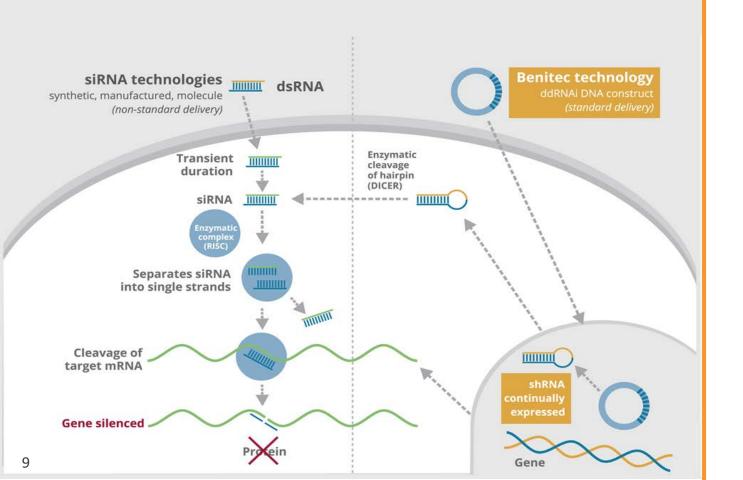


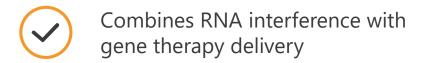
Pre-IND meeting with US FDA informed a clear and expeditious path to the clinic for HBV asset

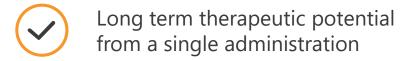


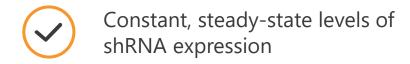
# PERMANENT GENE SILENCING

With DNA-Directed RNA Interference (ddRNAi)







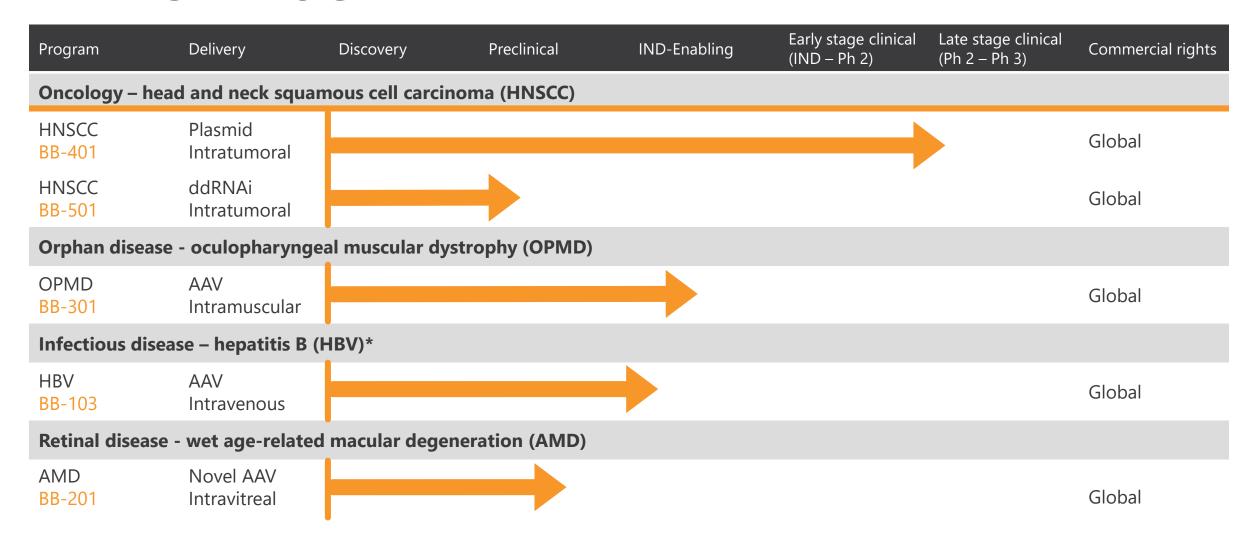


Silence a single gene or target multiple genes simultaneously

Simultaneous silencing of disease causing genes with co-expression of normal genes to restore function



