



# RNAi Therapy for Chronic HBV Infection

Bill Symonds, PharmD | Chief Development Officer | October 2017

NASDAQ: ABUS  
[www.arbutusbio.com](http://www.arbutusbio.com)

# Forward Looking Statements

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This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, and forward looking information within the meaning of Canadian securities laws (collectively, “forward-looking statements”). Forward-looking statements in this presentation include statements about, among others: meeting a significant unmet medical need and market opportunity; developing a curative regimen for HBV; accomplishing the objectives of ARB-1467, AB-423, AB-506 and AB-452; NDA filing and prospective royalties for Alnylam’s patisiran; receiving additional clinical data from the HBV pipeline in 4Q17; current cash funding the company into late 2018; and non-dilutive financing potential from non-HBV assets and LNP licensing.

With respect to the forward-looking statements contained in this presentation, Arbutus has made numerous assumptions regarding, among other things: stability of economic and market conditions; the effectiveness and commercial viability of the company’s products. While Arbutus considers these assumptions to be reasonable, these assumptions are inherently subject to significant business, economic, competitive, market and social uncertainties and contingencies. Forward-looking statements herein involve known and unknown risks, uncertainties and other factors that may cause the actual results, events or developments to be materially different from any future results, events or developments expressed or implied by such forward-looking statements. Such factors include, among others: the company’s product pipeline may not prove to be effective or commercially beneficial; and economic and capital market conditions may worsen. A more complete discussion of the risks and uncertainties facing Arbutus appears in Arbutus' Annual Report on Form 10-K and Arbutus' continuous disclosure filings which are available at [www.sec.gov](http://www.sec.gov) and at [www.sedar.com](http://www.sedar.com). Arbutus disclaims any obligation to update any forward-looking statements or to publicly announce the result of any revisions to any of the forward-looking statements contained herein to reflect future results, events or developments, except as required by law.

# Arbutus Investment Highlights

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- Chronic Hepatitis B is a large, global unmet medical need
- Our world class scientific and development teams have a track record of success in antivirals
- Each drug in our portfolio has potential to improve patient outcomes
- We are on a path to functional cures in HBV patients – key to approval
- LNP asset will drive value by enabling mRNA and gene-editing platforms

# Arbutus Pipeline Has The Necessary Components

Candidate	Stage of Development				Next Milestone
	Research	IND Enabling	Phase I	Phase II	
<b>ARB-1467</b> <i>RNAi</i>					<b>4Q17:</b> Cohort 4 data at AASLD <b>4Q17:</b> New combo study
<b>AB-423</b> <i>Capsid Inhibitor</i>					<b>4Q17:</b> Healthy volunteer data <b>4Q17:</b> Initiate HBV patient study
<b>AB-506</b> <i>Capsid Inhibitor</i>					<b>Mid-2018:</b> IND (or equivalent) filing
<b>AB-452</b> <i>HBV RNA Destabilizer</i>					<b>Mid-2018:</b> IND (or equivalent) filing
GalNAc RNAi					Candidate nomination
Checkpoint inhibitor					Lead optimization
cccDNA Targeting Agent					Lead optimization

# Significant Opportunity to Improve Cure Rates

Approved Therapies Show a Cure is Possible But Result in <5% Cure Rate

## Relative Efficacy of Approved HBV Therapies

	Entecavir <sup>1,2</sup>	Tenofovir <sup>3</sup>	PEG-IFN $\alpha$ -2a <sup>4,5</sup>
<b>HBeAg positive</b>	n = 354	n = 176	n = 271
HBV DNA undetectable	67%	76%	25% <sup>a</sup>
HBeAg seroconversion	21%	21%	27%
ALT normalisation	68%	68%	39%
HBsAg loss	2%	3.2%	2.9% <sup>b</sup>
<b>HBeAg negative</b>	n = 325	n = 250	n = 177
HBV DNA undetectable	90%	93%	63% <sup>a</sup>
ALT normalisation	78%	76%	38%
HBsAg loss	0.3%	0%	0.6% <sup>b</sup>

