



RNAi Based Human Therapy for Chronic Hepatitis B Infection

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Discovery On Target
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NASDAQ: ABUS

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Chronic HBV – Global Unmet Medical Need

350M people chronically infected with HBV



● Chronic HBV Infections ● HBV Genotypes (A–H)

800K people die every year as a consequence of HBV

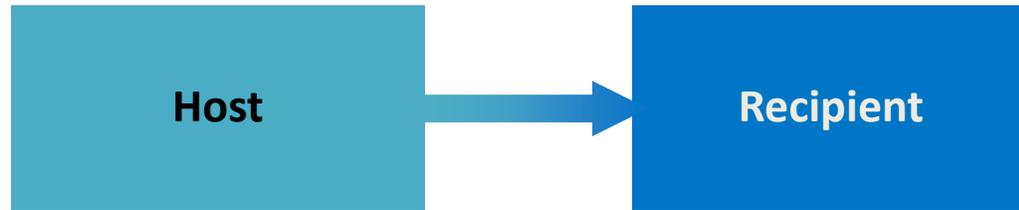
- 1 in 20 people worldwide have chronic HBV
- Virus is not cytopathic
- 25% lifetime risk for each HBsAg+ patient of HCC or cirrhosis
- Outcomes related to host immune responses

• Lozano R, Naghavi M, Foreman K et al. The Lancet 2012; 380: 2095-128

• World Health Organization: Fact Sheet No. 204. Hepatitis B, revised, August 2008. Geneva: WHO. www.who.int/mediacentre/factsheets/fs204/en/index.html

Transmission of HBV

Horizontal Transmission

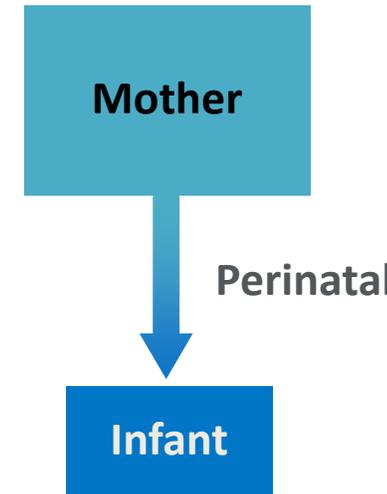


Child-to-Child
Contaminated Needles
Sexual
Health Care Worker
Transfusion

6% infected after age 5 years
become chronically infected

No clear risk factors in 20-30% of patients

Vertical Transmission



90% infected infants
become chronically infected

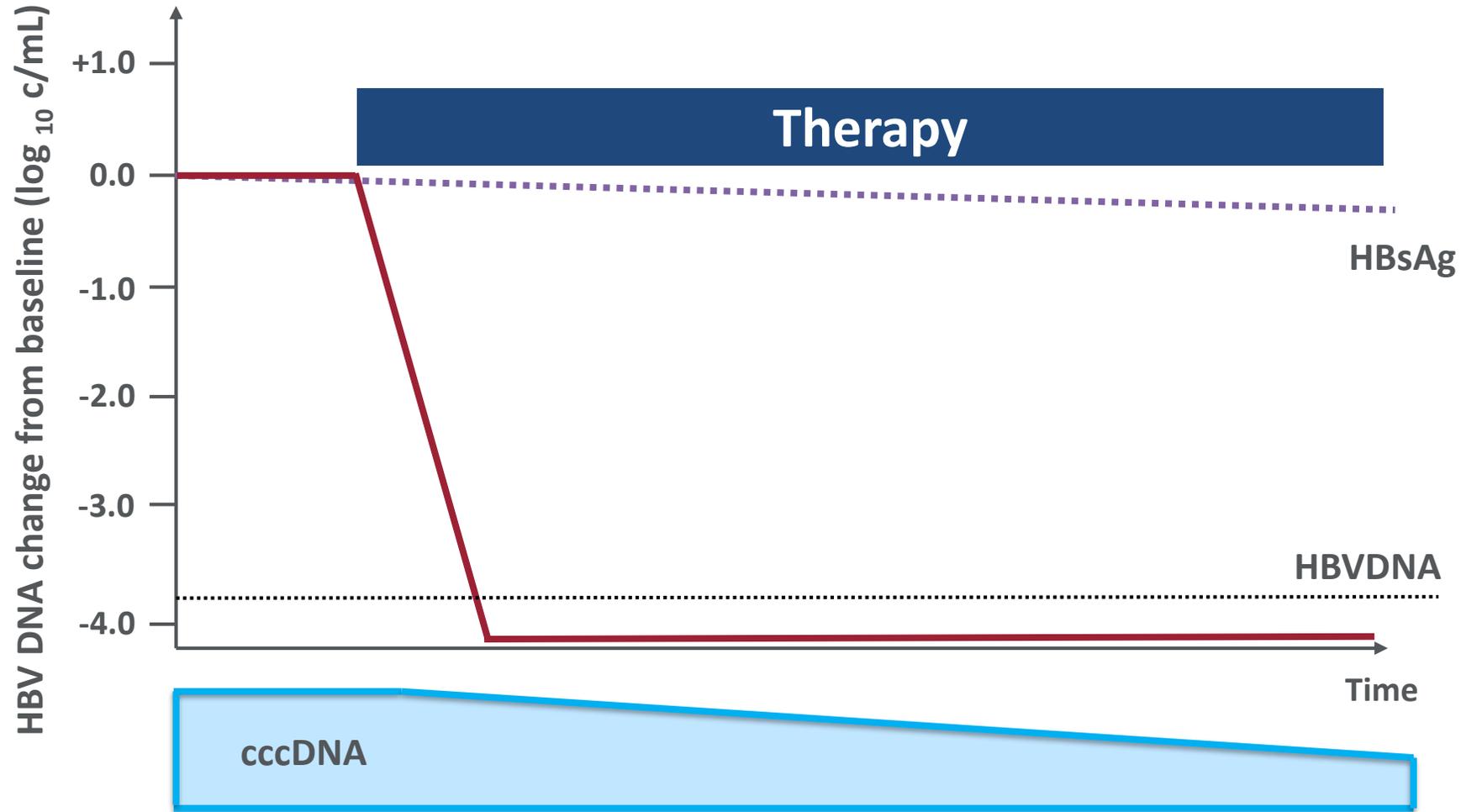
CDC Fact Sheet. <http://www.cdc.gov/ncidod/diseases/hepatitis/b/>. Accessed: October 2, 2004.
Lee. *N Engl J Med.* 1997;337(24):1733-1745.
Lavanchy. *J Viral Hepat.* 2004;11(2):97-107.