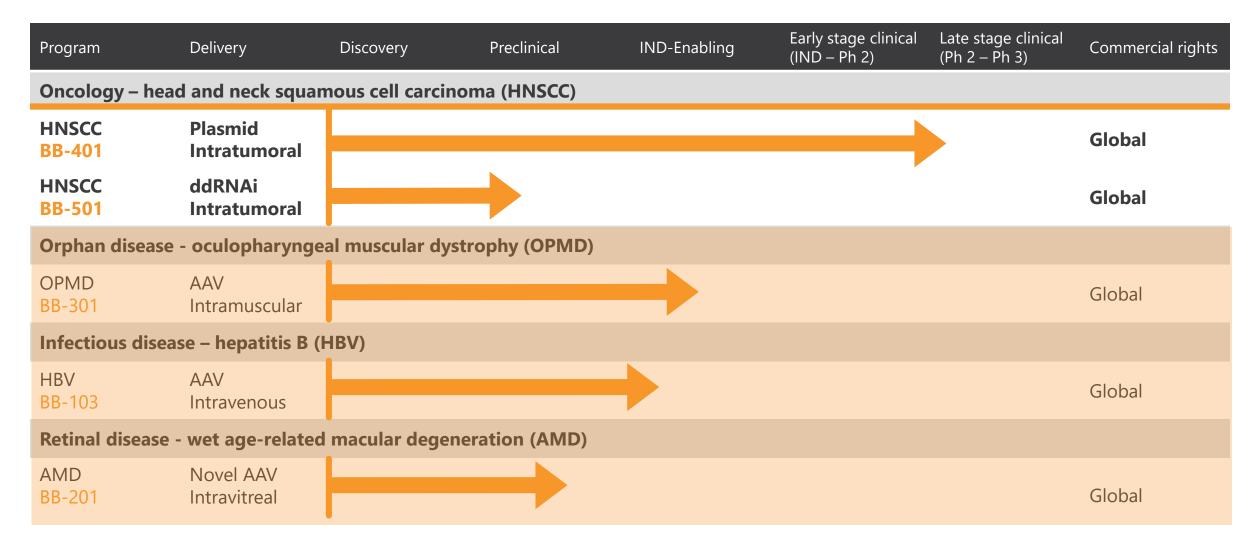
### **DIVERSE PROGRAM PIPELINE**



<sup>\*</sup>Continued development dependent on partnership or funding



### BENITEC PIPELINE





# HEAD AND NECK SQUAMOUS CELL CARINOMA (HNSCC)

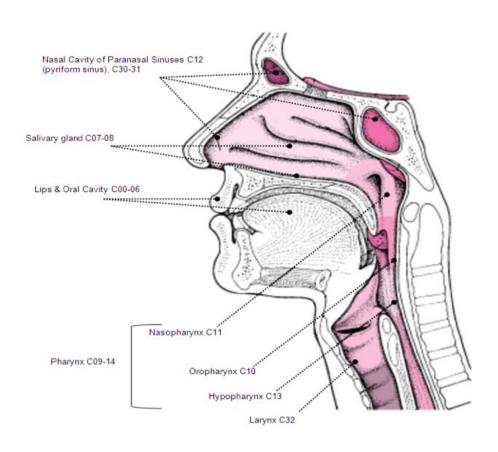
### **Incidence and Patient Mortality:**

- Global incidence of 119,000 in 2016 expected to increase to over 136,000 in 2026
- 50% of patients expected to develop recurrent or metastatic disease
- Median overall survival of 7.8 months and five year survival rate of 3.6% for patients with recurrent or metastatic disease
- Over 90% of HNSCC lesions overexpress epidermal growth factor receptor (EGFR)

#### **Unmet Medical Need:**

- Significant patient morbidity derived form loco-regional tumor growth and progression in confines of small anatomical space
- Durable tumor reduction or eradication
- Lack of biomarkers to reliably predict response to targeted therapy

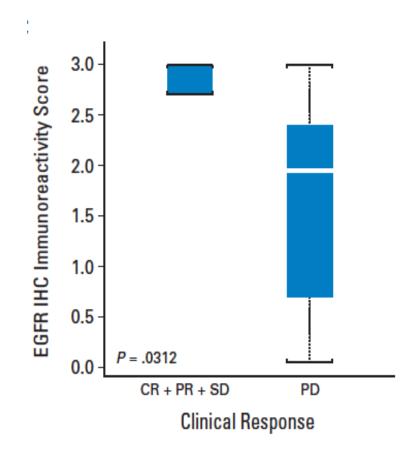
#### **Anatomical sites of HNSCC**





# BB-401: EXPRESSED ANTI-SENSE RNA AGAINST EGFR PHASE 1 SINGLE AGENT CLINICAL DATA

- BB-401 is comprised of plasmid DNA which produces a 39-nt antisense RNA with specificity against EGFR
- Phase I study of 17 patients with advanced, refractory HNSCC
- Safety and efficacy following direct intra-tumoral injection weekly for 4 weeks:
  - 29 % (5 patients) Objective Response
  - 2 patients experienced Complete Response
  - 3 patients Partial Responses (reduction >30% by RECIST)
  - 2 additional patients Stable Disease
  - 41% overall disease control rate
  - 6.5 months observed anti-tumor response
- Strong correlation between baseline level of EGFR expression and clinical response





# BB-401: FOLLOW-ON PHASE I STUDY IN COMBINATION WITH CETUXIMAB AND RADIATION

- 6 patients were treated in a Phase 1 study of BB-401 in combination with radiation and cetuximab
- 5 of 6 patients experienced an Objective Response (83%)
- 4 patients Complete Response & 1 patient Partial Response

**EFGR-AS** Injected Untreated Lymph Node Lymph Node Pre-treatment Post-treatment

Grandis et al, University of Pittsburgh Poster from ASCO 2015



### BB-401-01: PHASE 2 CLINICAL STUDY IN HNSCC

Intratumoral BB-401 in patients with recurrent or metastatic head and neck squamous cell carcinoma

# Key Entry Criteria Histologically or cytologically confirmed HNSCC Refractory to all available

- standard therapiesAt least one lesion amenable to injection
- Performance status (ECOG) 0-2

Multi Center Single Arm Study Fleming 2 Stage Design

0 response Stop for futility

1-2 responses Proceed to Stage 2

≥ 3 responses Stop for success

**Potential Outcomes** 

Endpoints after 2 cycles of BB-401 (1 cycle = 4 weekly injections BB-401)

- Overall response rate
- Disease control rate
- Duration of response
- Survival

Stage 2:

~15 patients

- Safety
- Quality of Life

Study now open\* with value inflection point at end of Stage 1

Stage 1:

12 patients



<sup>\*</sup>Approval in Australia in March 2018 and Russia in May 2018

# **HEAD & NECK SQUAMOUS CELL CARCINOMA**

### Clinical Candidate BB-401: Product Overview



Incidence to increase from 119,000 in 2016 to 136,000 in 2026 with global market estimated to be US\$4.1 billion in 2026 Morbidity caused by the spatial effects of tumors in the confined anatomical structures of the head and neck

Over 90% of HNSCC overexpress EGFR



BB-401 Product Profile EGFR targeted via expressed antisense RNA

In Phase I, strong correlation between BB-401 treatment versus EGFR overexpression Robust objective response rate versus other monotherapy treatments or when paired with SOC treatments



Value / Commercial Opportunity

Value inflection point at end of stage 1:

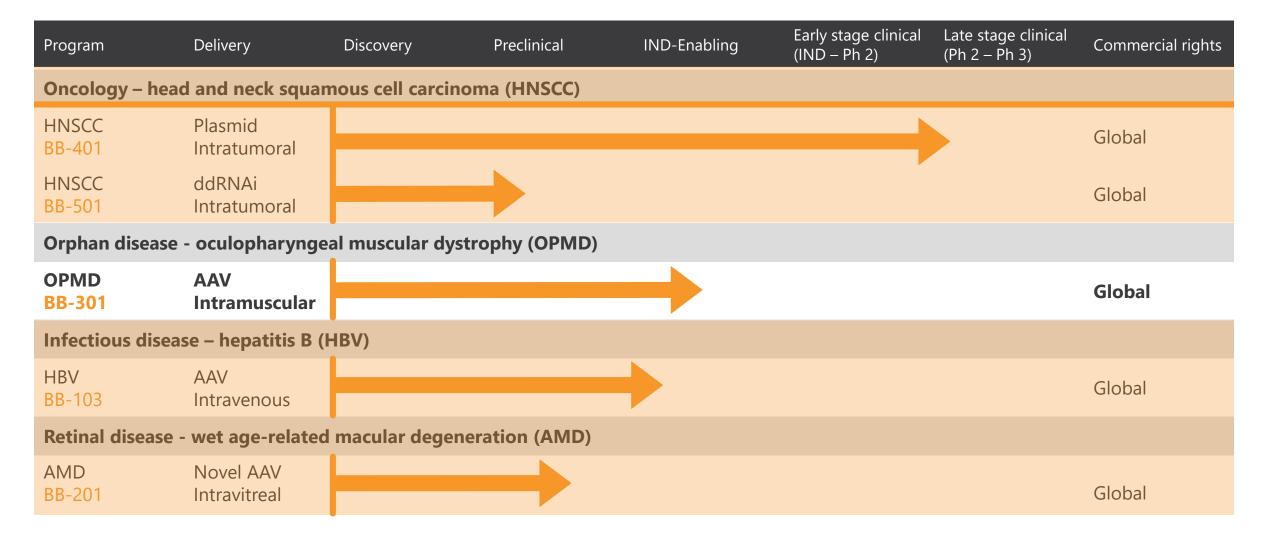
Phase 2 open label study in up to 30 patients initiated in Q1 2018