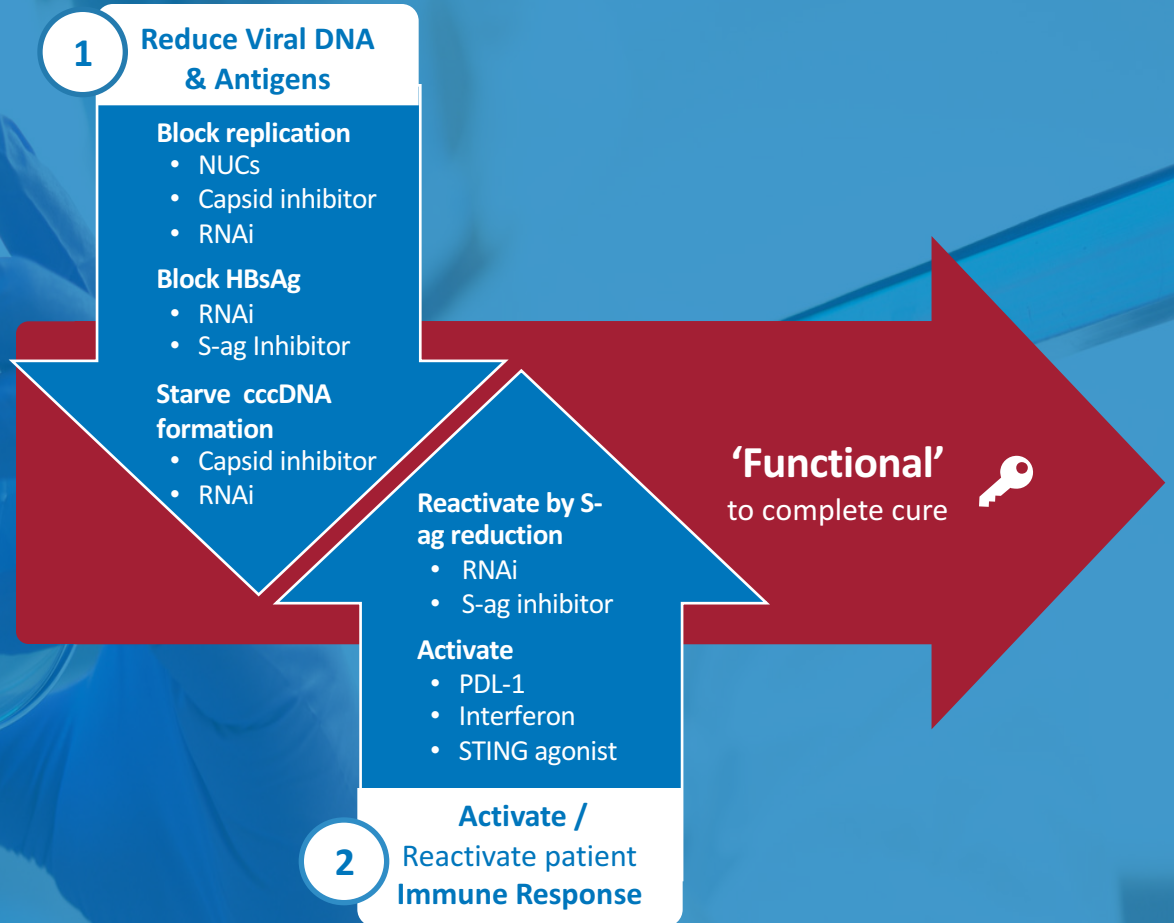
Results at 48 weeks

<sup>a</sup> HBV DNA < 400 copies/mL; <sup>b</sup> At 72 weeks

1. Chang T-T, et al. N Engl J Med 2006;354:1001–10.
2. Lai C-L, et al. N Engl J Med 2006;354:1011–20.
3. Marcellin P, et al. N Engl J Med 2008;359:2442–55.

4. Lau GKK, et al. N Engl J Med 2005;352:2682–95.
5. Marcellin P, et al. N Engl J Med 2004;351:1206–17.

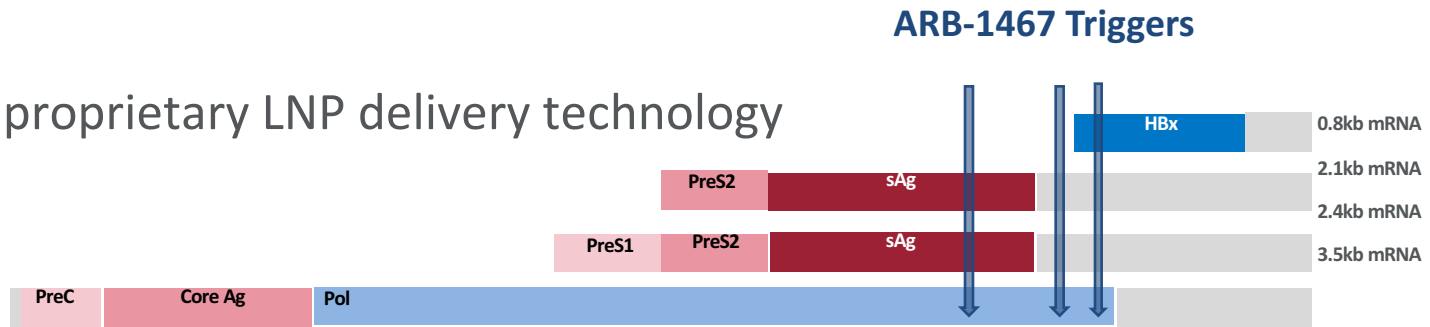
# Keys to Therapeutic Success in HBV



# ARB-1467 Has a Multi-Faceted Impact on HBV

- Unique 3-trigger design targets all HBV transcripts and prevents production of all antigens
- Preclinical studies show that ARB-1467 reduces:
  - HBV DNA
  - HBsAg
  - HBeAg
  - HBV core protein
  - cccDNA

