RNA Interference: A New Tool in the Toolbox for Treatment of HBV

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Discovery On Target
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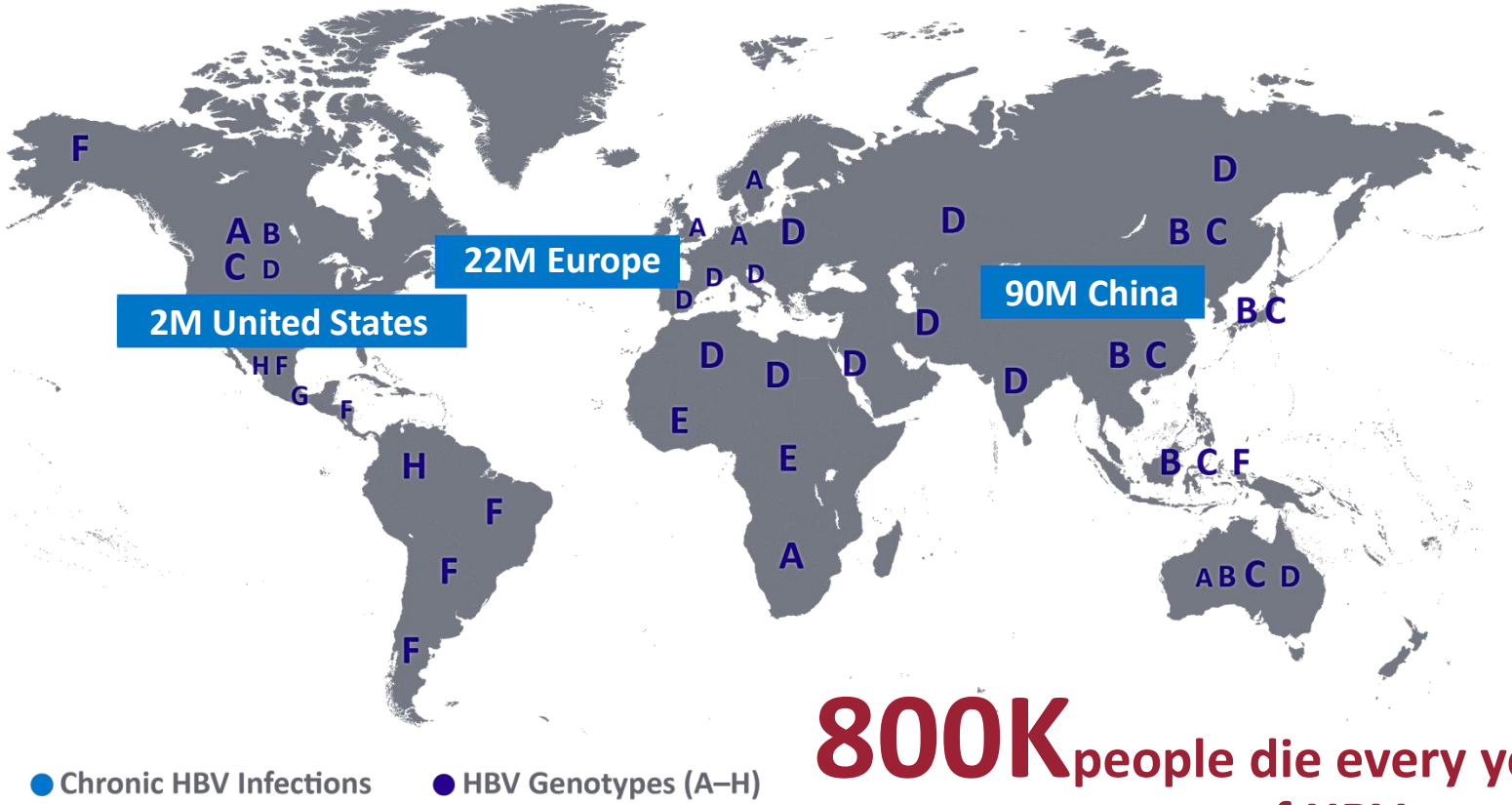
Chronic HBV – Global Unmet Medical Need

350M people chronically infected with HBV



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

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]

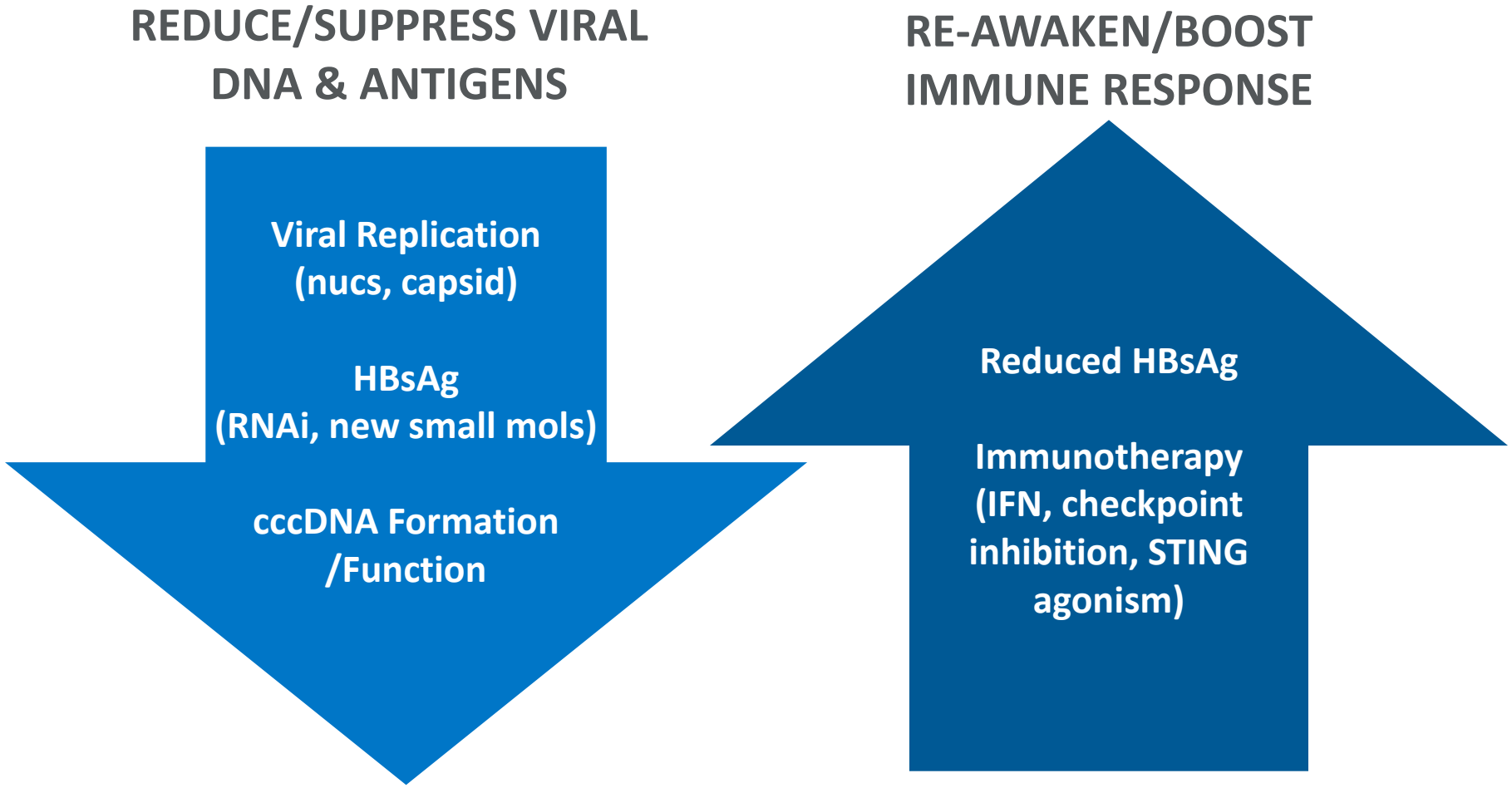
Approved therapies show a cure is possible but result in <5% cure rate