Selective direct targeting of malignant lesions could uniquely address the unmet medical need in HNSCC

BB-401 is intended to be paired with diagnostic against EGFR



### BENITEC PIPELINE





### OPMD DISEASE OVERVIEW

#### Disease:

- Rare autosomal dominant inheritance
- 1:100,000 (Europe)
- As high as 1:600 in specific populations
- Typical age of onset is late 40's or older

### **Characterized by:**

- Eyelid drooping (ptosis)
- Swallowing difficulty (dysphagia)
- Proximal limb weakness
- Death due to aspiration pneumonia & malnutrition

### Histopathology:

- Decrease of muscle fiber number
- Variation in the size of muscle fibers
- Fibrosis (connective tissue)

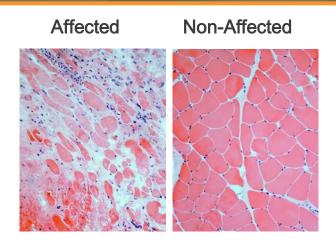




### TISSUE AND MOLECULAR ASPECTS OF OPMD

### Histopathology:

- Decrease of muscle fiber number
- Variation in the size of muscle fibers
- Fibrosis (connective tissue)
- Net effect: decrease in muscle force



#### PABPN1:

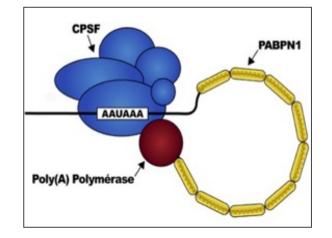
• A ubiquitous factor that promotes interaction between the poly(A) polymerase and CPSF (cleavage and polyadenylation specificity factor) and controls the length of mRNA poly(A) tails, mRNA export from the nucleus, and alternative poly(A) site usage.

#### In OPMD:

An autosomal dominant mutation results in trinucleotide repeat expansion in PABPN1

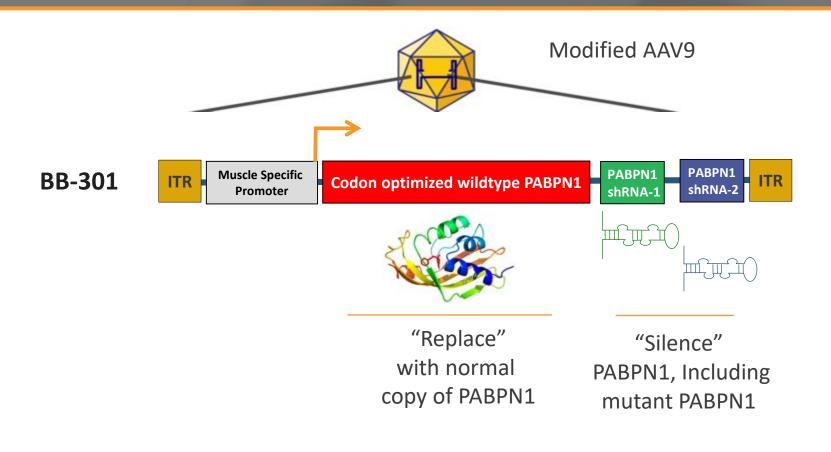
Normal OPMD

ATG  $(GCG)_6$  ----- - $(GCA)_3$  GCG GGG GCT GCG... ATG  $(GCG)_6$   $(GCG)_{1-7}$   $(GCA)_3$  GCG GGG GCT GCG...





### BB-301: A 'SILENCE AND REPLACE' BASED APPROACH



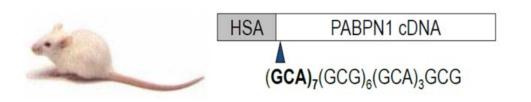
#### **AAV**

- Non-integrating, non-pathogenic viral delivery
- To date, AAV has been used in over 204 clinical trials
- Sustained expression (years) following single injection