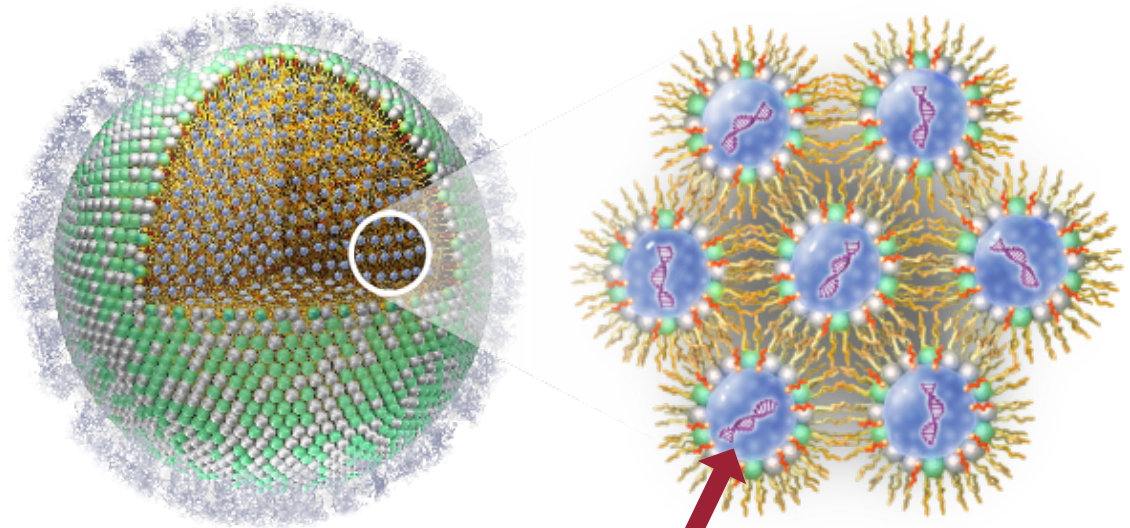
- Employs proprietary LNP delivery technology



# Arbutus is the Leader in LNP Technology

## LNP technology is Clinically Validated and Ideal for mRNA

- LNP are highly tuned mixtures of lipids.
- Protect nucleic acids in the blood, and provide access to the target cells.
- Validated in multiple clinical trials (over 400 patients).
- Arbutus has considerable expertise advancing LNP programs rapidly into the clinic.



**LNP are designed to deliver therapies based on RNAi, mRNA, and gene editing constructs**

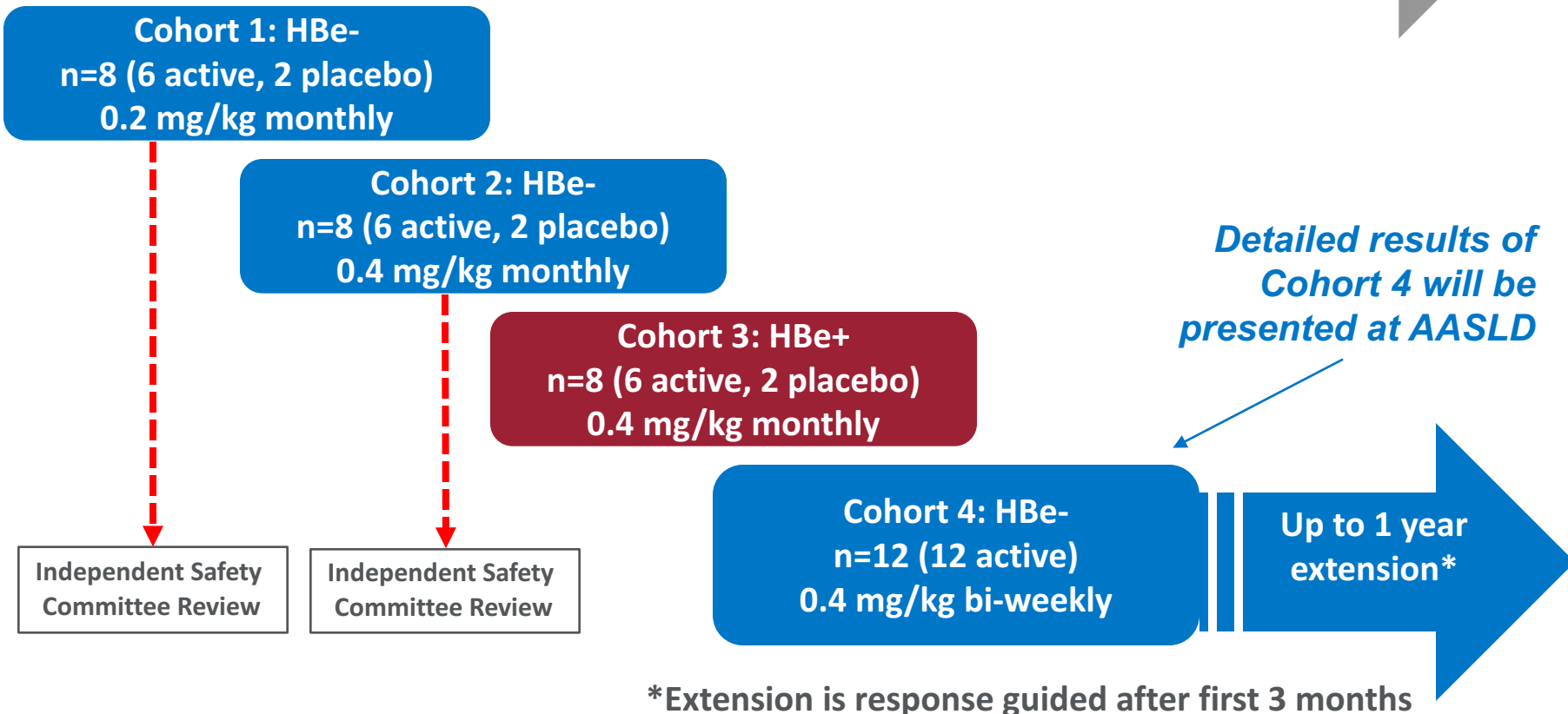
- PEG Lipid
- Amino Lipid
- Structural Lipid
- Cholesterol
- Nucleic Acid like mRNA