- Significant opportunity to improve cure rates

Results at 48 weeks
[a] HBV DNA < 400 copies/mL; [b] At 72 weeks

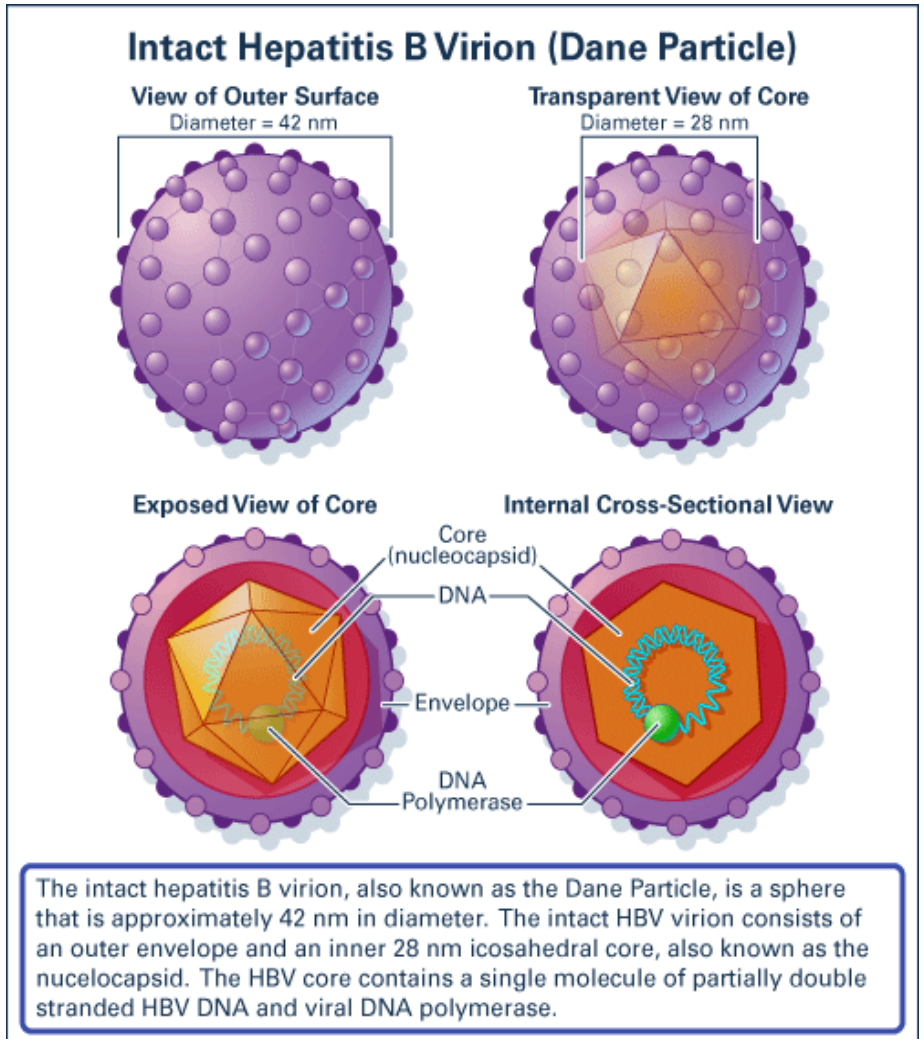
1. Chang T-T, et al. N Engl J Med 2006;354:1001–10.
2. Lai C-L, et al. N Engl J Med 2006;354:1011–20.
3. Marcellin P, et al. N Engl J Med 2008;359:2442–55.
4. Lau GKK, et al. N Engl J Med 2005;352:2682–95.
5. Marcellin P, et al. N Engl J Med 2004;351:1206–17.

How to Achieve a Cure?



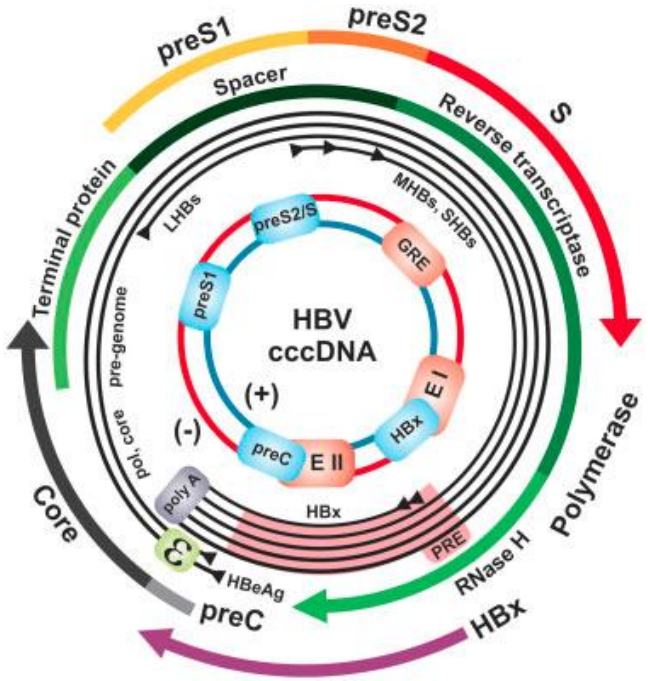
We anticipate that HBV cure will require combinations of drugs with different actions

The Hepatitis B Virus



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

Genome Structure of HBV



Glebe, D., etal, Sem. Liver Dis, 33, 2013, 103

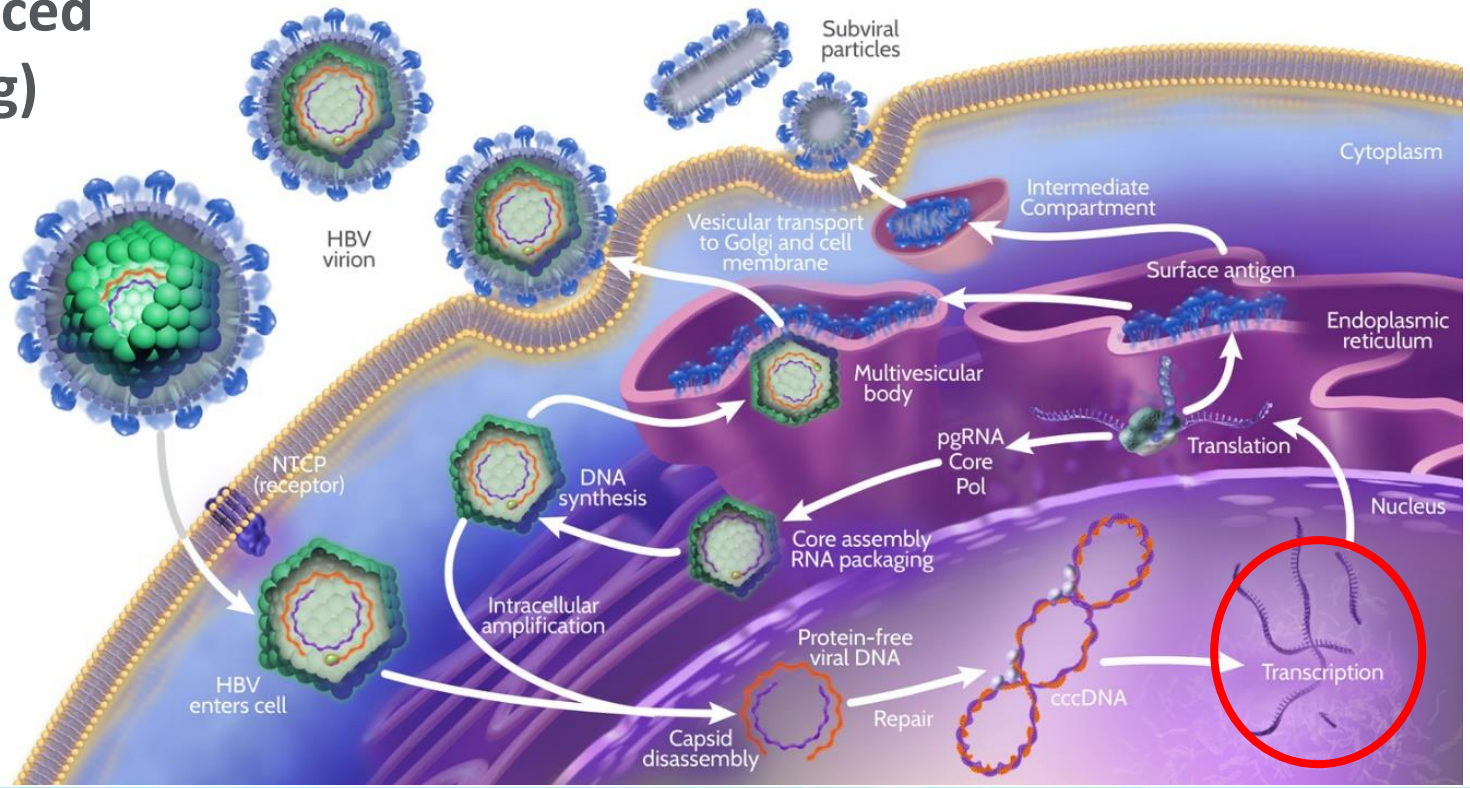
- 4 Promoter elements
- 2 enhancer elements
- 10 transcription start sites

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)