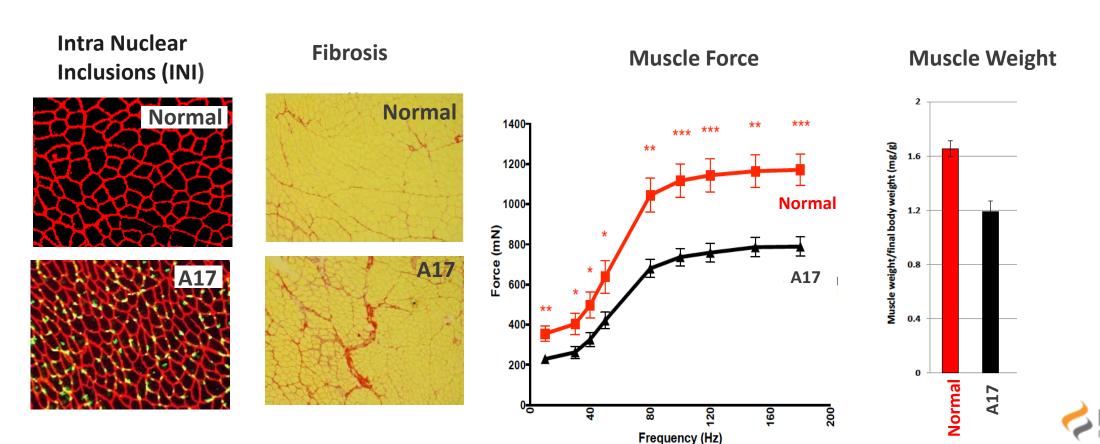
Insensitive to shRNA



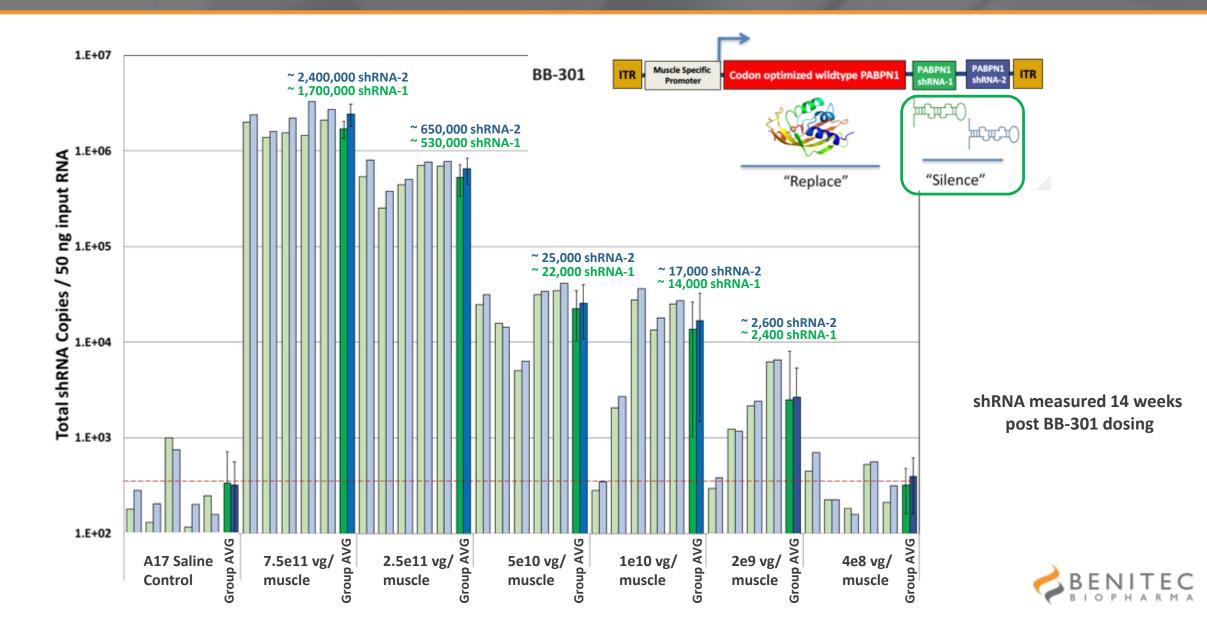
# PRE-CLINICAL MODEL OF OPMD: THE 'A17' MOUSE



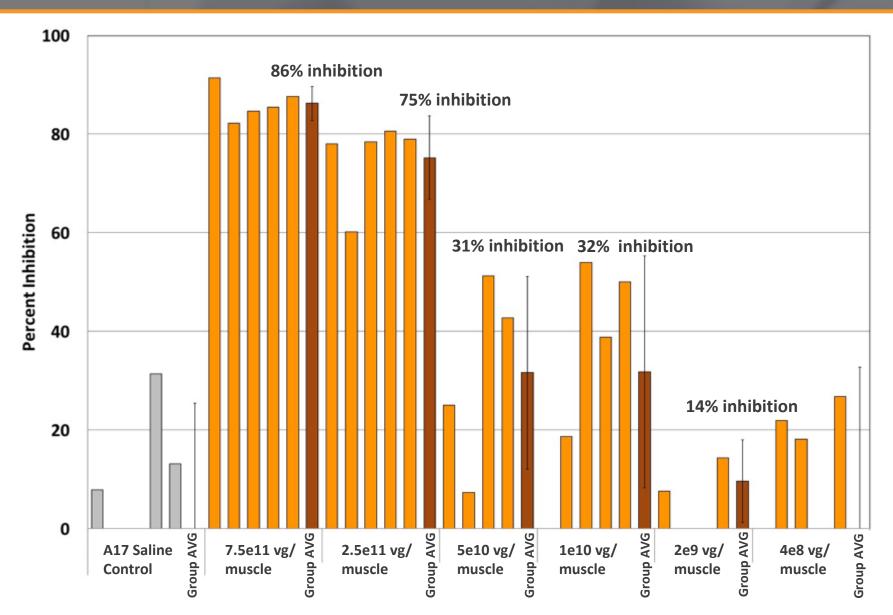
- Transgenic mouse: express a mutated bovine PABPN1 driven by the human skeletal actin promoter in addition to the endogenous PABPN1
- Recapitulates severe muscle atrophy
- Mimics many of the disease pathologies



# BB-301: EXPRESSION OF SHRNA IN TA MUSCLES OF A17 MICE



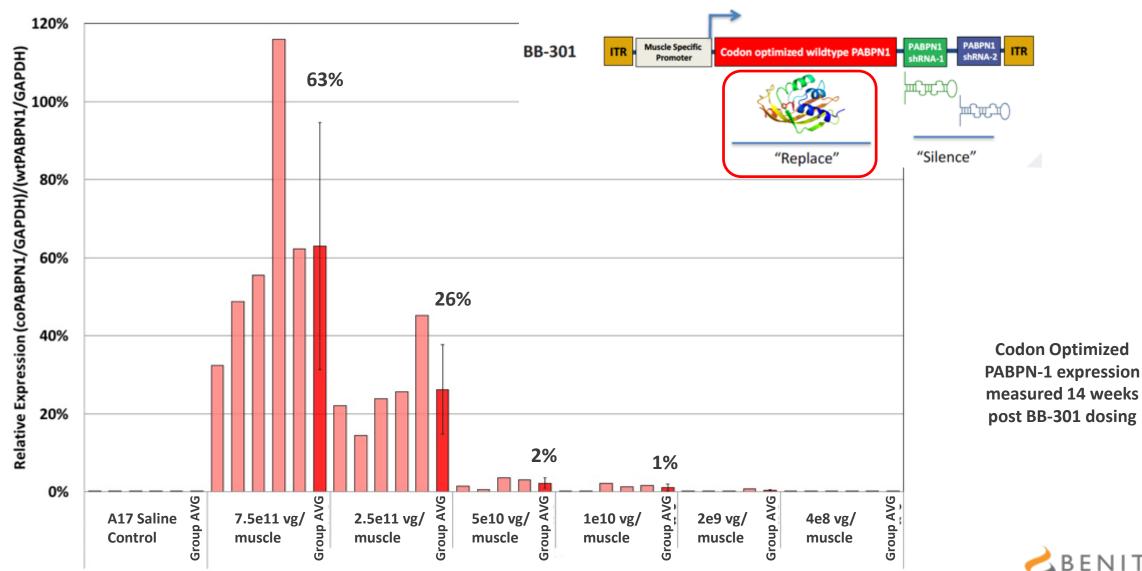
# BB-301 SILENCES PABPN1 EXPRESSION (INCLUDING MUTANT PABPN1) IN AN OPMD MOUSE MODEL