# ARB-1467 Phase II: Measuring HBsAg Reduction

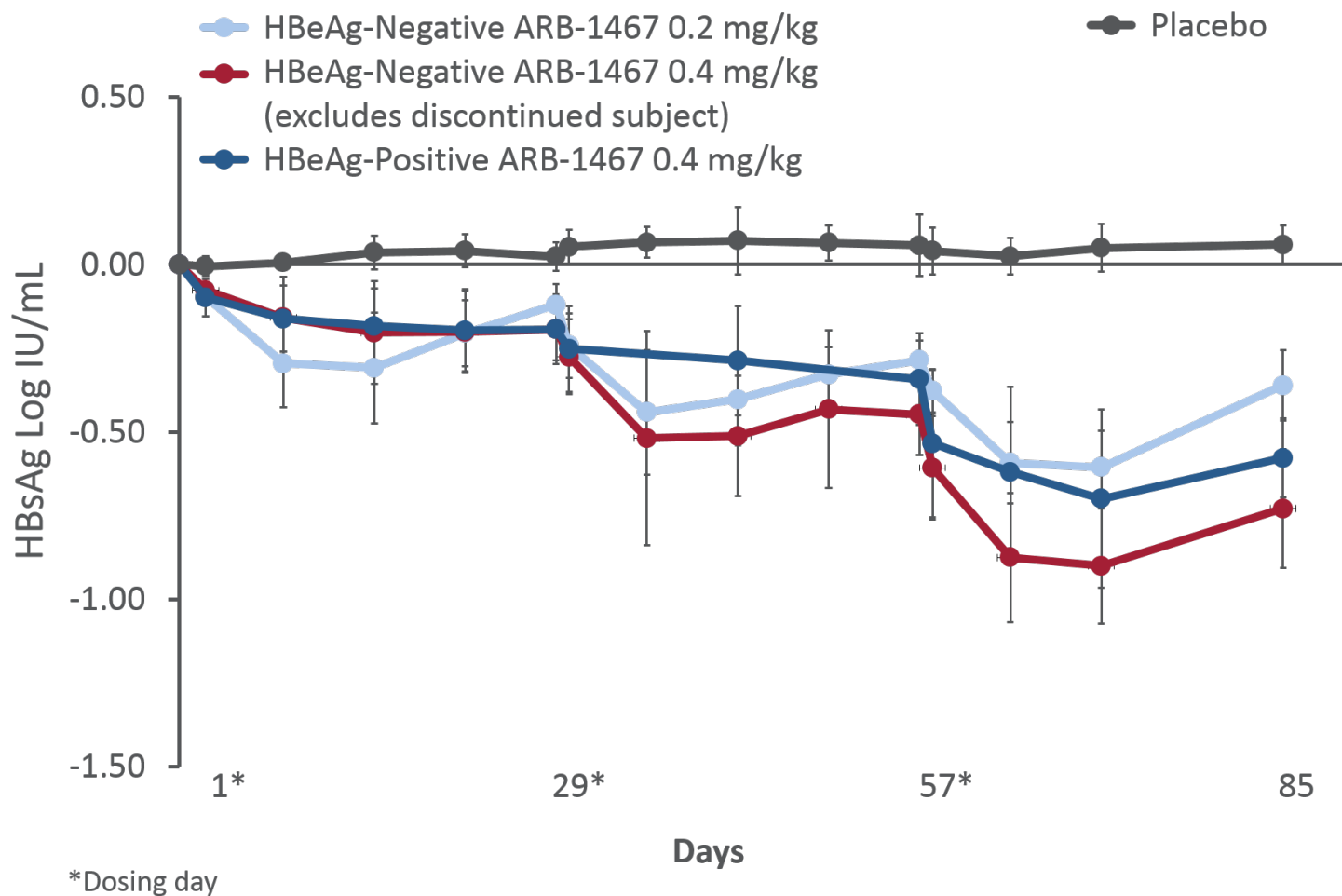
## Phase II Study in HBV Patients on Nuc Therapy