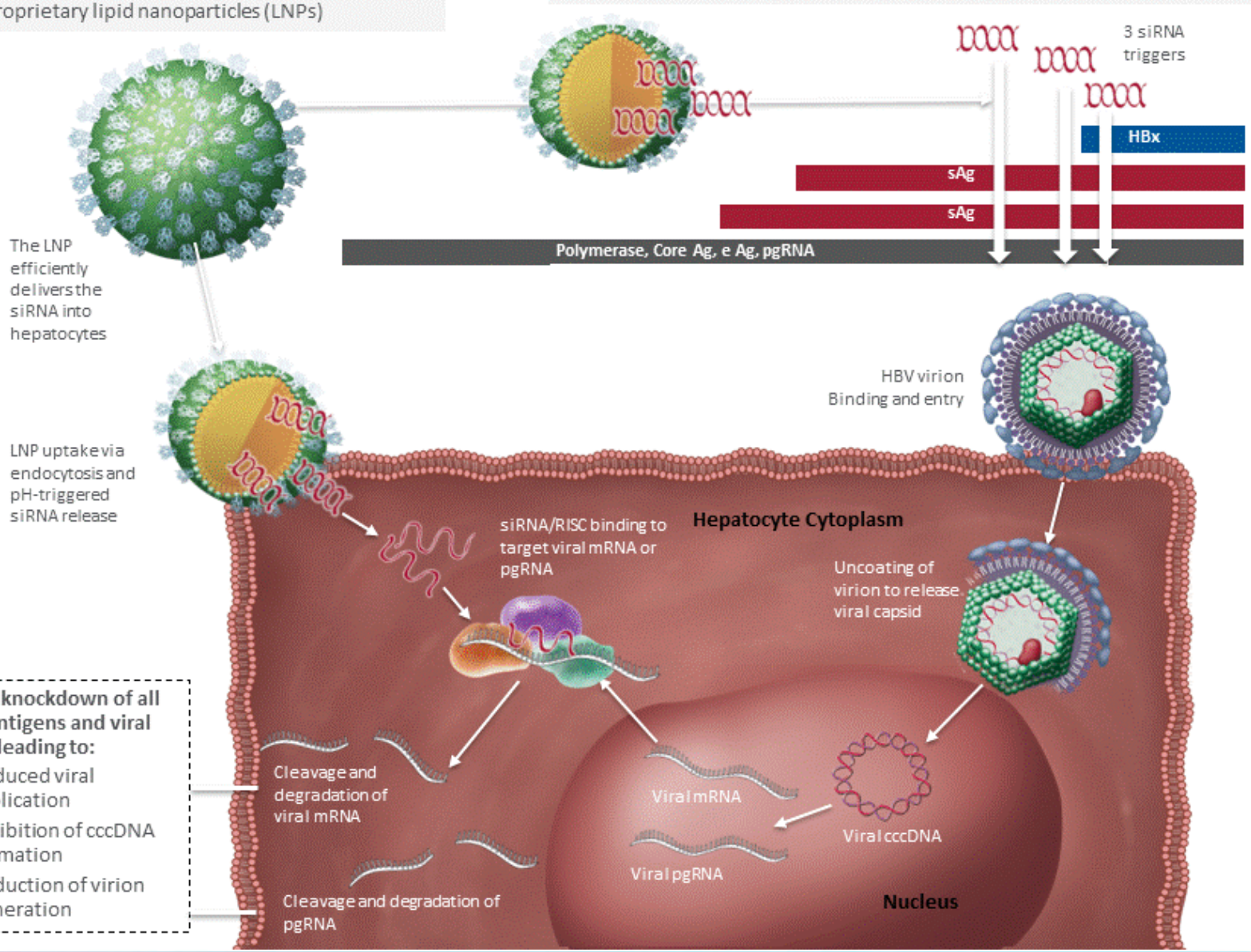
The Hepatitis B Virus

- Host immune response is attenuated by viral antigens
- 10^{13} virons produced per day
- 1000× more subviral particles produced comprised of surface antigen (HBsAg)
- RNA interference targets HBsAg at the level of transcription



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

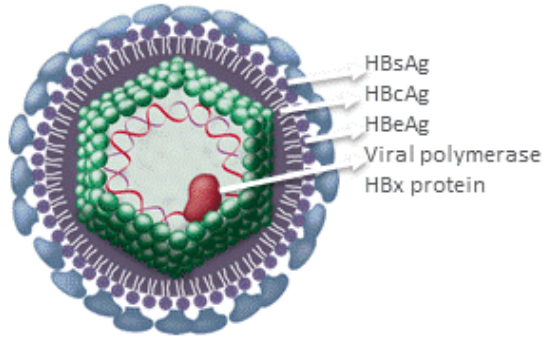
2. **The 3 siRNA triggers within ARB-1467** are designed to target all 4 viral RNA transcripts encoded by the HBV genome at sites that are highly conserved across HBV genotypes



Broad knockdown of all HBV antigens and viral RNAs leading to:

- Reduced viral replication
- Inhibition of cccDNA formation
- Reduction of virion generation