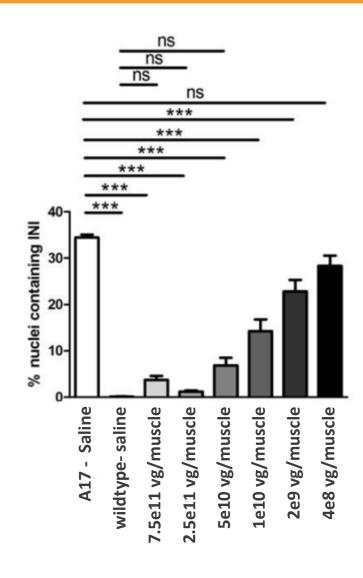
PABPN-1 Inhibition measured 14 weeks post BB-301 dosing

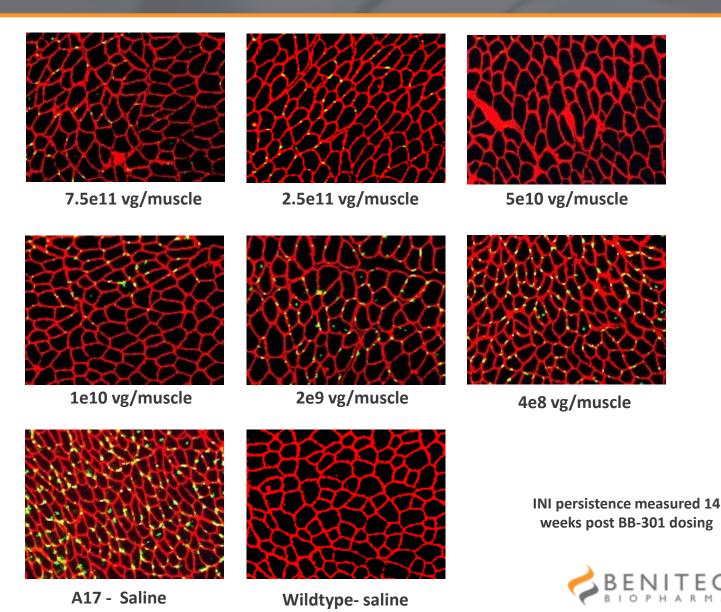


# BB-301 RESTORES NORMAL PABPN1 LEVELS IN A17 MOUSE MODEL

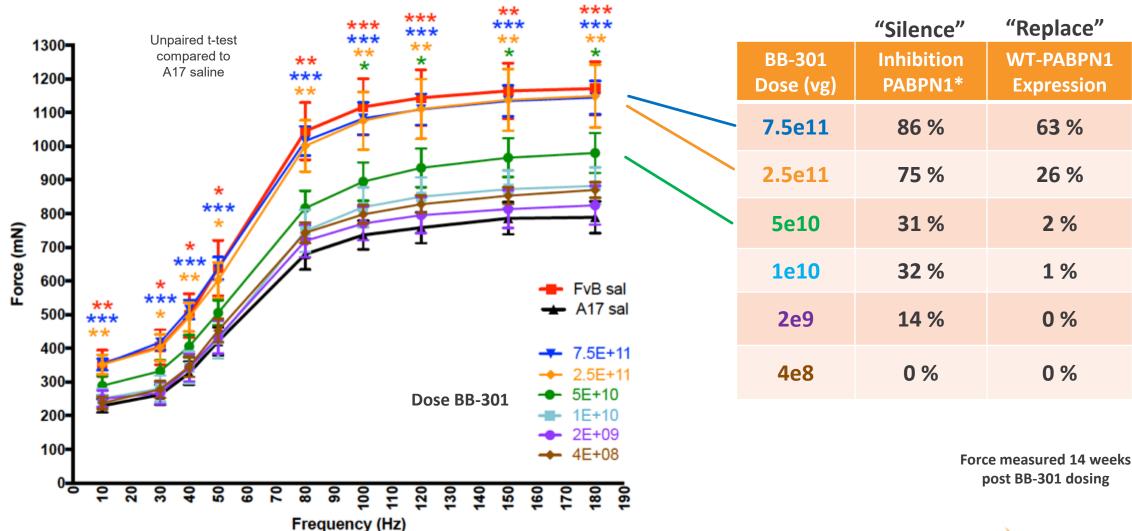


# BB-301 REVERSES INTRANUCLEAR INCLUSIONS IN A17 MOUSE MODEL





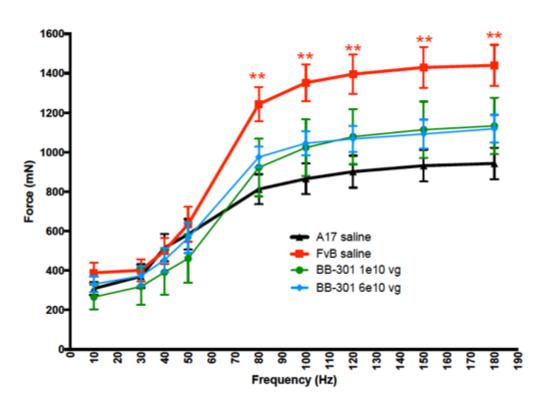
# BB-301 RESTORES MUSCLE FORCE IN OPMD MOUSE MODEL



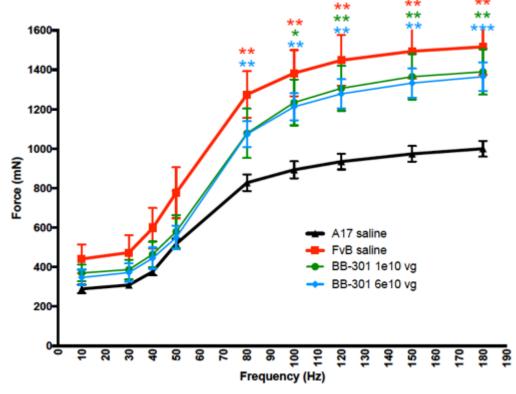


# BB-301: RESTORATION OF MUSCLE FUNCTION TAKES TIME





### 20 weeks post BB-301 Dosing



BB-301 Dose (vg)	Inhibition PABPN1*	WT-PABPN1 Expression
6e10	88 %	91 %
1e10	63 %	13 %



