Hepatitis B in focus: new biology, new targets and real hope for finite therapy

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Disclosures

- I am an employee and shareholder in Arrowhead Pharmaceuticals, Inc.

- Thanks to Nid Afdal, MD from Springbank Pharmaceuticals for providing slides for this presentation.

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Agenda

- Brief Introduction and the basis for new therapeutic approaches
- Three examples of novel drug classes
- Conclusions

Worldwide prevalence of chronic HBV infection

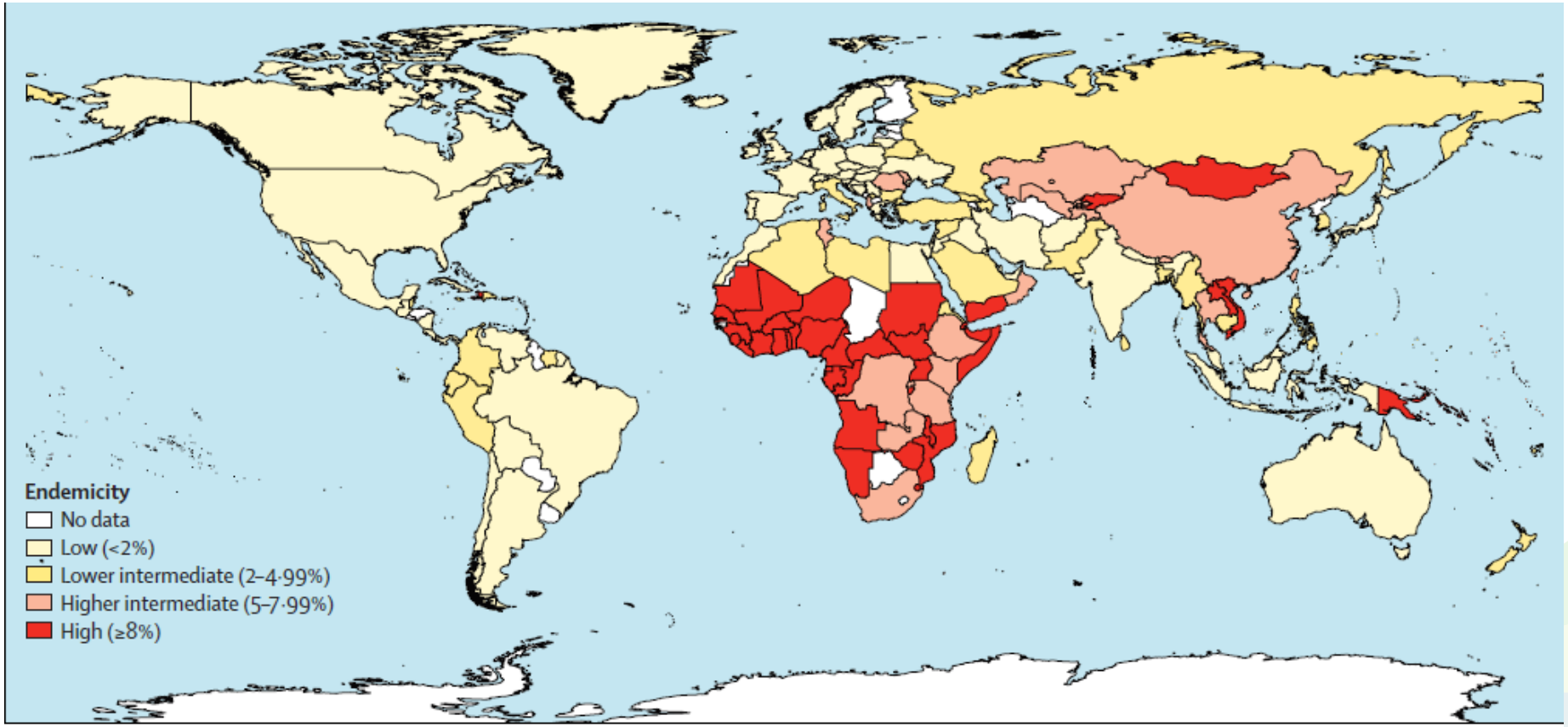

Figure 2: Global HBsAg endemicity (1957–2013)

Schweitzer et al. (2015), Lancet 386:1546-55

Globally an estimated 250-400 million people are chronically HBV infected

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HBV – The Good and the Bad

- Vaccination and peri-natal intervention have been widely exploited and have reduced the incidence of new chronically infected patients. Eradicating new infections is a feasible public health goal
- Spontaneous or drug-induced HBsAg sero-clearance (functional cure) is associated with low risk of hepatic failure or HCC
- Lifelong effective NUC therapy is also associated with reduced risk of hepatic failure or HCC