Duration of Treatment: 3 months    Follow-up: 12 months after the first dose



# ARB-1467 Multi-Dosing Shows Additive, Stepwise HBsAg Reduction

## HBsAg Mean Log (IU/mL) Change from Baseline



# ARB-1467 Drives Significant HBsAg Reduction

Reductions of  $\geq 1.0 \log_{10}$  in 5/11 patients (after 3 doses at 0.4 mg/kg)

- Potential to achieve greater reductions with continued dosing
- 17/18 patients in Cohorts 1-3 received all three monthly doses

Cohort	ARB-1467 (mg/kg)	HBeAg	Multiple Dose HBsAg Reduction ( $\log_{10}$ IU/mL)				
			N	Mean <sup>a</sup>	Max <sup>c</sup>	>0.5 $\log^c$	>1.0 $\log^c$
1	0.2	Negative	6	-0.6	-1.3	5	1
2	0.4	Negative	5 <sup>d</sup>	-0.9	-1.3	4	3
3	0.4	Positive	6	-0.7	-1.6	4	2
Placebo	N/A		6 <sup>e</sup>	0.0	-0.1	0	0

<sup>a</sup> The mean serum HBsAg reduction is the nadir value of the arithmetic mean of all values observed at each time point.

<sup>b</sup> Maximum HBsAg reduction is the best single reduction among all patients in a cohort.

<sup>c</sup> Number of patients reaching this threshold

<sup>d</sup> Multiple dose results in Cohort 2 exclude one patient that discounted at day 36 due to "HBV blip" associated with acute HEV infection

<sup>e</sup> Placebo results are based on six subjects (two from each cohort).

Streinu-Cercel, et al. Abstract SAT-155. The EASL International Liver Congress™; April 19-23, 2017; Amsterdam, The Netherlands.

# ARB-1467 was Generally Safe and Well Tolerated

Patients, N (%)	HBeAg-Negative ARB-1467 0.2 mg/kg n=6	HBeAg-Negative ARB-1467 0.4 mg/kg n=6	HBeAg-Positive ARB-1467 0.4 mg/kg n=6	Placebo n=6
Any AE	5 (83)	5 (83)	2 (33)	5 (83)
Grade 3-4 AE	1 (17)	0	0	0
Serious AE	1 (17)*	0	0	0
Discontinuation due to AE	0	1 (17)**	0	0
Grade 3 or 4 lab abnormalities	4 (67)	5 (83)	4 (67)	4 (67)

\*Left cochleovestibular deficit, not related to study treatment.

\*\*Subject discontinued treatment after the 2<sup>nd</sup> dose of ARB-1467 due to "HBV blip"(HBV-DNA 88 IU/mL) –]