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

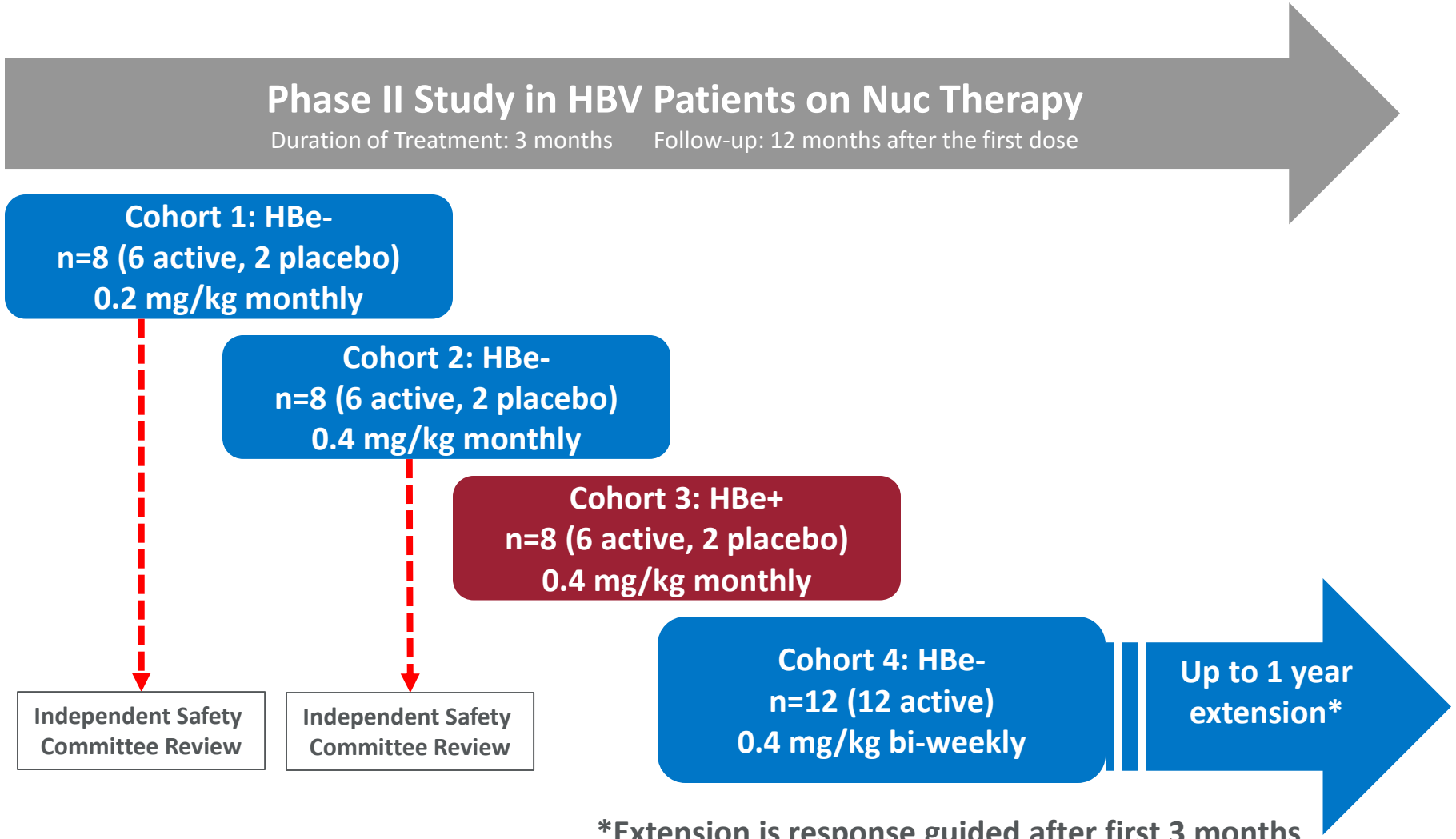
5. **ARB-1467 is suitable for use:**

- 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

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

ARB-1467 Phase II: Measuring HBsAg Reduction



*Extension is response guided after first 3 months

ARB-1467 Drives Significant HBsAg Reduction

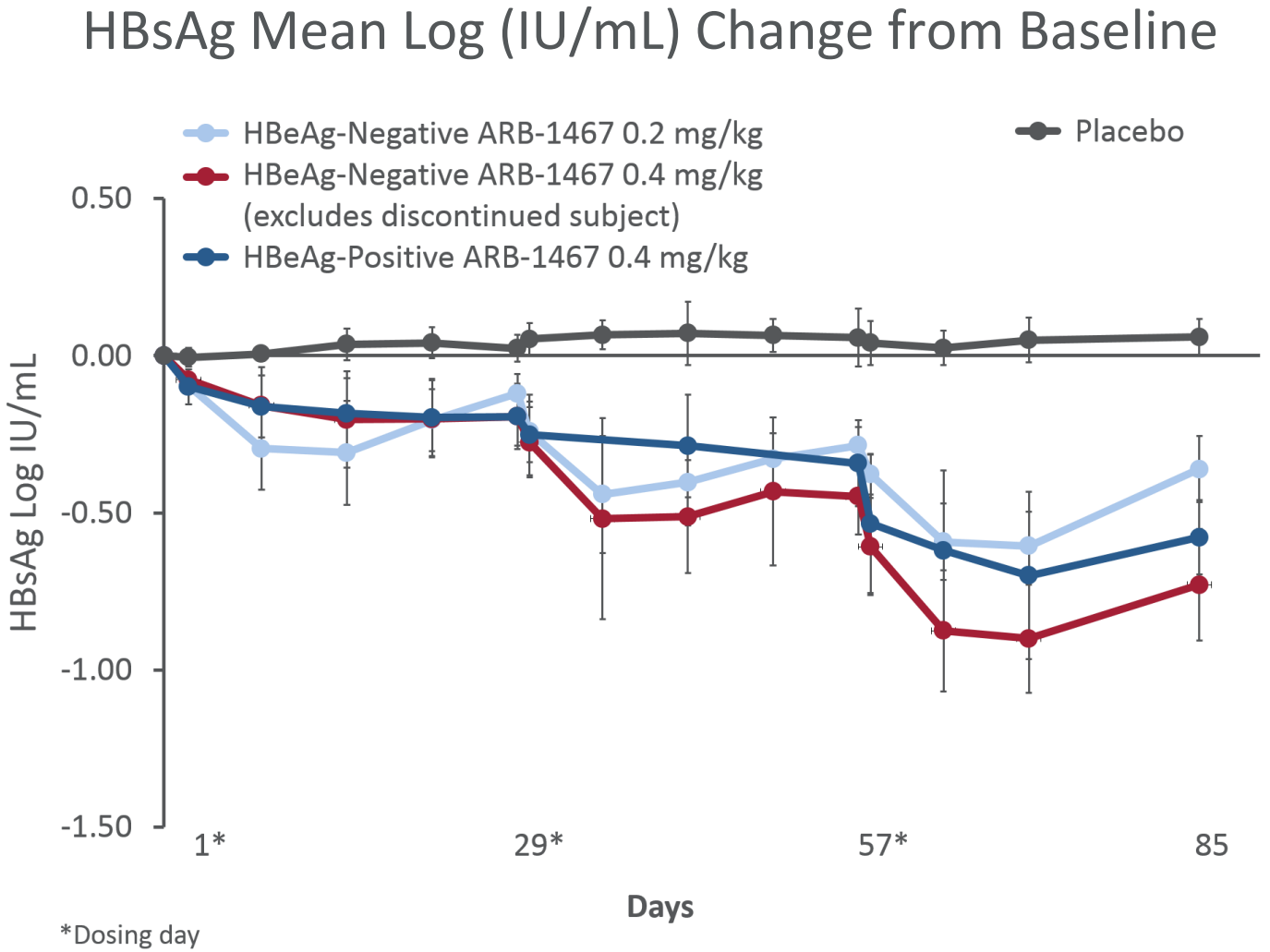
Reductions of ≥ 1.0 log10 in 5/11 patients (after 3 doses at 0.4 mg/kg)

- 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



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.

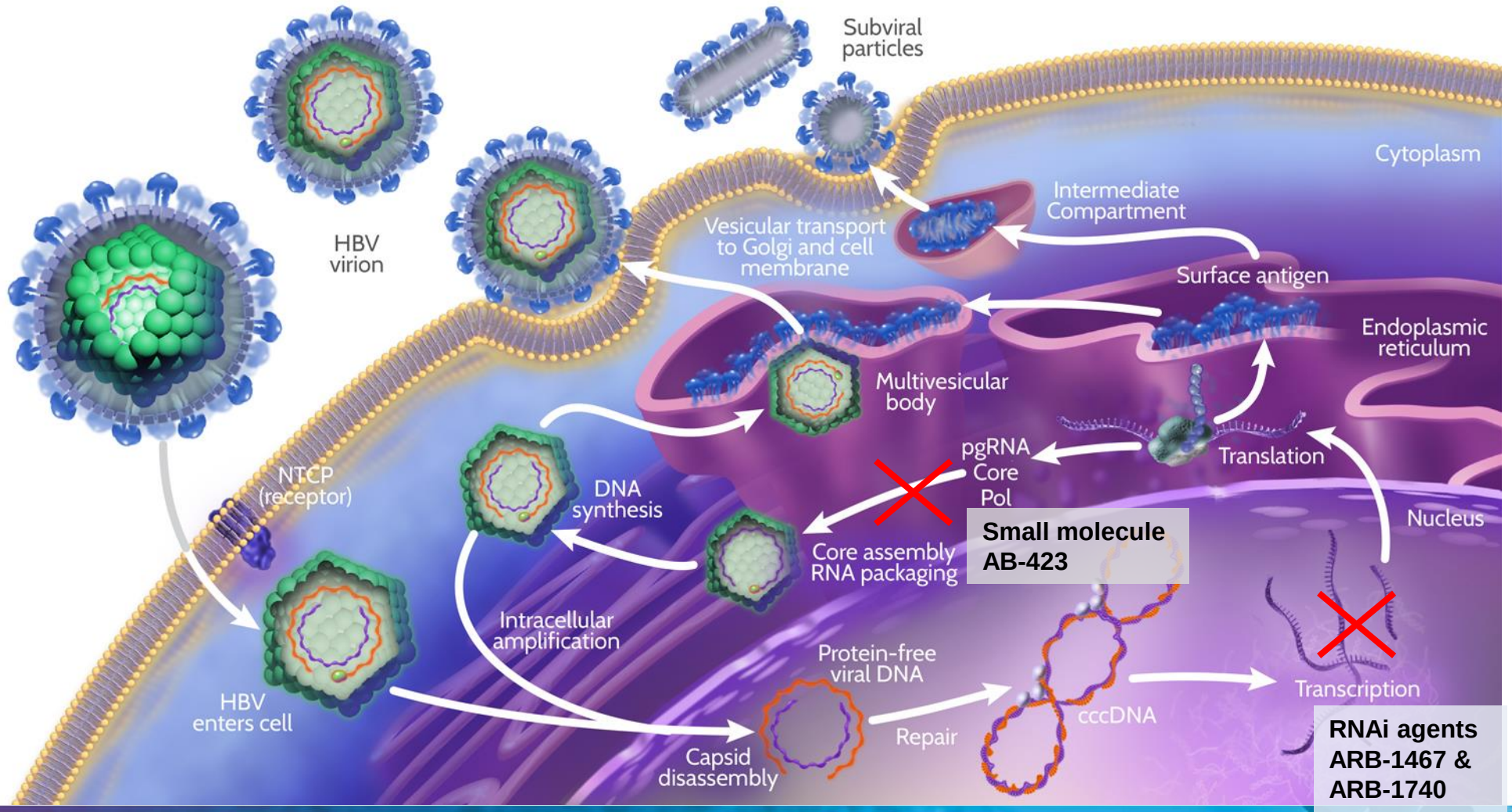
ARB-1467 Next Steps to Advance Development