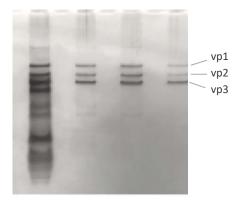
### BB-301: SCALABLE MANUFACTURING



50 Liter Reactor

- Produced with scalable baculovirus based methodologies and purification processes to control cost of goods.
- Using a modified AAV capsid for the generation of highly active BB-301 particles
- Benitec has developed a product specific process for producing high titer, highly pure BB-301:
  - Yields exceed 1e14 vector genomes/liter
  - Recovery yields in final product range from 30 40 %
- GMP grade clinical material produced at leading Contract Manufacturing Organization
- Currently manufacturing at 50L scale
- Clinical product to be generated at 250L scale

Silver stain of SDS protein gel showing output of purification steps (3 capsid bands expected in final product)



BB-301 Post 1st Purification BB-301 Post 2nd Purification

BB-301 Final Material Reference Materia



# BB-301-01: PHASE 1/2A CLINICAL STUDY IN OPMD

Intramuscular BB-301 in OPMD patients with swallowing dysfunction\*

### **Key Entry Criteria**

- Aged 35 to 80
- Clinical diagnosis of OPMD
- Genetic diagnosis of OPMD
- Swallowing dysfunction
- No prior myotomy

### **Multicenter Dose Escalation Study**

Cohort 1 – Low Dose (~3-5 BB-301)

> Cohort 2 – Medium Dose (~3-5 BB-301)

> > Cohort 3 – High Dose (~3-5 BB-301)

> > > Maximum Effective Dose ~12 patients BB-301

# Endpoints Through 52 Weeks

- Safety & tolerability
- Quantitative clinical improvement in swallowing
- Patient reported improvement in swallowing and quality of life

<sup>\*</sup>Study design and parameters subject to change based on nonclinical toxicology results and clinical and regulatory feedback



### OPMD: KEY FEATURES IN BB-301 DEVELOPMENT

#### **Non-Clinical:**

- OPMD phenotypes (muscle strength, dystrophy, intranuclear inclusions, fibrosis) in A17 mice are reversible
- Initial studies published in Nature Communications
- Ongoing safety and toxicology studies being performed in sheep models

### Manufacturing:

- Produced using scalable baculovirus based manufacturing methodologies
- Currently manufacturing at 50L scale
- Clinical product to be generated at 250L scale

#### **Regulatory:**

- Orphan Drug Designation granted in EU (2017) and US (2018) which can lower cost of approval, potentially reduce development costs and provide seven year market exclusivity at approval
- Pre-IND meeting and scientific advice meetings completed in US, Canada, UK, France and Denmark
- Two large sheep safety studies requested by regulators to be completed at end of 2018
- IND submission targeted for Q1 2019

#### Clinical:

- Direct one time injection of BB-301 into throat muscles for the treatment of OPMD-related dysphagia
- Benitec working hand in hand with key opinion leaders and physicians to define the clinical development plan
- Initial clinical study to start once IND or other regulatory filing is approved



### OCULOPHARYNGEAL MUSCULAR DYSTROPHY

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



Oculopharyngeal muscular dystrophy (OPMD)

Rare, autosomal dominant, heritable monogenic disease

Estimated 12,000 effected patients in Western countries.

Eyelid drooping, swallowing difficulties, proximal limb weakness, death due to aspiration pneumonia and malnutrition



**BB-301 Product Profile** 

Designed to treat dysphagia associated with OPMD

'Silence and Replace' – unique gene therapy mechanism

Silence: mutant PABPN1 gene

Replace: Simultaneously introduces normal PABPN1 gene to restore function



Value / Commercial Opportunity

Near term value inflection point:

**1Q19 clinic entry** 

Commercial opportunity in excess of US\$1 billion

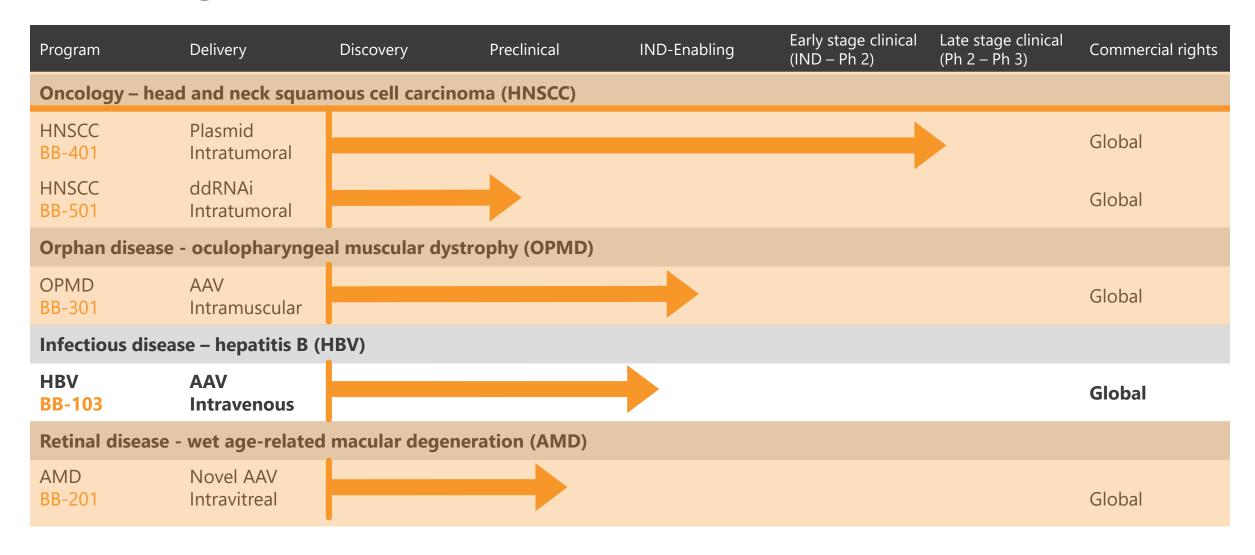
Significant unmet medical need with no direct competition