Approved Therapies for Chronic HBV Infection

Nucleosides/Nucleotides			
Tenofovir Alafenamide	VEMLIDY®	Gilead Sciences	2016
Tenofovir	VIREAD®	Gilead Sciences	2006
Telbivudine	TYZEKA™	Idenix/Novartis	2006
Entecavir	BARACLUDE™	Bristol-Myers Squibb	2005
Adefovir Dipivoxil	HEPSERA™	Gilead Sciences	2002
Lamivudine	EPIVIR-HBV®	GlaxoSmithKline	1998
Interferons			
Peginterferon alfa-2a	PEGASYS®	Roche Laboratories	2005
Interferon alfa-2b recombinant	INTRON® A	Schering/Merck	1992

**Preferred Therapies
– AASLD Guidelines**

Viral Suppression Requires Long-term Therapy

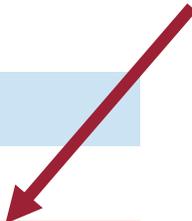


Werle et al, Gastroenterology 2004

Relative Efficacy of Approved HBV Therapies

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

Approved therapies show a cure is possible but result in <5% cure rate



- Significant opportunity to improve cure rates

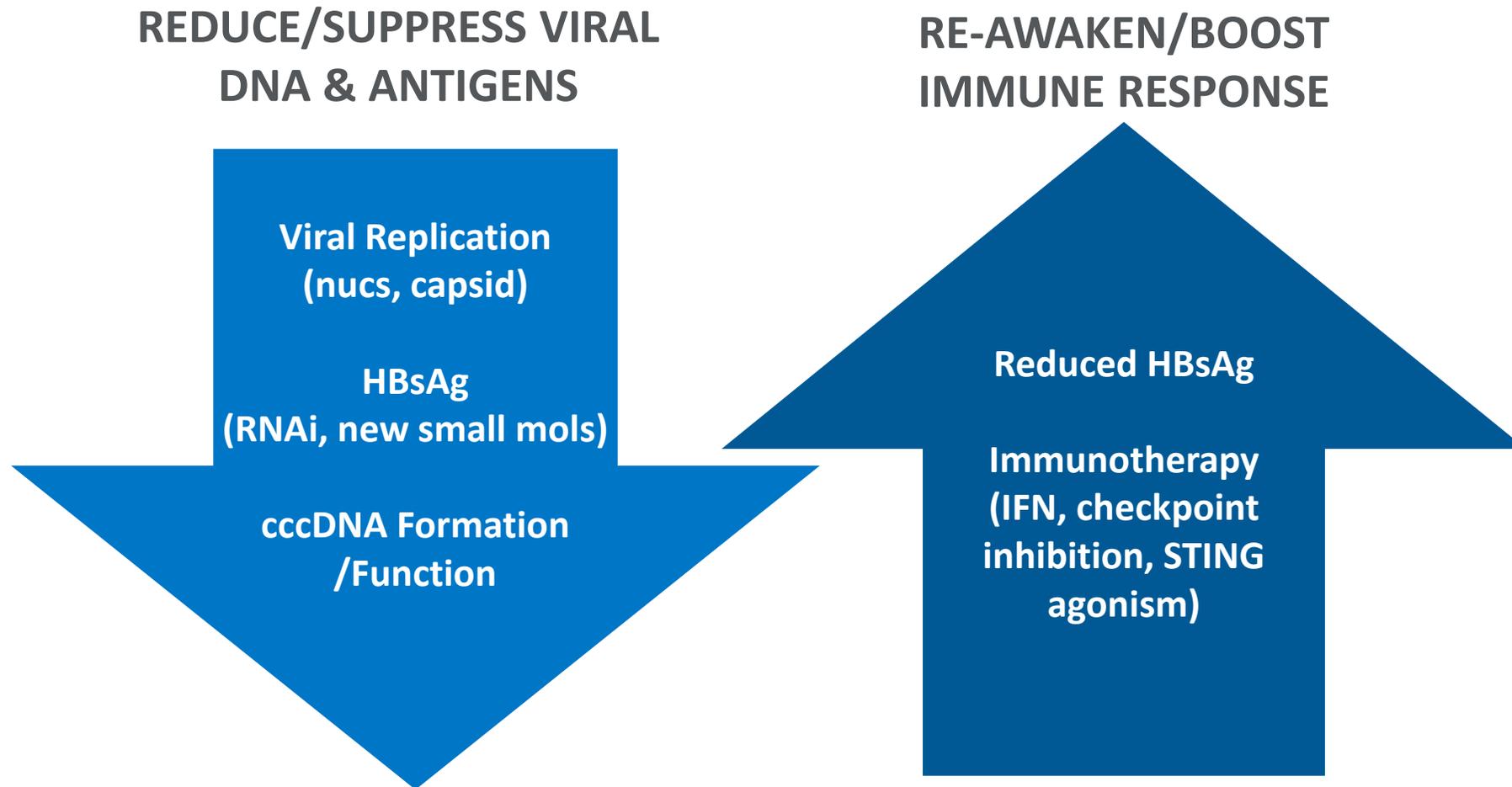
Results at 48 weeks

^a HBV DNA < 400 copies/mL; ^b 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.

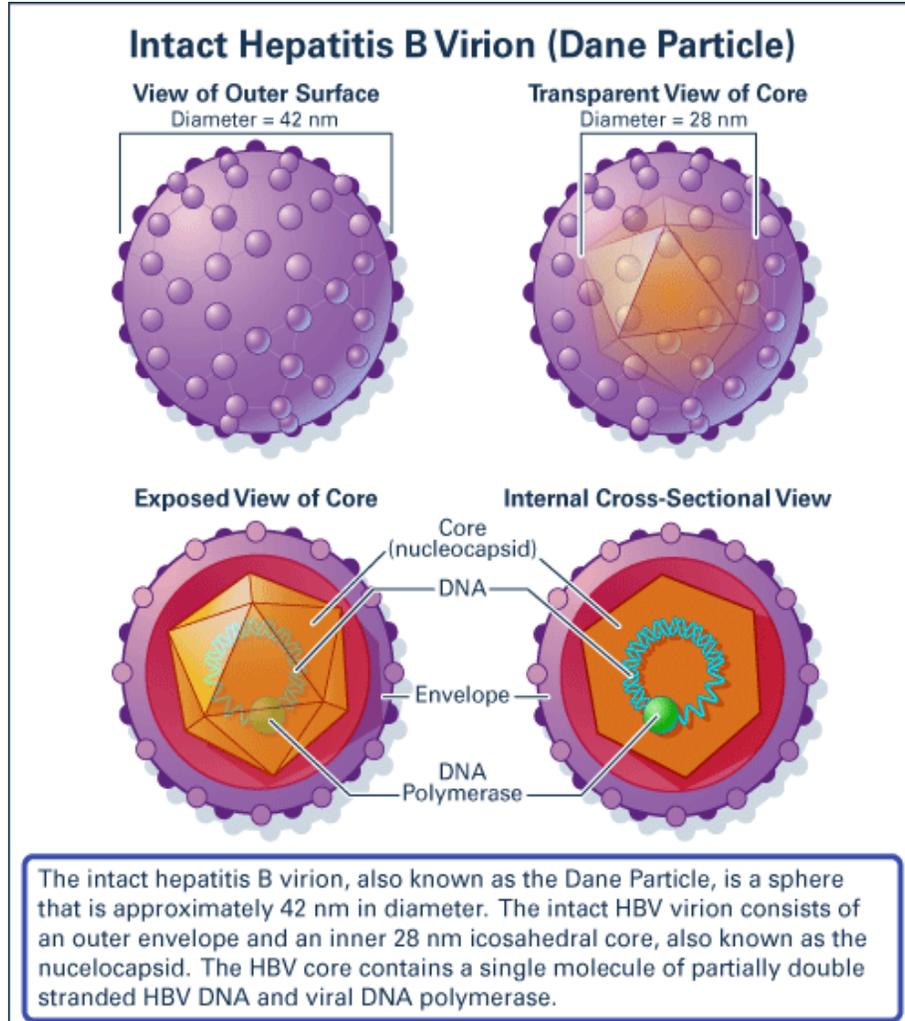
4. Lau GKK, et al. N Engl J Med 2005;352:2682–95.
 5. Marcellin P, et al. N Engl J Med 2004;351:1206–17.