- 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

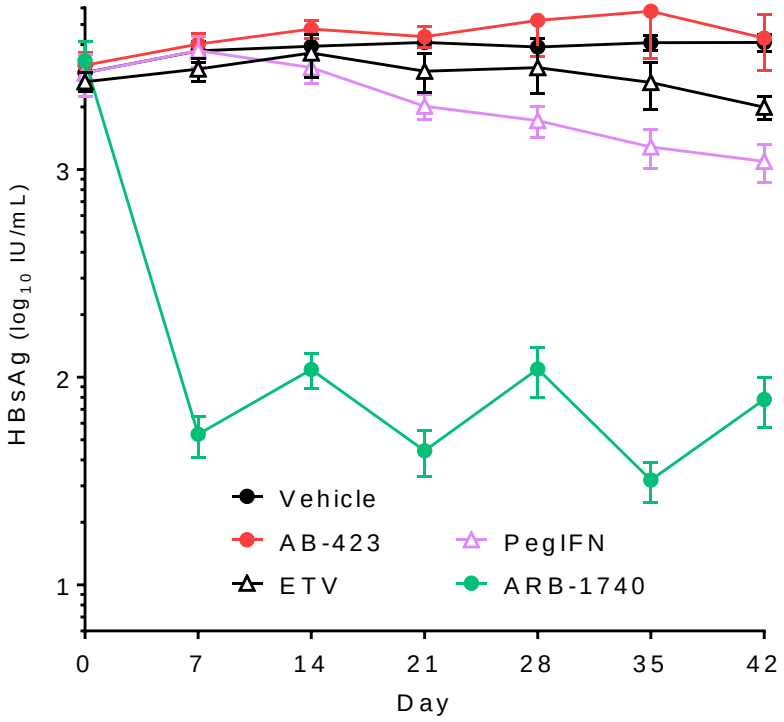
- Approved drug

LNP siRNA + pegIFN

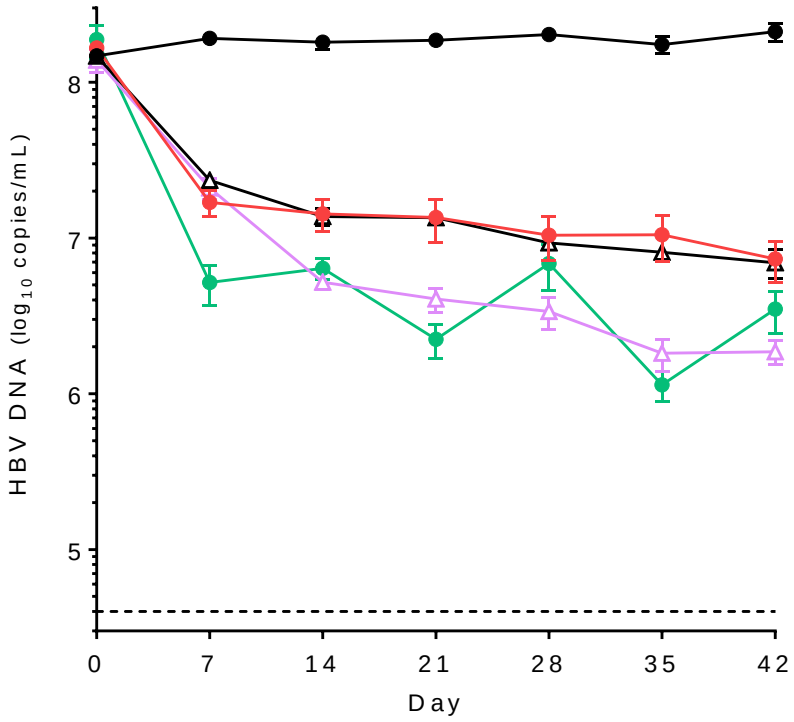
Preclinical study in infected humanized mouse model

- Each agent has stand-alone activity against HBV virus

Serum HBsAg



Serum HBV DNA



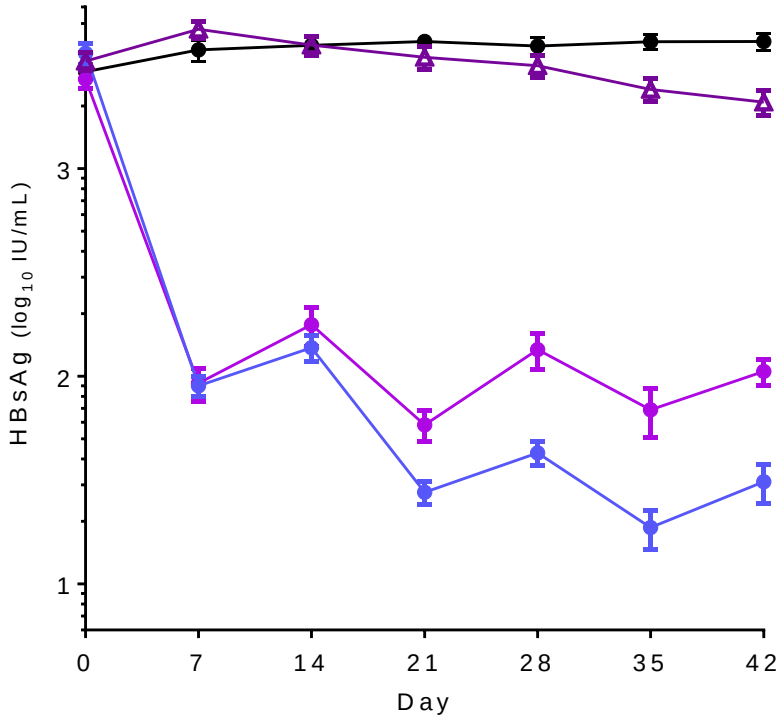
	Treatment for 6 weeks		
	Dosage	Route	Frequency
AB-423	100 mg/kg	PO	BID
ETV	1.2 µg/kg	PO	QD
PegIFN	30 µg/kg	SQ	2×/wk
ARB-1740	3 mg/kg	IV	biweekly

LNP siRNA + pegIFN

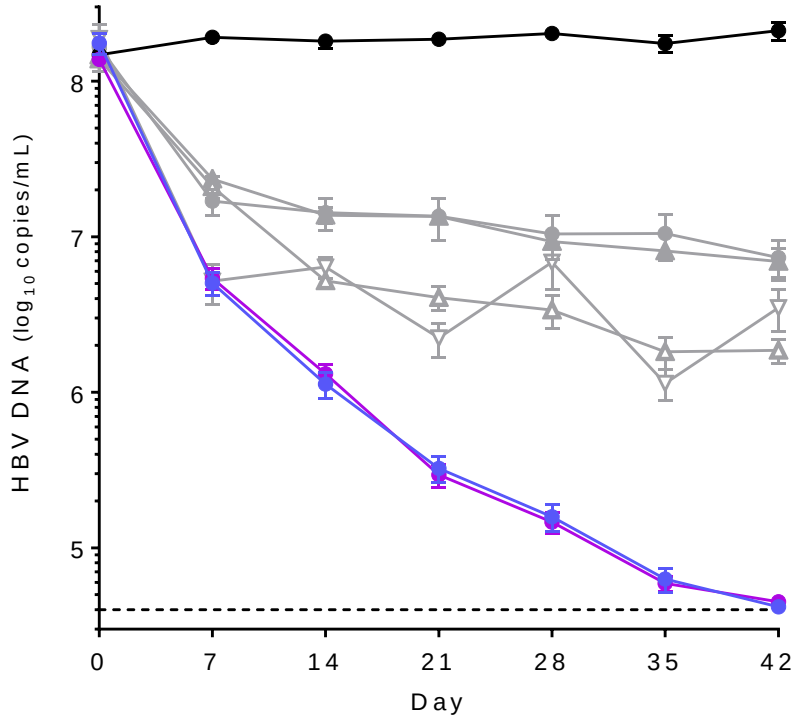
Preclinical study in infected humanized mouse model

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

Serum HBsAg



Serum HBV DNA



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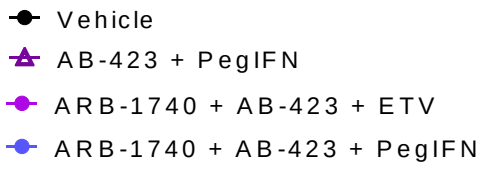
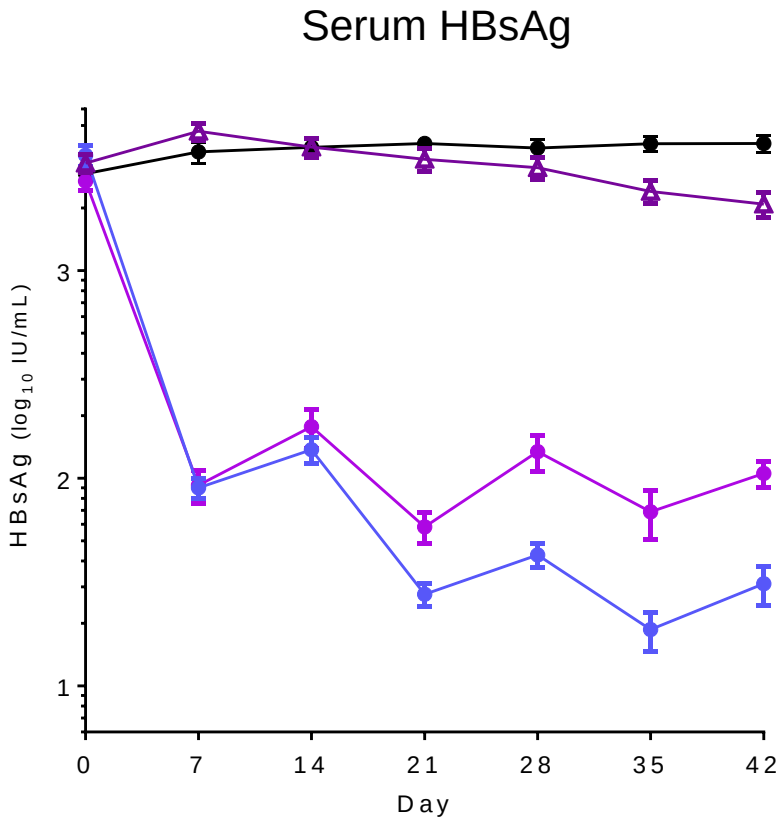
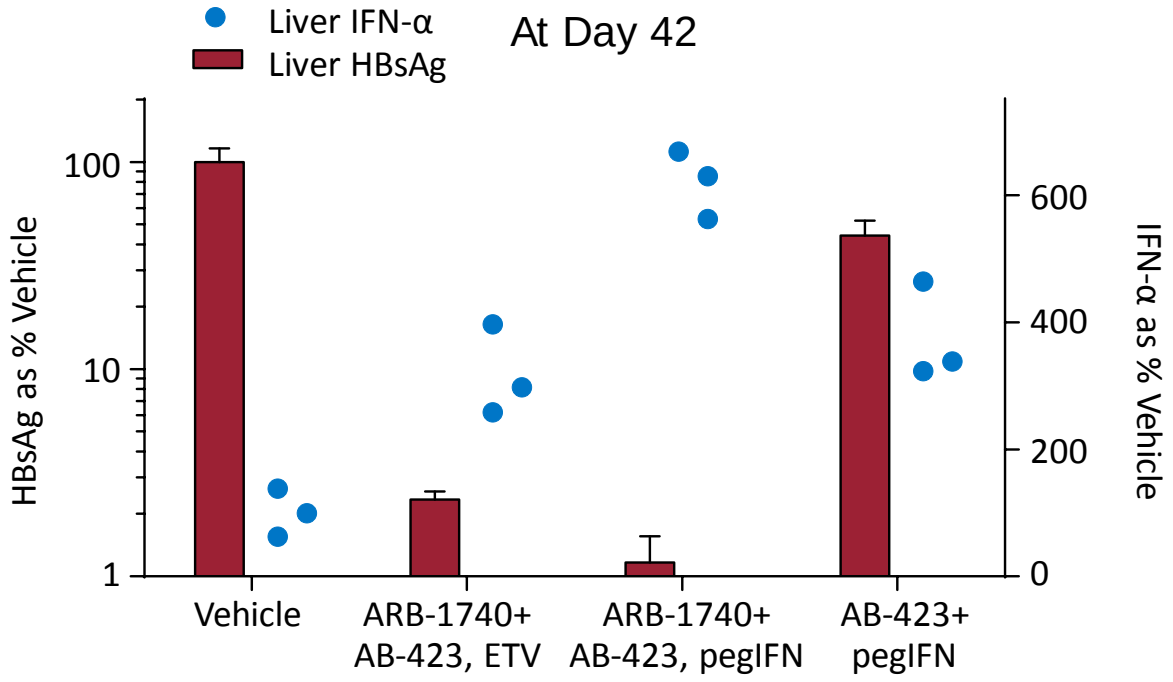