Orphan with cost efficient commercialization path

Potential for silence and replace approach for other monogenic diseases



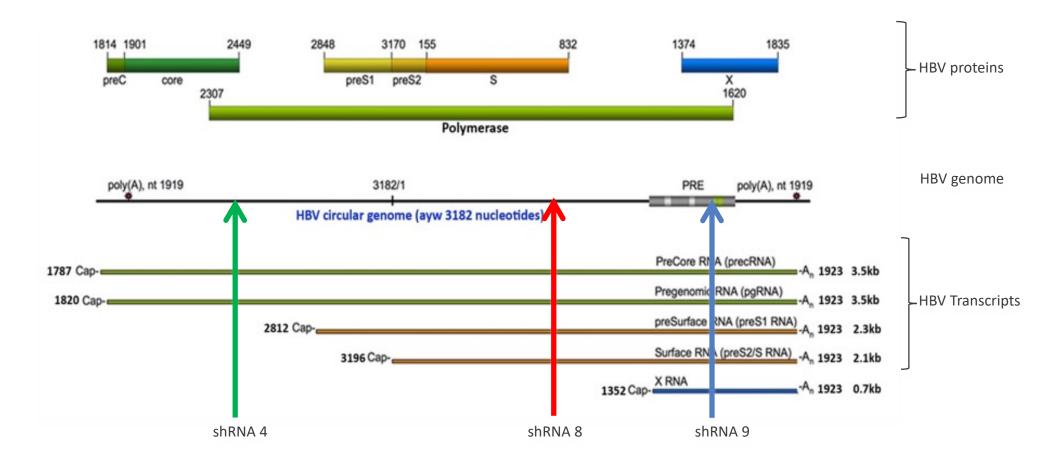
### BENITEC PIPELINE



<sup>\*</sup>Continued development dependent on partnership or funding



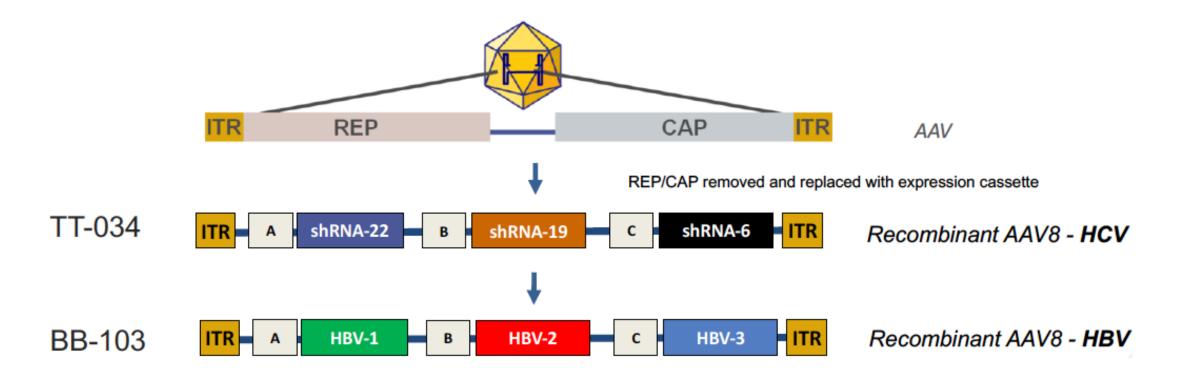
# BB-103 POSITIONS INHIBITORY shrna ACROSS WELL CONSERVED SEQUENCES IN THE HBV GENOME



<sup>\*</sup> Sequences selected for shRNA are well conserved across HBV genotypes A-H



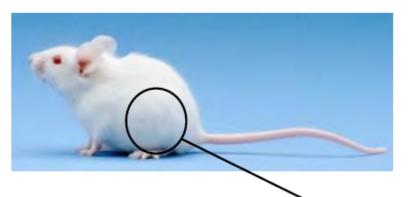
# BB-103 BUILDS UPON THE LEARNINGS FROM BENITEC'S FIRST IN MAN TRIAL WITH TT-034 IN HCV



Safety and Efficacy Study in Single Doses of TT-034 in Patients with Chronic Hepatitis C Clinical Trials.gov Identifier: NCT10899092



# PXB MOUSE, A CHIMERIC ANIMAL WITH A LIVER HIGHLY REPLACED BY HUMAN HEPATOCYTES



**Transplantation** 

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



cDNA-uPA/SCID Liver weight: 0.7 – 1 g

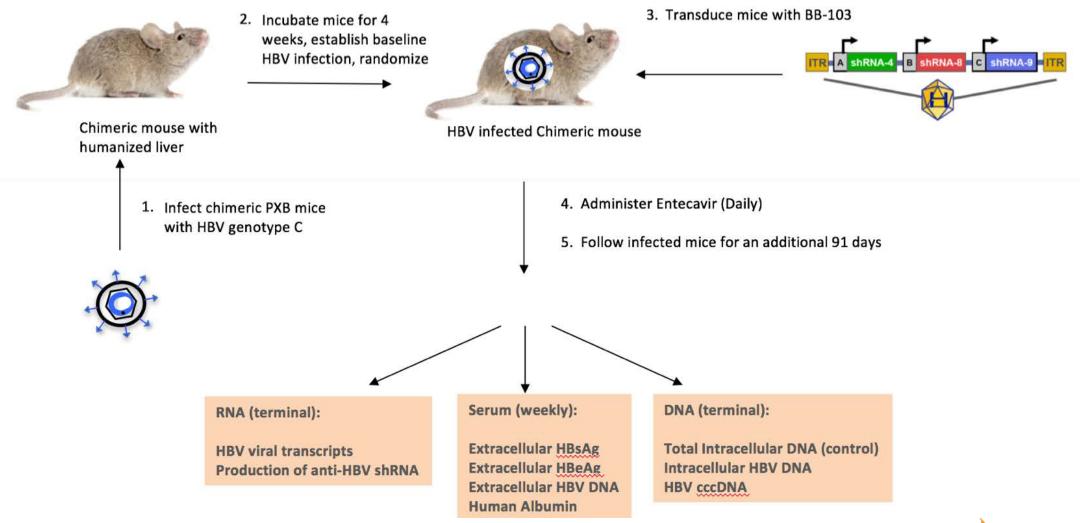


PXB-Mouse® Liver weight: 2 – 2.5 g (RI: 98 %)