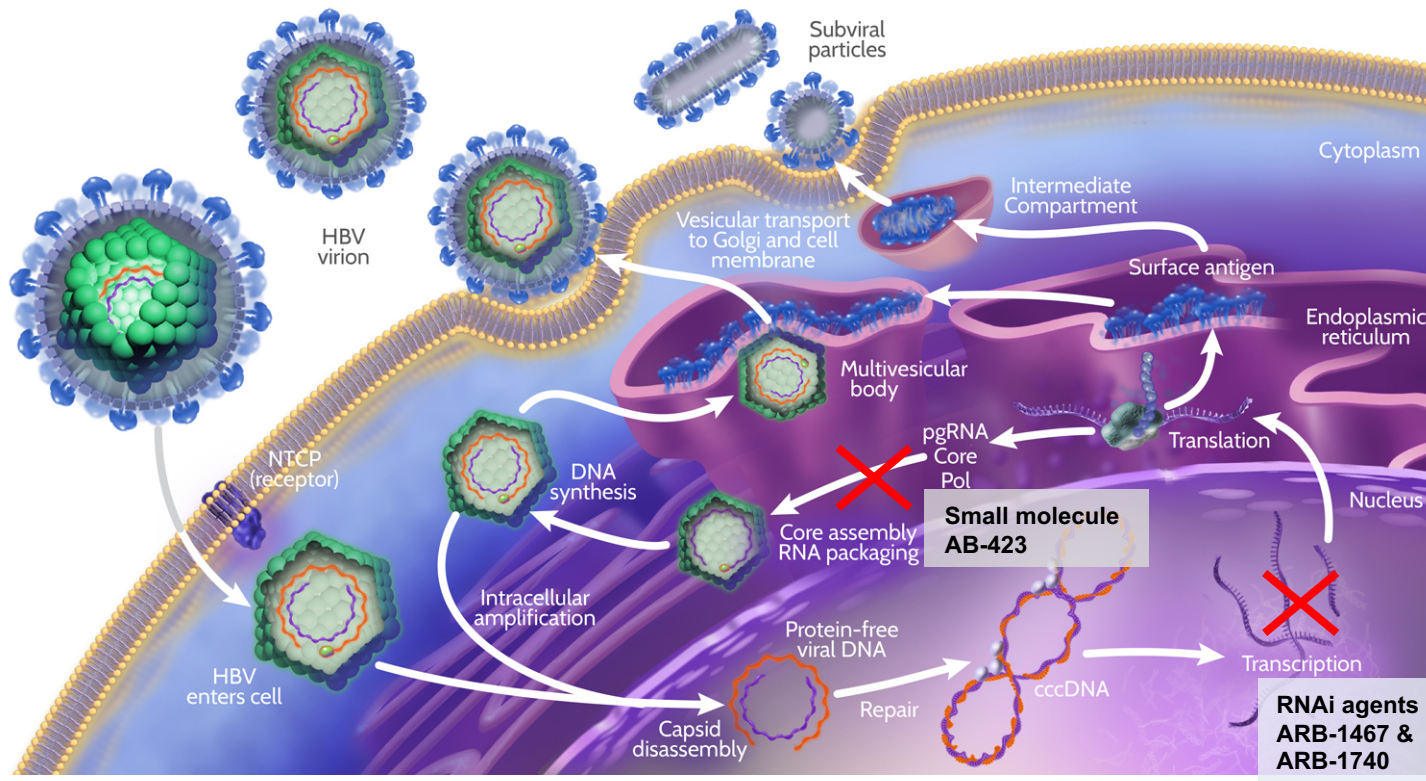
ALT increase up to 627 U/L on Day 36 of the study associated with HEV super-infection. ALT returned to baseline by Day 60.

- Most AEs were mild and transient. Only two AEs were reported by two subjects; erythema (0.2 mg/kg) and upper respiratory tract infection (placebo). All other AEs were reported by single subjects
- Isolated elevated glucose, decreased lymphocytes and low phosphate values seen across all treatment groups, including placebo
- 17/18 (94%) subjects received all three monthly doses
- No infusion reaction AEs were reported

Streinu-Cercel, et al .Abstract SAT-155. The EASL International Liver Congress™; April 19-23, 2017; Amsterdam, The Netherlands.

# Learning from Preclinical Models to Guide Next Steps in Clinic

## Preclinical study in infected humanized mouse model with LNP siRNA + pegIFN Combo



### ARB-1467 & ARB-1740 (RNA interference)

- Three siRNAs packaged in a lipid nanoparticle delivery system

### AB-423 (Core/Capsid Inhibitor)

- Orally administered small molecule
- Misdirects capsid assembly and inhibits pgRNA encapsidation

### Pegylated Interferon

- Approved drug

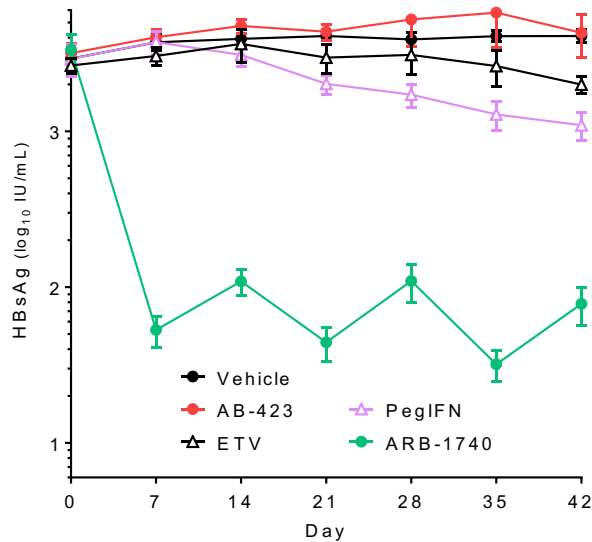
Lee, ACH et al. Exploring Combination Therapy for Curing HBV: Preclinical Studies with Capsid Inhibitor AB-423 and a siRNA Agent, ARB-1740. Presented at AASLD 14 Nov 2016, Boston