HBsAg Removal Correlated with ↑ Host Immune Response

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

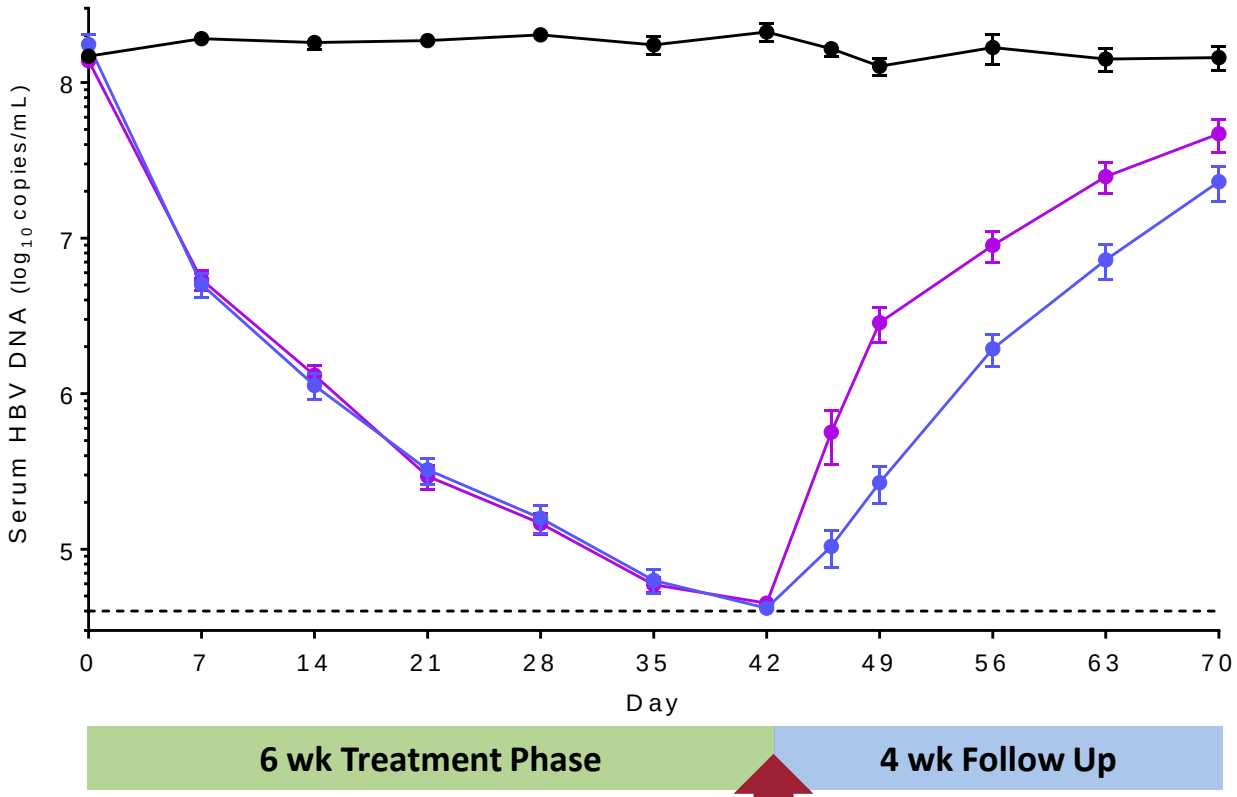


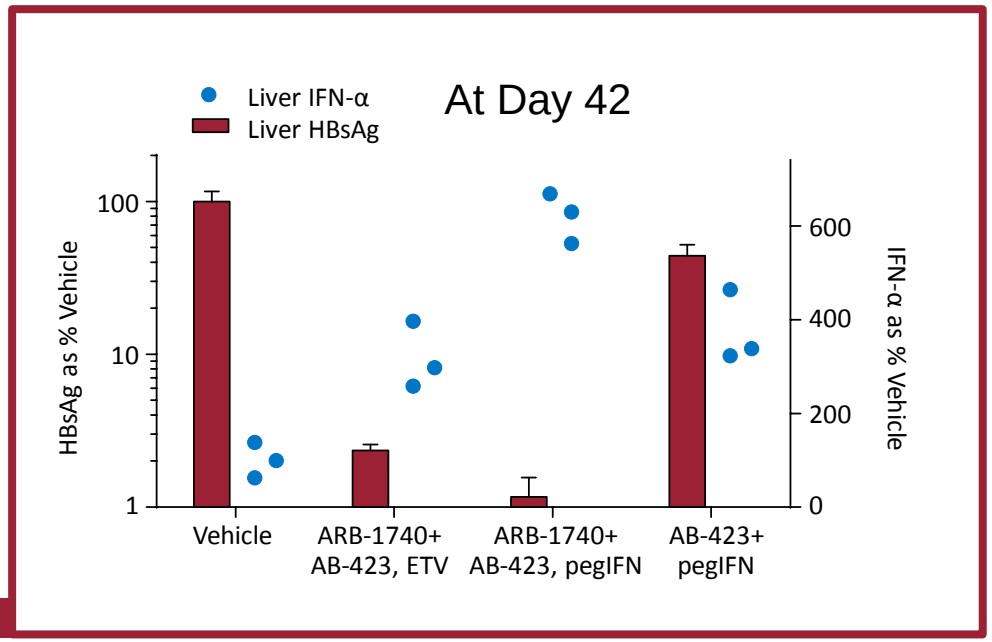


Slower Off-treatment Viral Rebound Correlated with ↑ Host Immune Response

Infected humanized mouse model

Model lacks T and B cells (adaptive immunity)