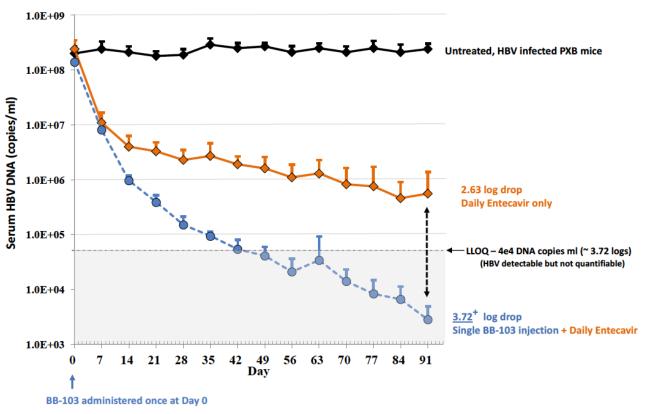
### IN VIVO INFECTIOUS STUDIES USING PXB MICE



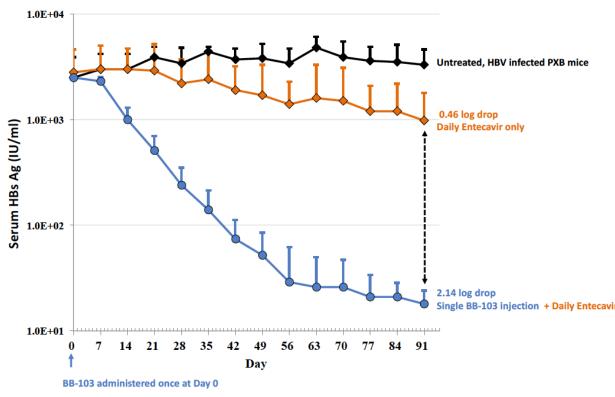


# A SINGLE DOSE OF BB-103 + DAILY ENTECAVIR RESULTS IN >4 LOG SUPPRESSION OF HBV DNA AND >2 LOG HBsAg

#### **Reduction in HBV serum DNA**

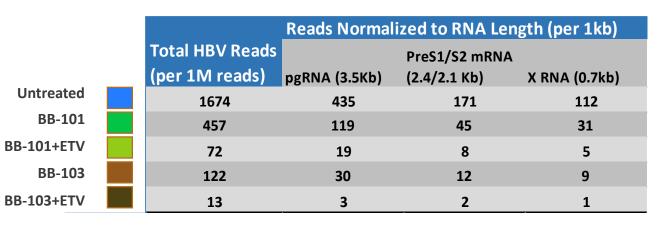


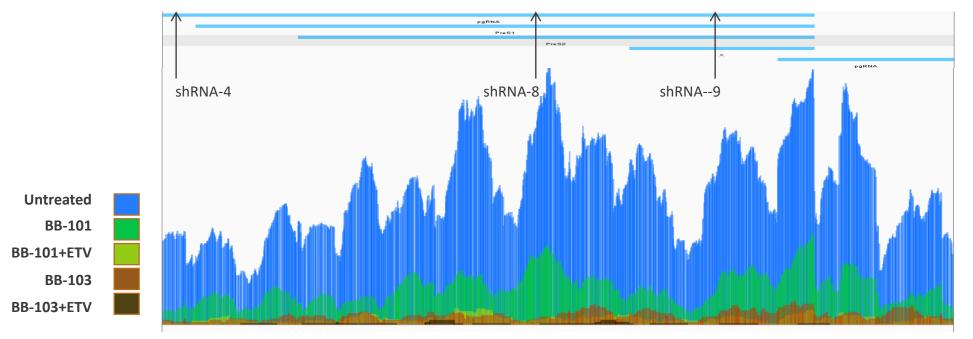
### Reduction in HBsAg (s-antigen)





# BB-103 + ENTECAVIR REDUCES HBV VIRAL RNA BY > 99%







### **HEPATITIS B**

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



**Hepatitis B (HBV)** 

WHO estimates HBV infects 257 million people resulting in up to 780,000 deaths per year

HBV viral proteins, especially HBsAg causes hepatic inflammation, liver dysfunction, acute hepatic failure, cirrhosis, or HCC

Need for effective therapies that promote restoration of a host immune response through targeted HBsAg knockdown



**BB-103 Product Profile** 

Designed as a single dose treatment to be added on top of existing SOC

Designed against well conserved sequences in all major HBV genotypes

Superior efficacy: BB-103 combined with ETV showed a >4 log drop in HBV DNA and >2 log drop in HBsAg



Value / Commercial Opportunity

Near term value inflection point: With partnership or funding could be clinic ready late in 2019

Pre-IND FDA meeting informed a clear and expeditious path to the clinic

Leverages use of TT-034 clinical data, Benitec's first in man HCV study



# PROGRAM SUMMARY









# BB-401: Oncology (HNSCC)

- EGFR antisense asset (BB-401) entered clinic in 1Q18 in P2 study in recurrent or metastatic HNSCC
- Discovery stage program using proprietary ddRNAi platform, to develop follow-on anti-EGFR strategies (BB-501)

# BB-301: Orphan disease (OPMD)

- Unique single vector 'silence and replace' mechanism
- Pre-IND meetings complete in US and EU
- IND filing planned 1Q 2019
- Commercial opportunity in excess of US\$1 billion

# BB-103: Infectious disease (HBV)

- Preclinical POC with significant reduction in viral load and HbsAg when combined with SOC
- Pre-IND April 2017 informed direct path to clinic entry
- Seeking partnerships to move into the clinic

# BB-201: Retinal disease (AMD)

- Novel viral capsids for delivery to retinal cells via intravitreal injection
- Molecular analyses ongoing from PoC study in NHP – additional work required to progress BB-201 in AMD
- Possible delivery platform for other retinal diseases



# **INVESTMENT HIGHLIGHTS**







# Novel combination of gene therapy and gene silencing

- BB-401 (oncology) in clinic with Phase 2 study. BB-301 (OPMD) in clinic early 2019
- Validated ddRNAi technology, with human safety data
- Robust pipeline in oncology, orphan genetic disorders, retinal disease and infectious disease

### Capital market access

- Listed on ASX (BLT) and NASDAQ (BNTC)
- US\$50M capital raised since 2014
- US shelf registration statement filed

### **Strong in-house capabilities**

- Deep gene therapy expertise
- In-house manufacturing expertise for process optimization and scalability





NASDAQ: BNTC | ASX: BLT

CONTACT: info@benitec.com