# Each Agent has Independent Activity Against HBV

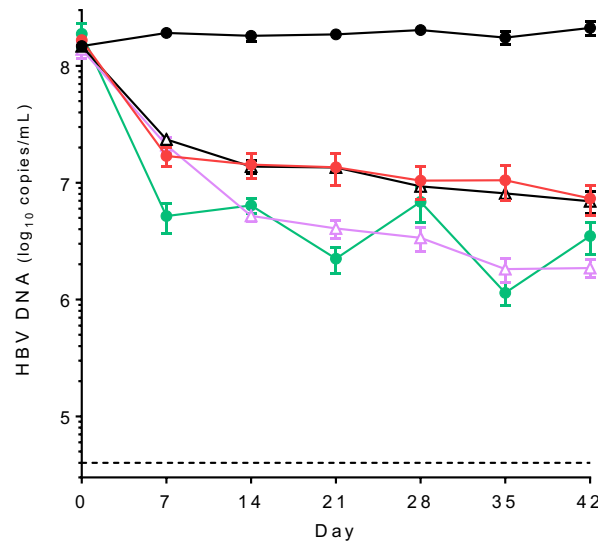
## siRNA knocks down HBsAg and HBV DNA



Serum HBsAg



Serum HBV DNA

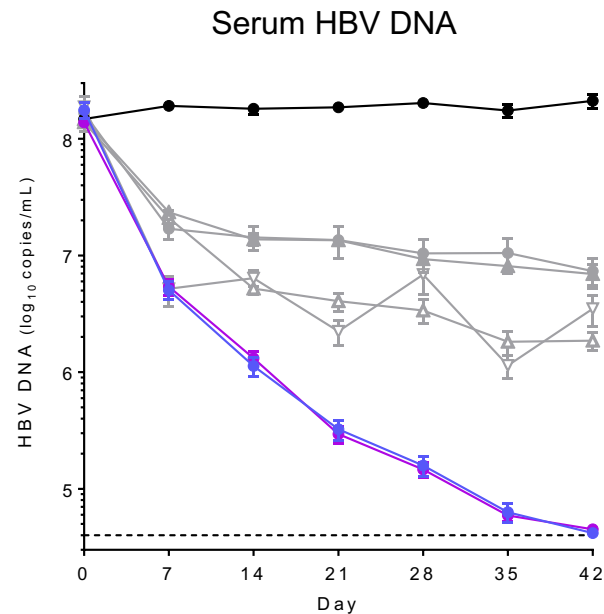
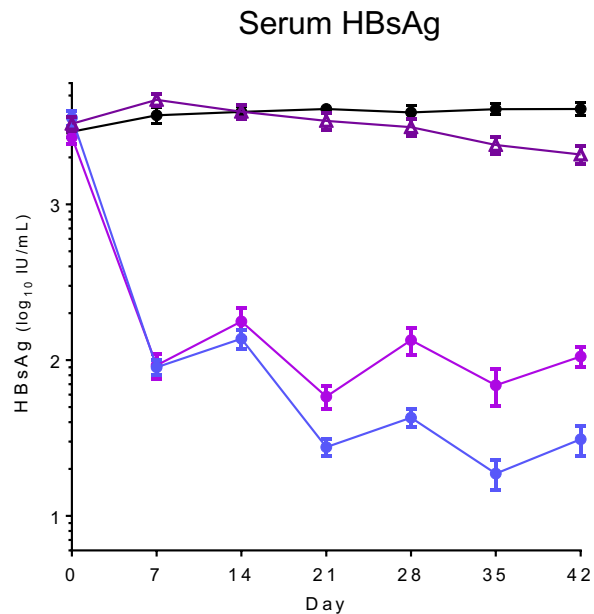


Treatment for 6 weeks			
	Dosage	Route	Frequency
AB-423	100 mg/kg	PO	BID
ETV	1.2 µg/kg	PO	QD
PegIFN	30 µg/kg	SQ	2×/wk
ARB-1740	3 mg/kg	IV	biweekly

Lee, ACH et al. Exploring Combination Therapy for Curing HBV: Preclinical Studies with Capsid Inhibitor AB-423 and a siRNA Agent, ARB-1740. Presented at AASLD 14 Nov 2016, Boston