How to Achieve a Cure?



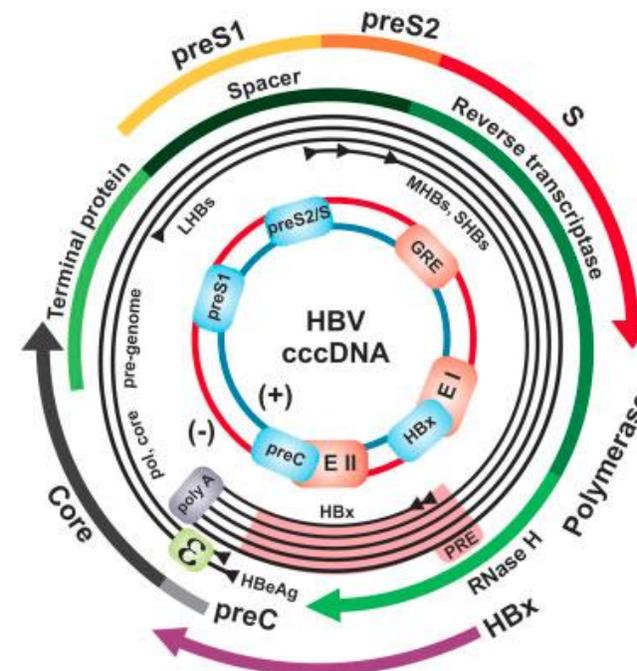
We anticipate that HBV cure will require combinations of drugs with different actions

The Hepatitis B Virus



Source: Gerlich, W. 2013. *Virology Journal*, 10:239

Genome Structure of HBV



Glebe, D., et al, *Sem. Liver Dis*, 33, 2013, 103

- 4 Promoter elements
- 2 enhancer elements
- 10 transcription start sites

5 mRNAs:

- Pregenomic/core/pol (3.5 kb)
- Precore (3.5 kb)
- PreS1 (2.4 kb)
- PreS2/S (2.1 kb)
- X (0.7 kb)

1. ARB-1467 is a novel antiviral agent in which 3 anti-HBV siRNA “triggers” are packaged inside proprietary lipid nanoparticles (LNPs)

2. The 3 siRNA triggers within ARB-1467 are designed to target all 4 viral RNA transcripts encoded by the HBV genome at sites that are highly conserved across HBV genotypes

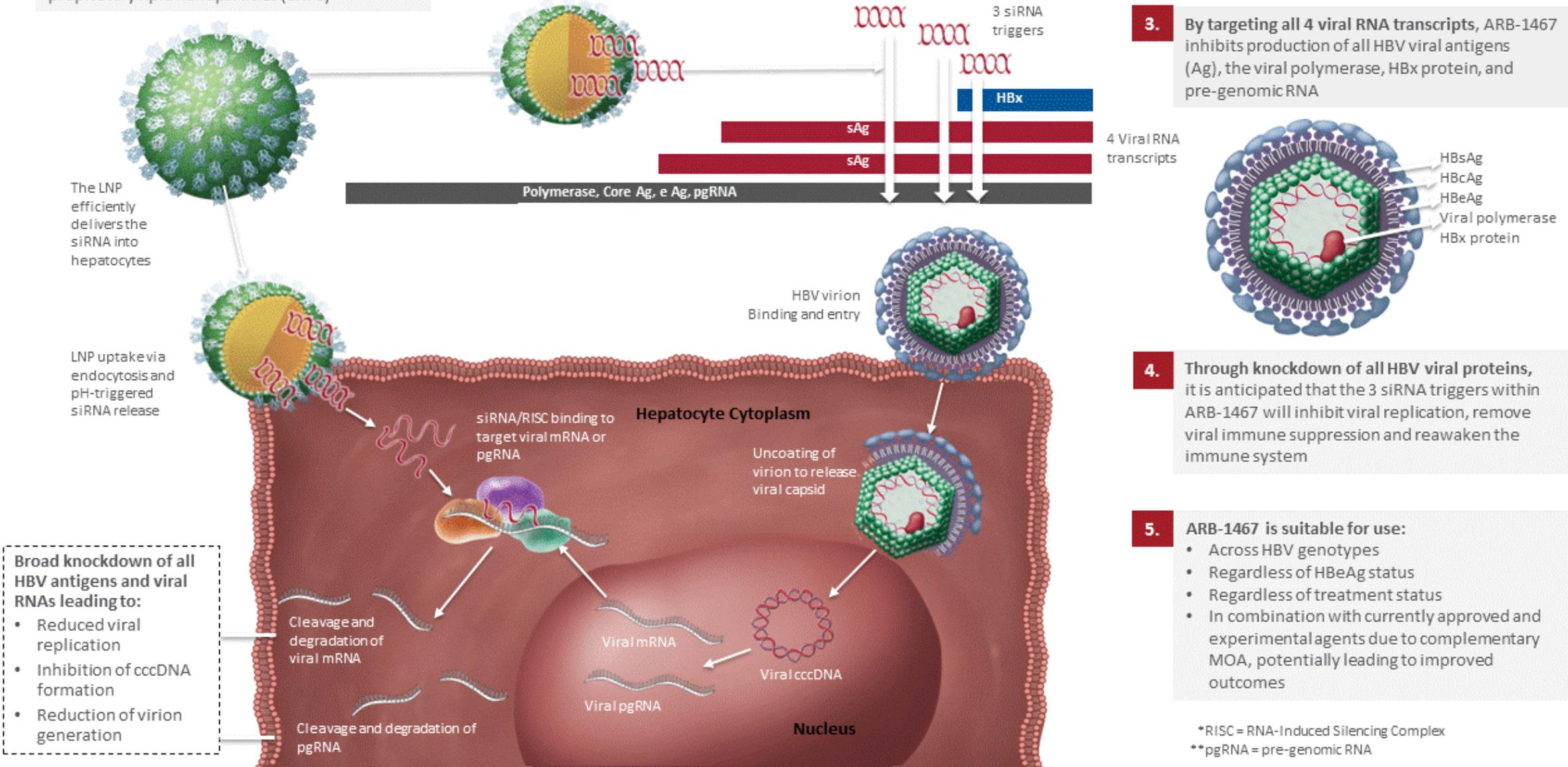
3. By targeting all 4 viral RNA transcripts, ARB-1467 inhibits production of all HBV viral antigens (Ag), the viral polymerase, HBx protein, and pre-genomic RNA