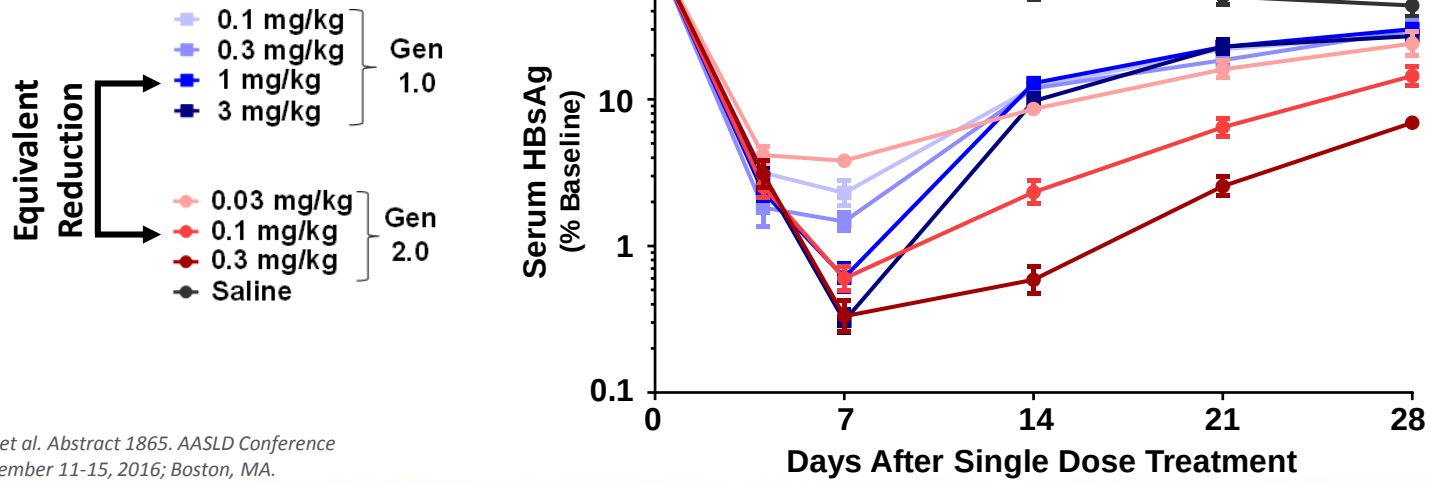




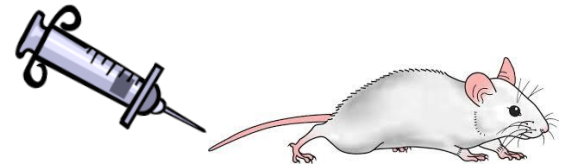
ARB-1467 and ARB-1740

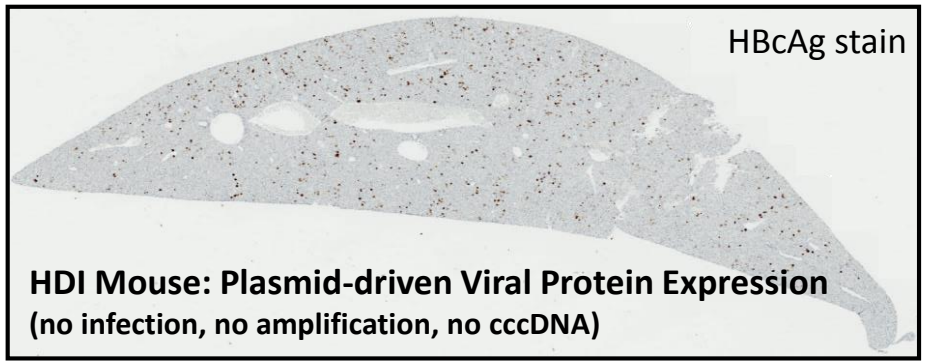
Clinical experience versus preclinical modeling

- **ARB-1467 and ARB-1740 both** have:
  - Unique 3-trigger design targets all HBV transcripts and, in addition to inhibiting viral replication, prevents production of all antigens
  - Employ proprietary LNP delivery technology
- **ARB-1740** Phase II, Cohorts 1 and 2 showed activity, but no significant potency advantage over ARB-1467



Thi, et al. Abstract 1865. AASLD Conference November 11-15, 2016; Boston, MA.





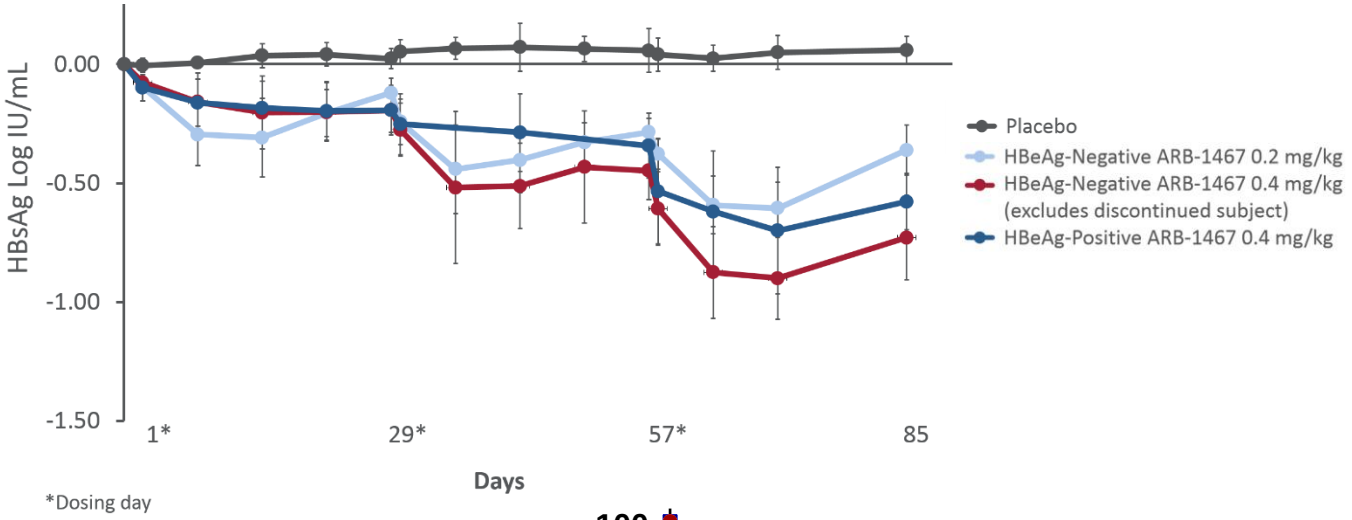
HDI Mouse: Plasmid-driven Viral Protein Expression
(no infection, no amplification, no cccDNA)

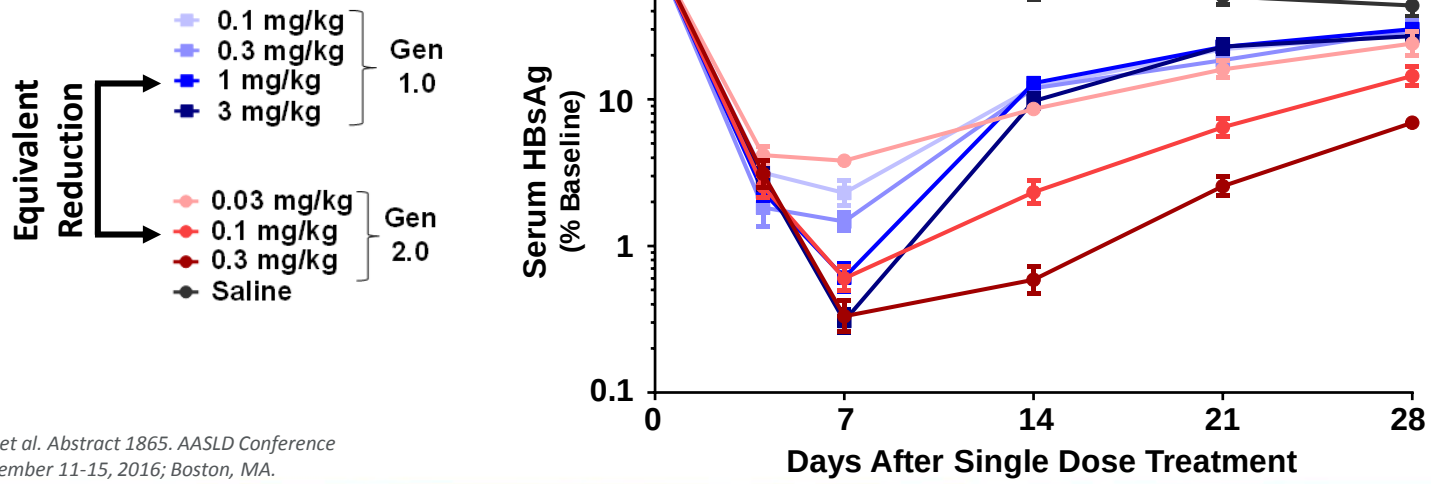
Immunocompromised mouse given hydrodynamic (rapid large volume) injection of plasmid encoding HBV genes

- Simplified model – no cccDNA, no adaptive immune system
- Showed multi-log HBsAg reductions from single dose at dosages used in clinic

ARB-1467 and ARB-1740

Clinical experience versus preclinical modeling





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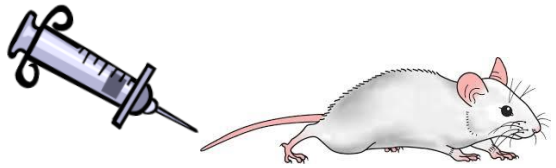