# Triple Combo Containing Interferon Shows Better Antigen Control

## Preclinical study in infected humanized mouse model



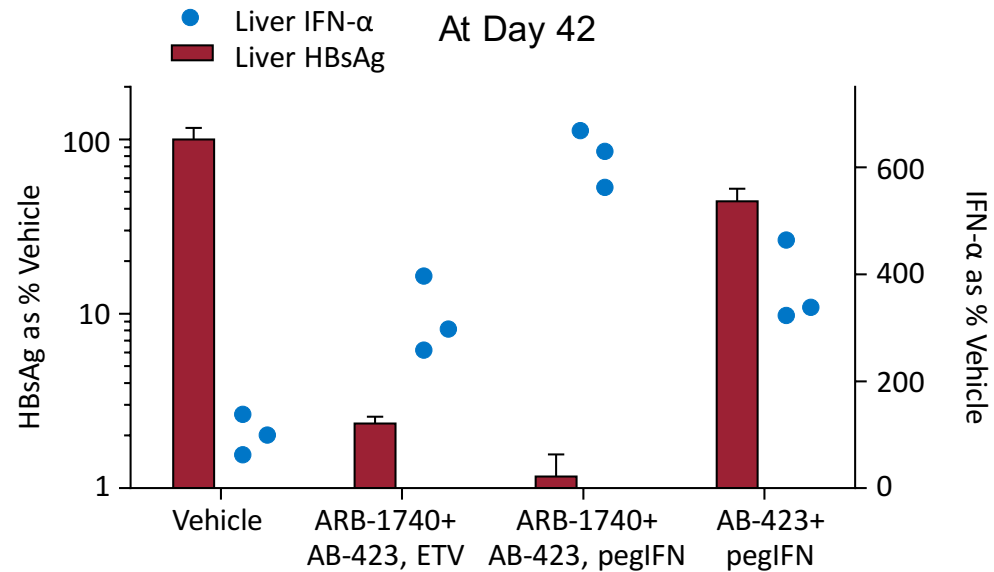
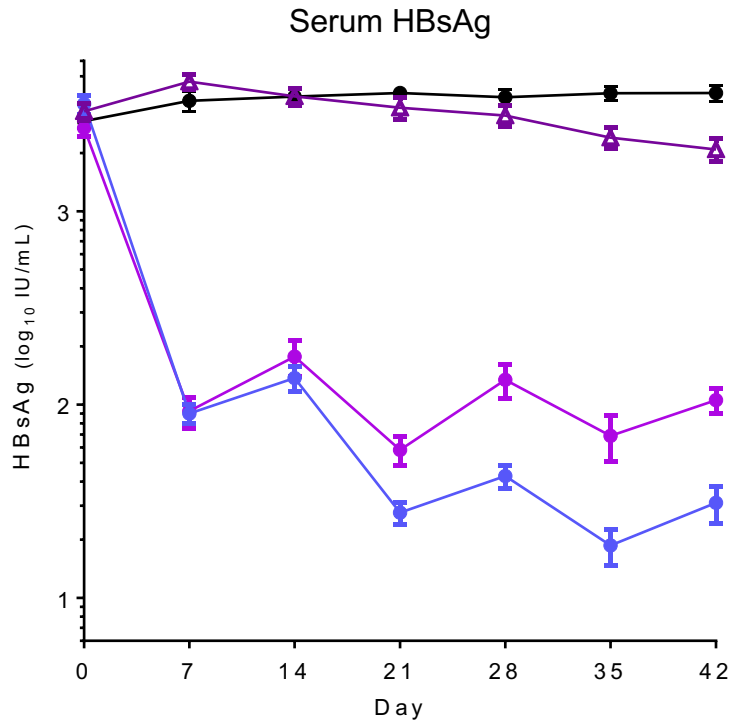
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ARB-1740	3 mg/kg	IV	biweekly

- Vehicle
- ▲ AB-423 + PegIFN
- ARB-1740 + AB-423 + ETV
- ARB-1740 + AB-423 + PegIFN

Lee, ACH et al. Exploring Combination Therapy for Curing HBV: Preclinical Studies with Capsid Inhibitor AB-423 and a siRNA Agent, ARB-1740. Presented at AASLD 14 Nov 2016, Boston

# HBsAg removal by ARB-1740 correlated with $\uparrow$ in human IFN- $\alpha$ expression

Immune response enhanced by addition of IFN to the RNAi combination



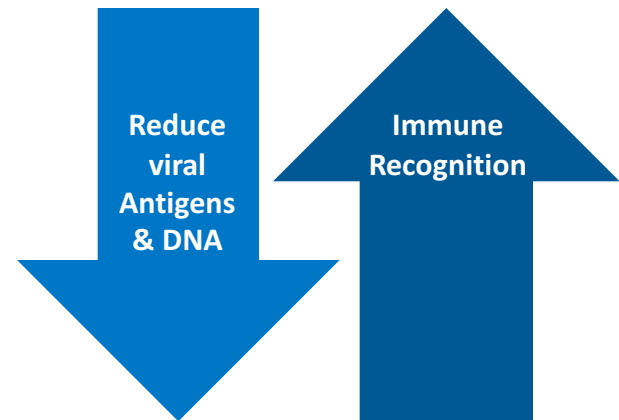
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# ARB-1467 Next Steps to Advance Development

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- ARB-1467 is a clinically validated RNA interference agent for the treatment of chronic HBV infection
- ARB-1467 drives significant HBsAg reduction in both eAg-neg and eAg-pos patients
- Longer term ARB-1467 studies with nucs and IFN to begin in 4Q17
- Humanized mouse data support the hypothesis that HBV antigen removal will promote immune recognition and viral control
- Combination of ARB-1467 with approved drugs and/or novel MOA agents can enhance control of HBV and drive progress closer towards cure



**ARB-1467 Cohort 4 data in 2H17**  
**Longer term ARB-1467 studies with nucs and IFN to begin in 4Q17**

A microscopic image of a cell, likely a yeast cell, with a blue overlay. The cell is shown in cross-section, revealing internal structures. The text "THANK YOU" is overlaid on the left side of the image.

**THANK YOU**

Acknowledgements:

Colleagues and team members at Arbutus, who have together made this progress possible