4. Through knockdown of all HBV viral proteins, it is anticipated that the 3 siRNA triggers within ARB-1467 will inhibit viral replication, remove viral immune suppression and reawaken the immune system

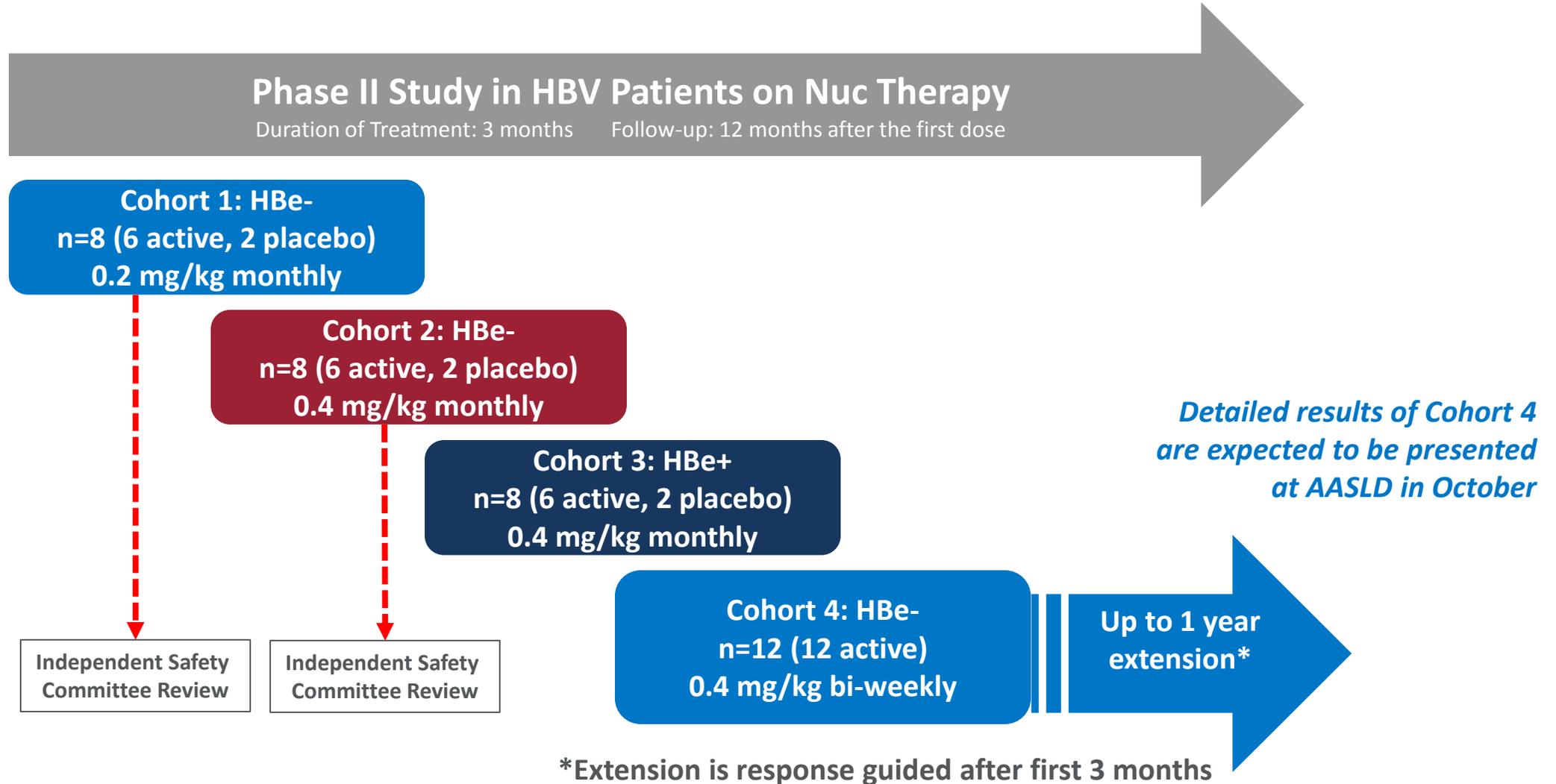
5. ARB-1467 is suitable for use:

- Across HBV genotypes
- Regardless of HBeAg status
- Regardless of treatment status
- In combination with currently approved and experimental agents due to complementary MOA, potentially leading to improved outcomes

*RISC = RNA-Induced Silencing Complex
 **pgRNA = pre-genomic RNA



ARB-1467 Phase II: Measuring HBsAg Reduction



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 ^a	Max ^c	>0.5 log ^c	>1.0 log ^c
1	0.2	Negative	6	-0.6	-1.3	5	1
2	0.4	Negative	5 ^d	-0.9	-1.3	4	3
3	0.4	Positive	6	-0.7	-1.6	4	2
Placebo	N/A		6 ^e	0.0	-0.1	0	0

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

^b Maximum HBsAg reduction is the best single reduction among all patients in a cohort.