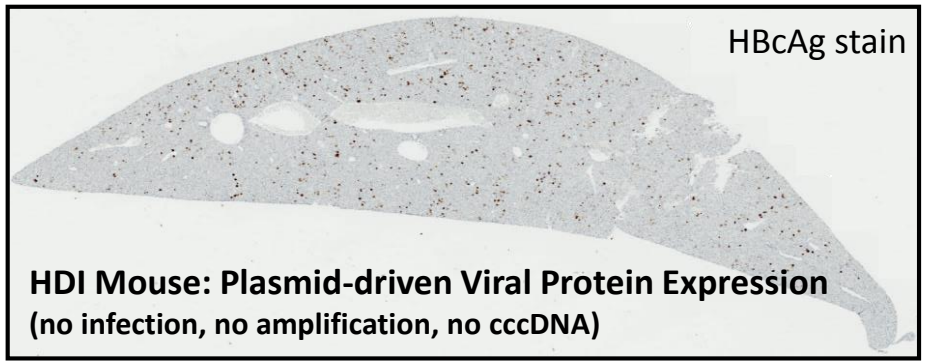

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Clinical Experience
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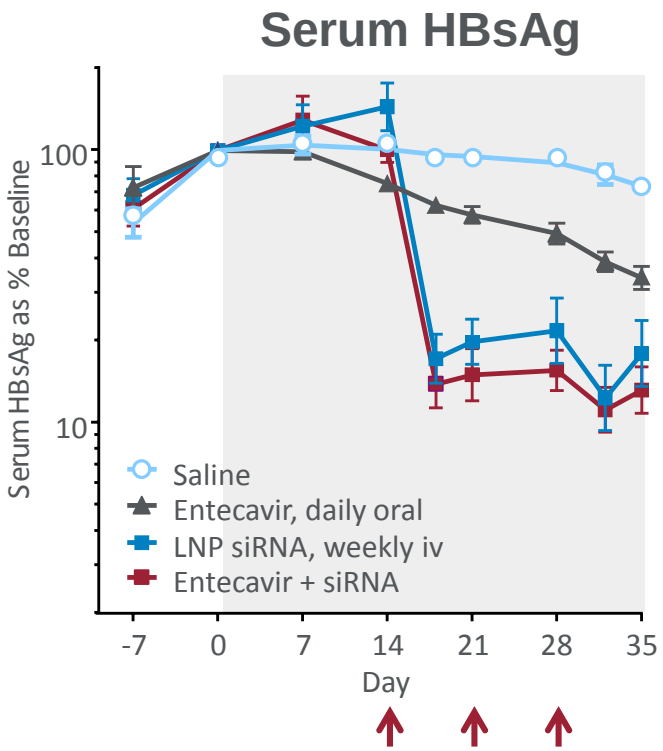
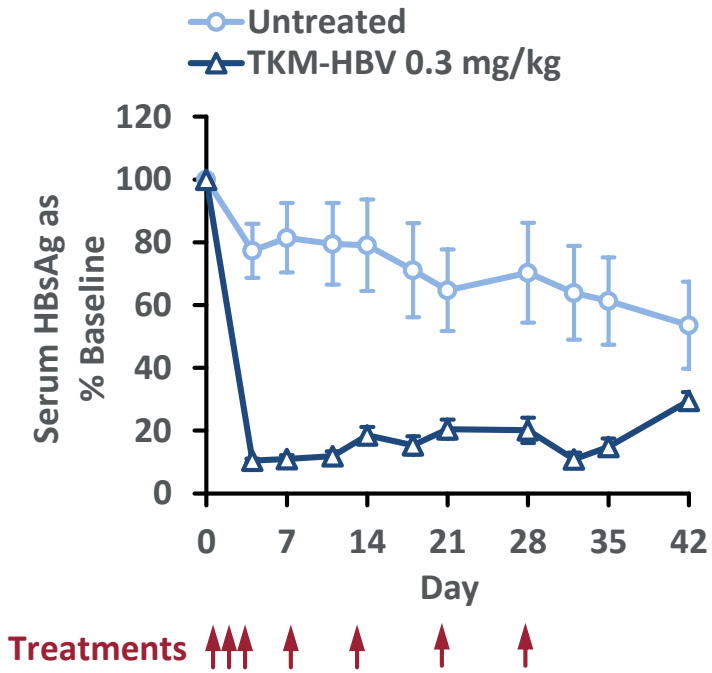
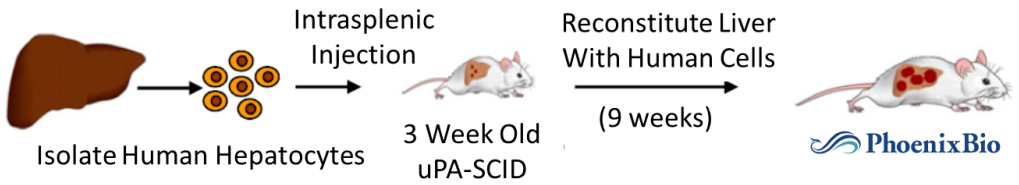
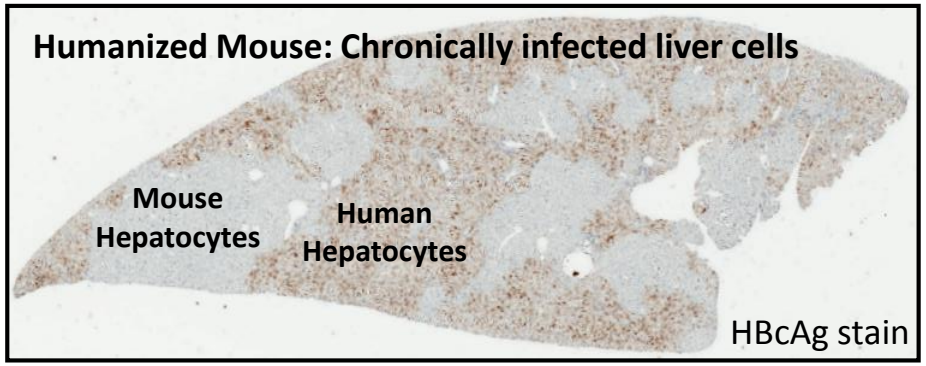








LNP siRNA dose:
1 mg/kg (day 14), 0.5 mg/kg (day 21, 28)
ETV dose: 30 mg/kg/day, PO, Days 0-35

Immunocompromised mouse carrying humanized liver infected with HBV genotype C

- More complex model – cccDNA present in infected human cells, no adaptive immunity
- Requires higher doses than HDI mouse
- No evidence of additivity from repeat doses at greater frequency than tested in clinic

MacLachlan, I. 10th Annual Meeting of the Oligonucleotide Therapeutics Society. October 15, 2014; San Diego, CA.

Preclinical Models Mimicking Chronic Human HBV

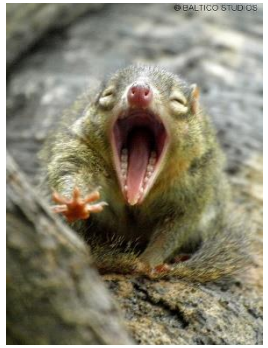
Each have their advantages and drawbacks

- 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	✗	✓	✗
Viral Replication	✗	✓	✗
HBV DNA	✓	✓	✓
HBsAg	✓	✓	✓
HBeAg	✓	✓	✓
HBcAg	✓	✓	✓
cccDNA	✗	✓	✗
Adaptive Immunity	✗	✗	✓

Woodchuck

Chimp

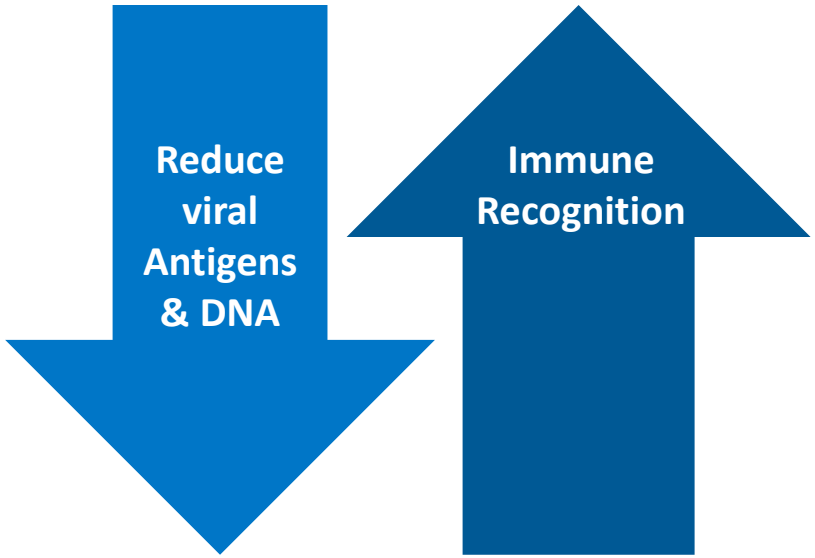


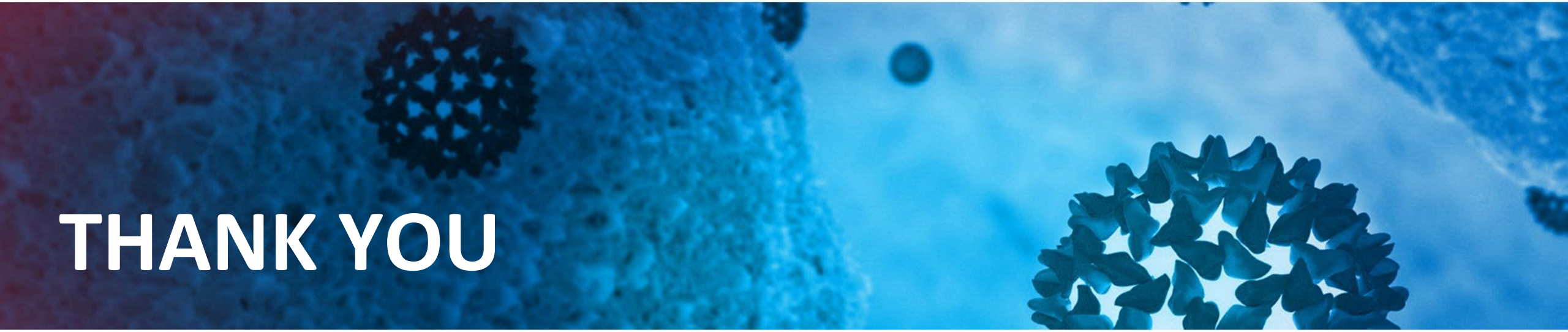
Tree shrew

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