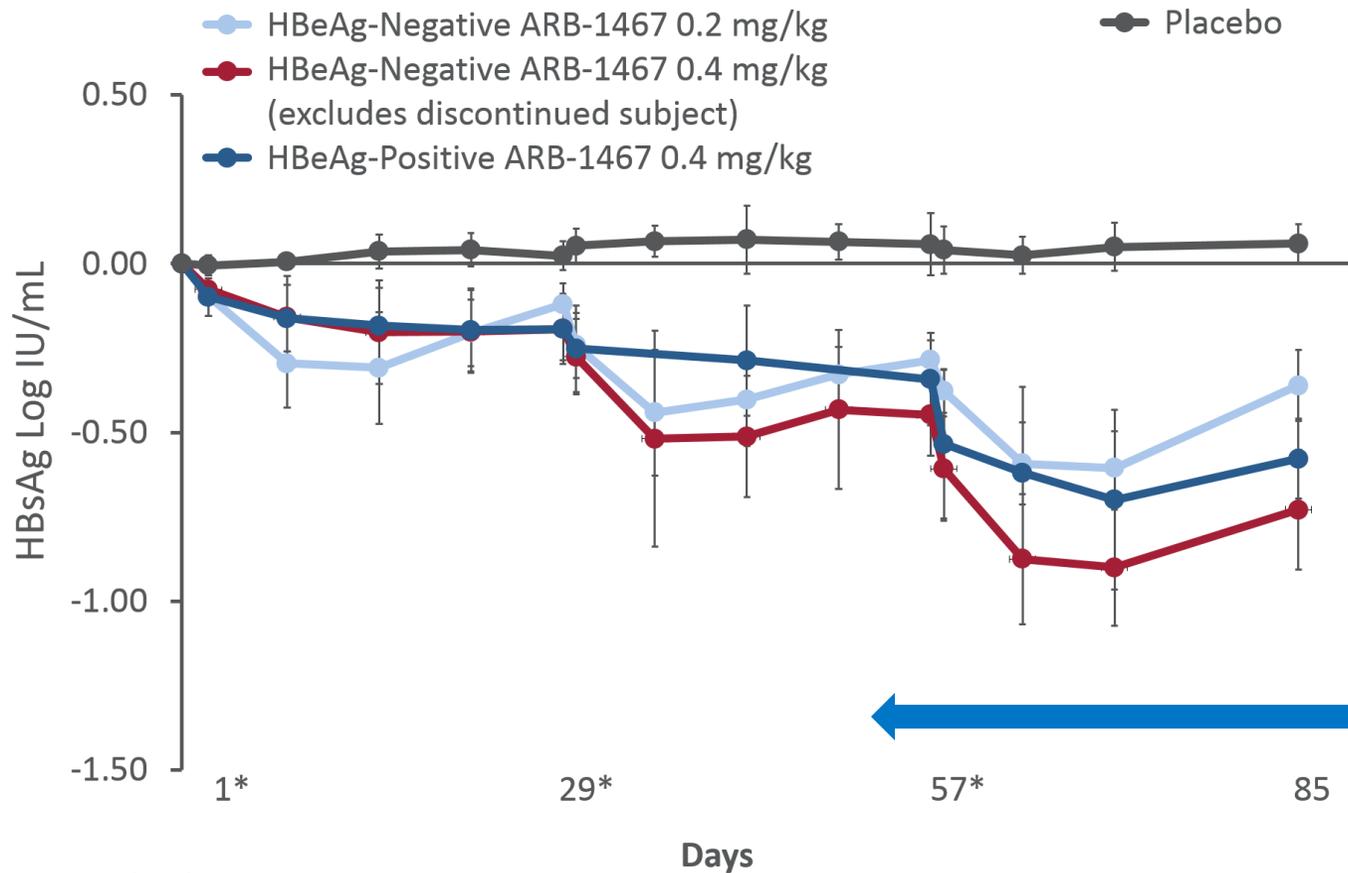
^c Number of patients reaching this threshold

^d Multiple dose results in Cohort 2 exclude one patient that discontinued at day 36 due to “HBV blip” associated with acute HEV infection

^e Placebo results are based on six subjects (two from each cohort).

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

HBsAg Mean Log (IU/mL) Change from Baseline



*Topline results from Cohort 4:
HBeAg-Negative ARB-1467 0.4 mg/kg (N=12)*

*Average 1.4 log HBsAg reduction
after 5 biweekly doses*

*Dosing day

Overall Safety

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 2nd 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.

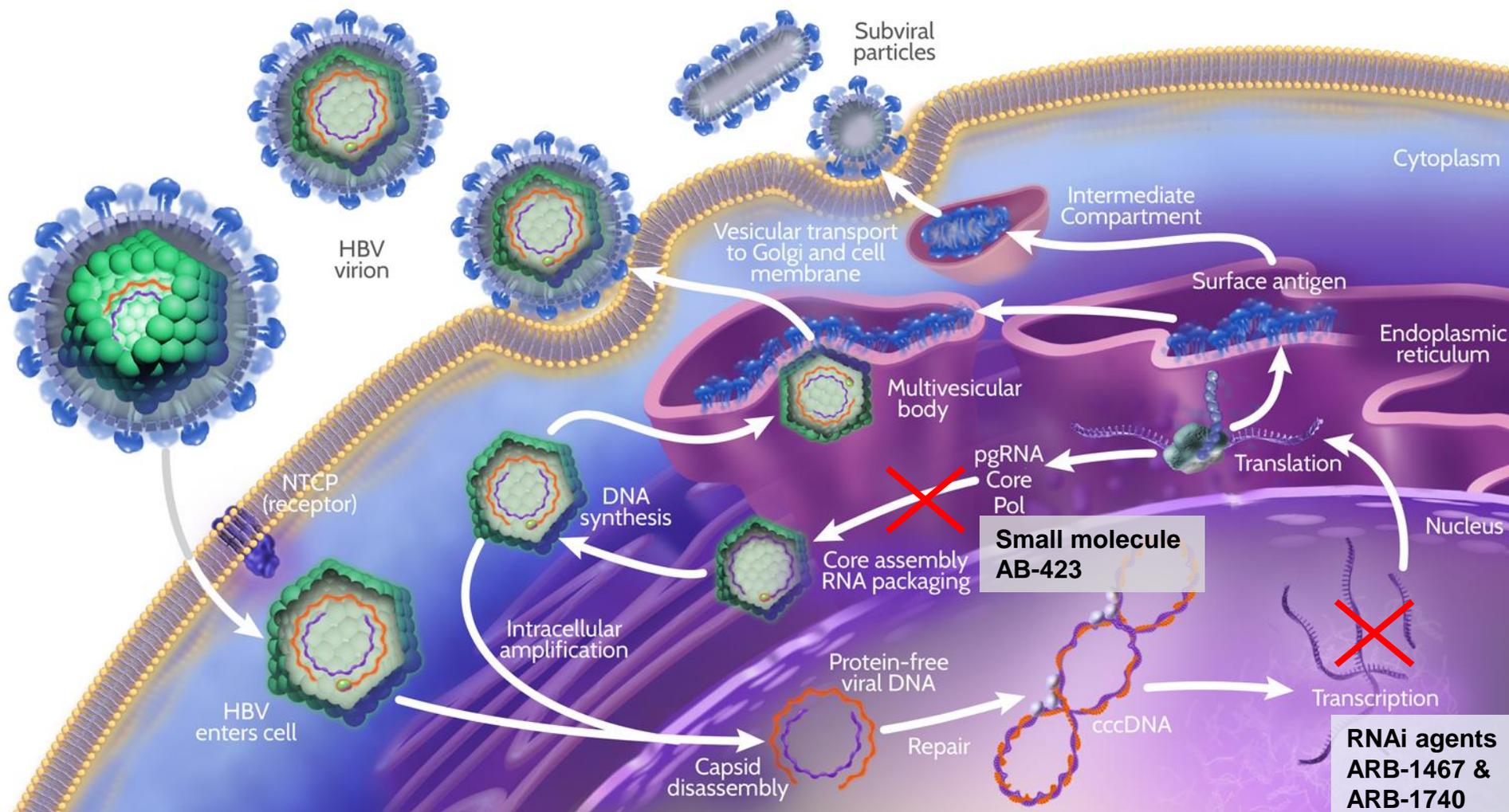
ARB-1467 Next Steps to Advance Development

- Potential for greater HBsAg reductions with more frequent, continued dosing
 - Cohort 4: biweekly dosing, extended dosing
- 2017 Studies planned to assess longer duration and combination with immune stimulator to maximize HBsAg reduction
- Future combinations will include multiple Arbutus agents

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

LNP siRNA + pegIFN Combo

Preclinical study in infected humanized mouse model



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

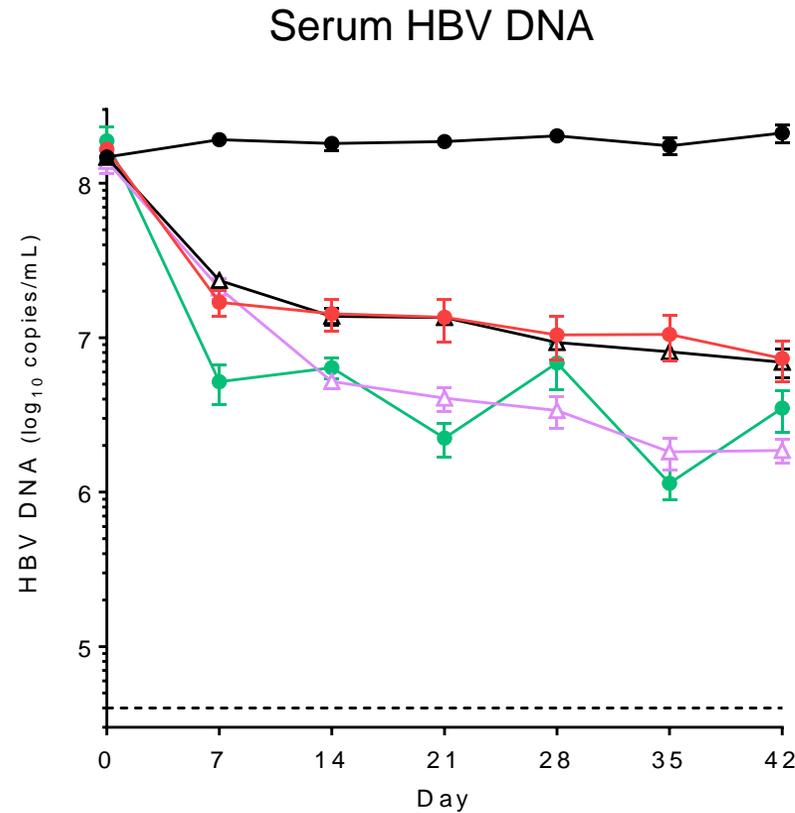
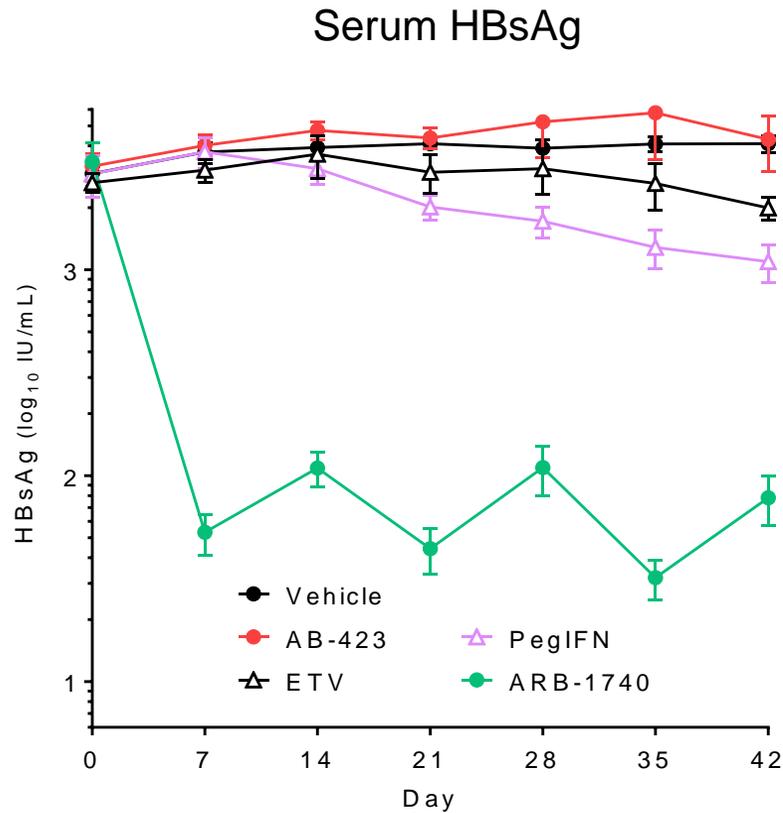
Pegylated Interferon

- Approved drug

LNP siRNA + pegIFN Combo

Preclinical study in infected humanized mouse model

- Each agent has stand-alone activity against HBV virus



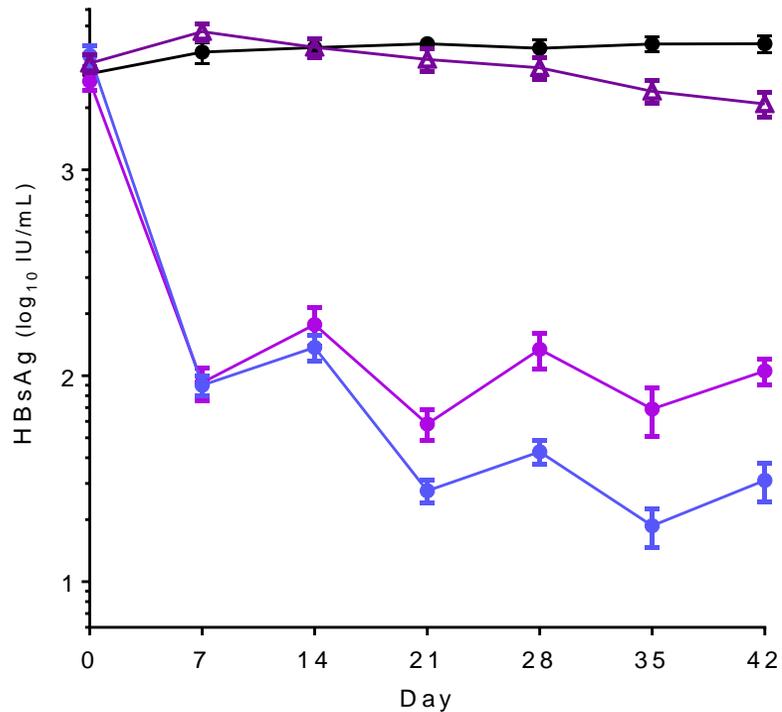
Treatment for 6 weeks			
	Dosage	Route	Frequency
AB-423	100 mg/kg	PO	BID
ETV	1.2 µg/kg	PO	QD
PegIFN	30 µg/kg	SQ	2×/wk
ARB-1740	3 mg/kg	IV	biweekly

LNP siRNA + pegIFN Combo

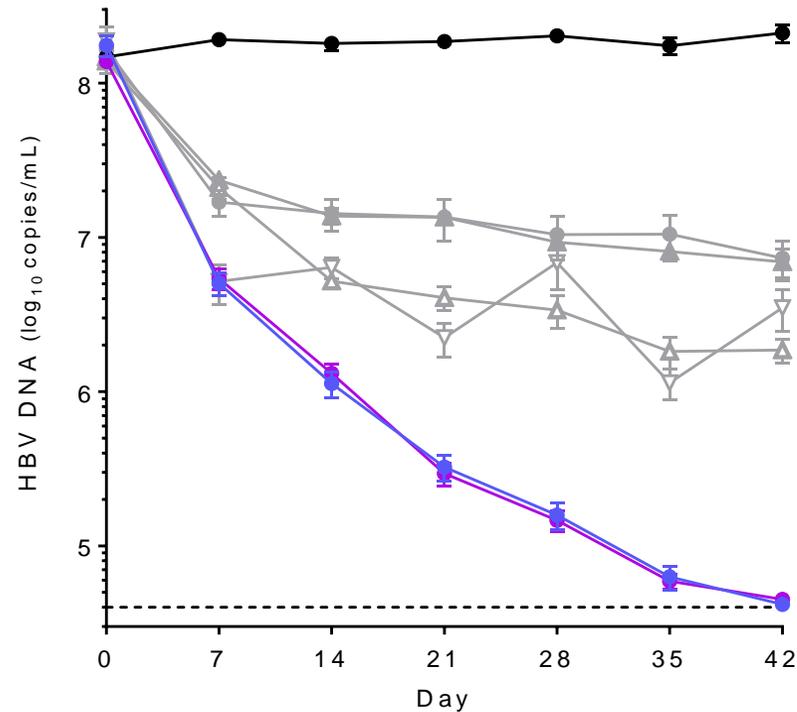
Preclinical study in infected humanized mouse model

- Triple combo containing pegIFN has additional benefit of more antigen control

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	2x/wk
ARB-1740	3 mg/kg	IV	biweekly

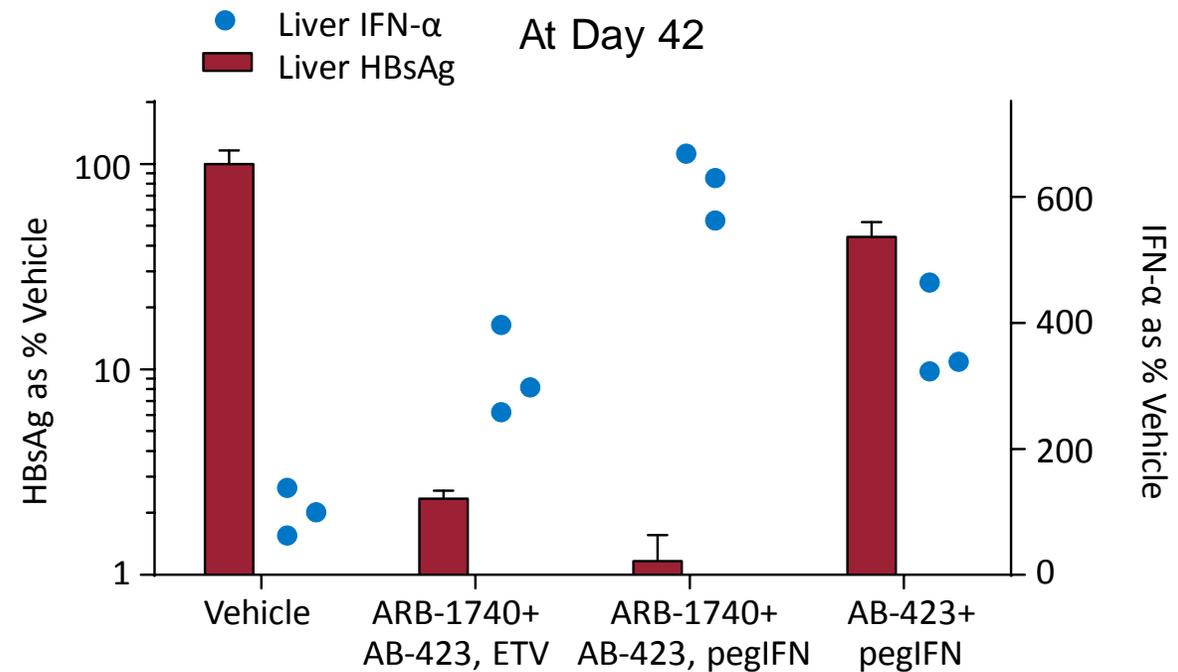
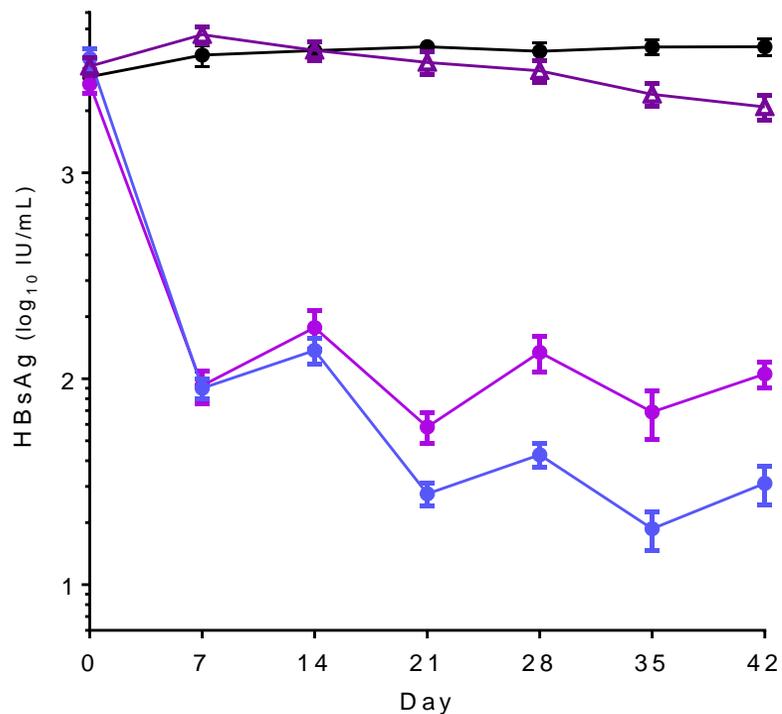
- Vehicle
- ▲ AB-423 + PegIFN
- ARB-1740 + AB-423 + ETV
- ARB-1740 + AB-423 + PegIFN

HBsAg Removal Correlated with ↑ Host Immune Response

Infected humanized mouse model

- HBsAg removal by ARB-1740 correlated with gain in human IFN- α expression
- In vivo human hepatocyte innate immune response was further potentiated by combining ARB-1740 with pegylated interferon

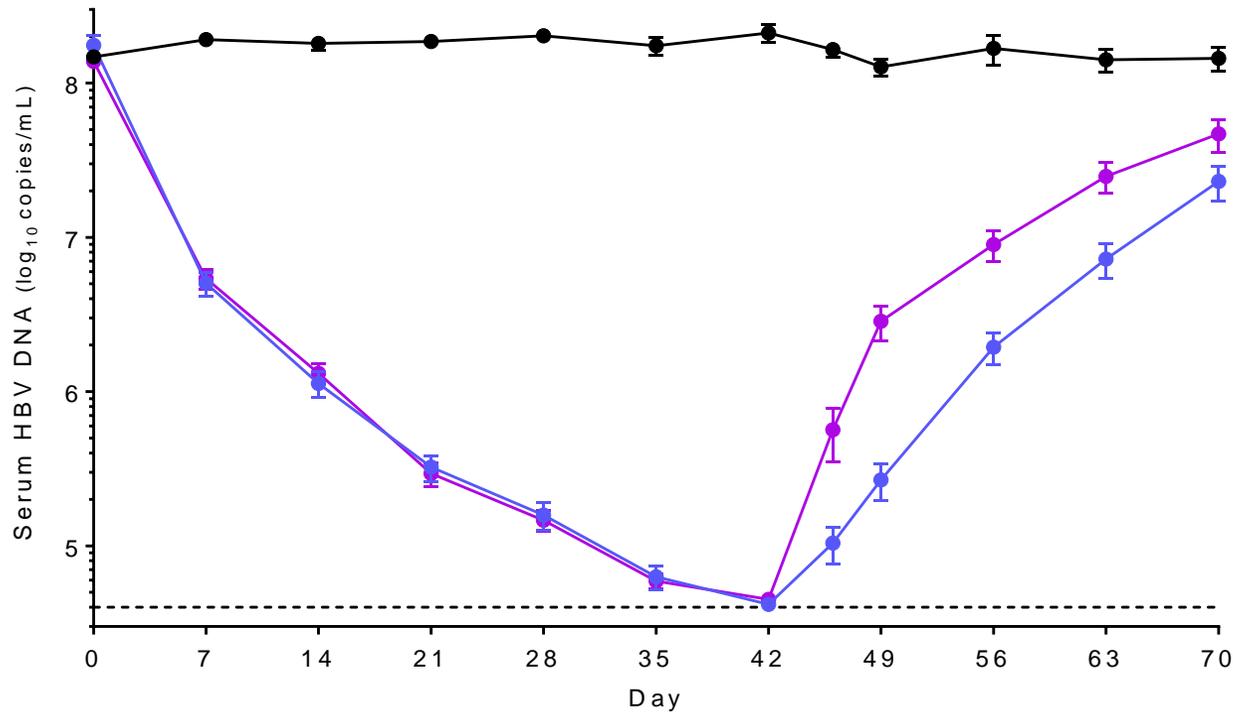
Serum HBsAg



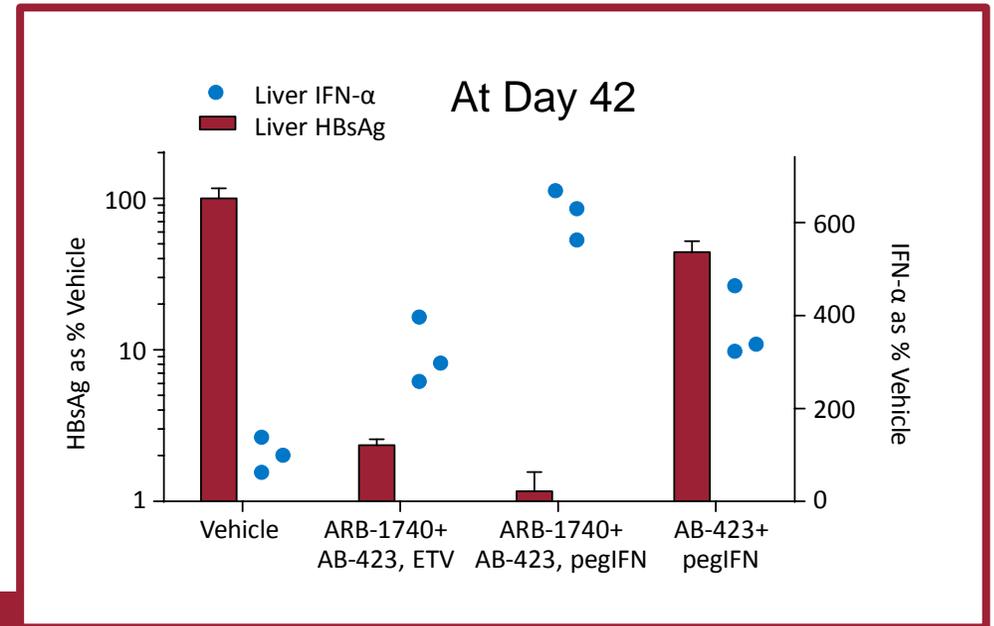
Slower Off-treatment Viral Rebound Correlated with ↑ Host Immune Response

Infected humanized mouse model

*Model lacks T and B cells
(adaptive immunity)*



6 wk Treatment Phase 4 wk Follow Up



Preclinical Models Mimicking Chronic Human HBV

- No model yet ‘predictive’ of HBV cure
- Preclinical investigations can provide supportive data to help inform the design of investigative human trials

Features of Model	Mouse Models		
	Hydrodynamic Injection	Chimeric Humanized Liver	AAV Tolerance (Immune competent)
Viral Infection	x	✓	x
Viral Replication	x	✓	x
HBV DNA	✓	✓	✓
HBsAg	✓	✓	✓
HBeAg	✓	✓	✓
HBcAg	✓	✓	✓
cccDNA	x	✓	x
Adaptive Immunity	x	x	✓



Woodchuck



Chimp

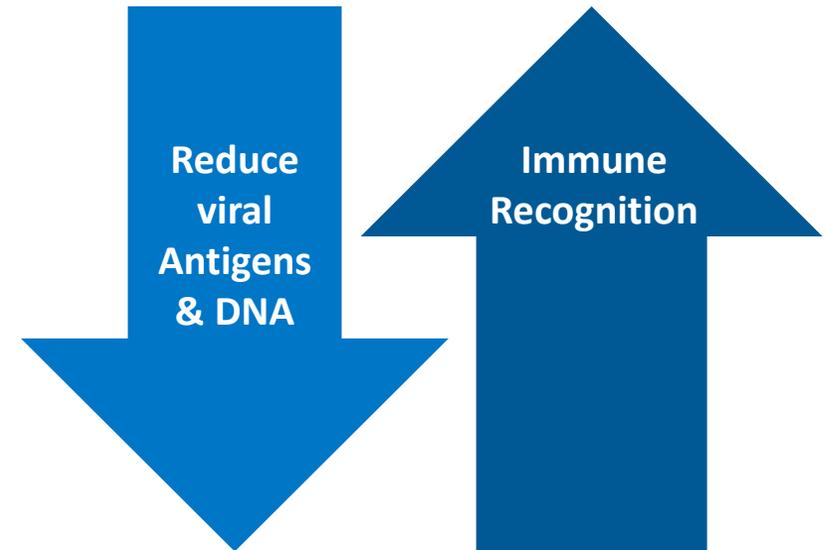


Tree shrew

RNAi combination results in an AAV mouse model will be presented at AASLD in October

Summary

- ARB-1467 is a clinically validated RNA interference agent for the treatment of cHBV
- 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





THANK YOU

Acknowledgements:

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

NASDAQ: ABUS

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