- **However** – functional cure is rare today (spontaneously ~0.5%/yr) and must occur before age 50 to reduce risk
- NUC treatment rates are low ---- adherence is a major issue
- Close to 1 million annually are dying due to hepatic failure or HCC

HBV Has Been Stuck in a Therapeutic Rut

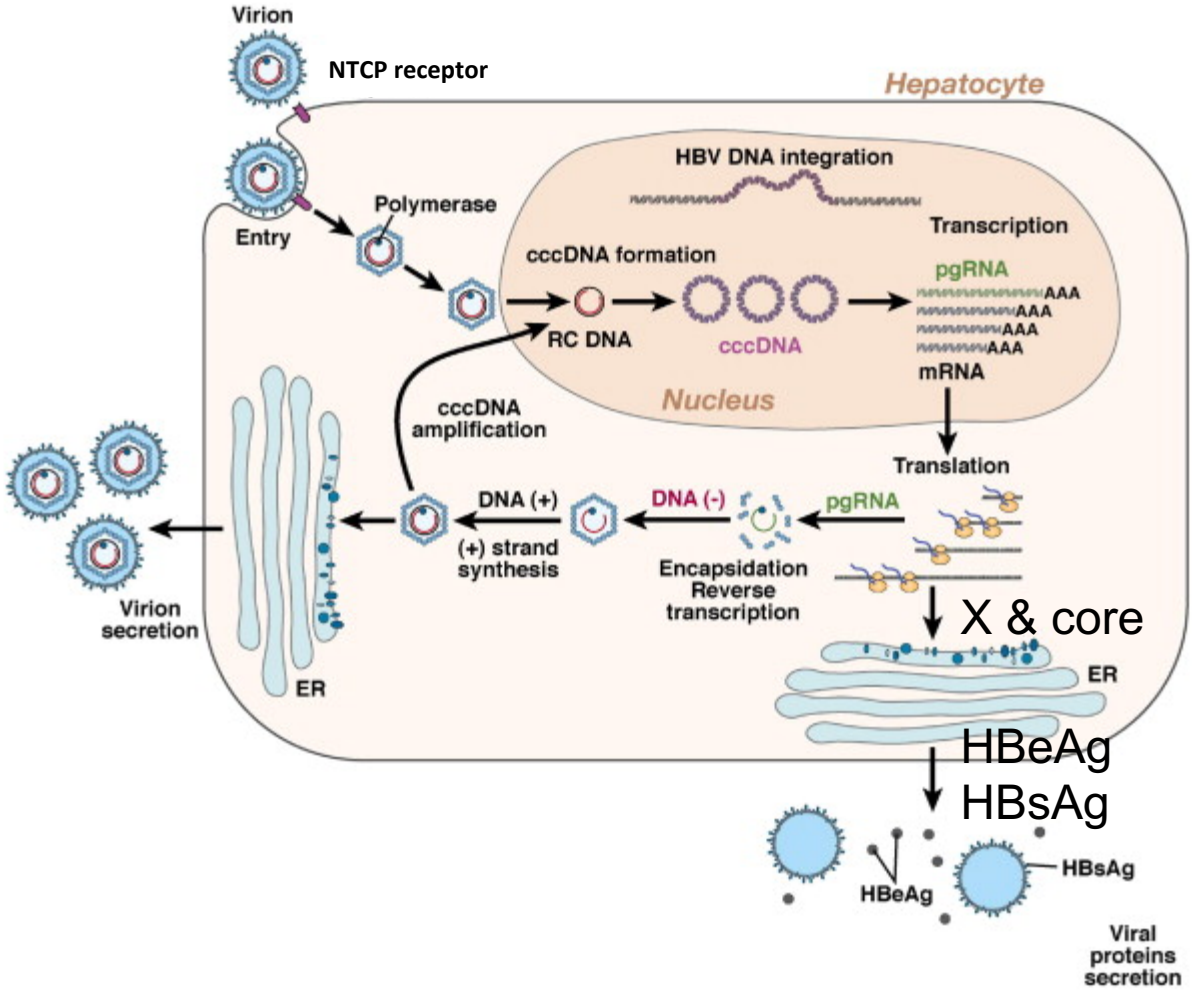
- Interferon alpha cure rates highly dependent on genotype
  - Genotype A in early trials had "respectable" HBsAg clearance rates (~25%) in early trials
  - With those patients rare today, interferon in large Western trials yields single digit HBsAg clearance rates – with unacceptable tolerability
  - Various trials attempting combination therapy with nucleos(t)ide inhibitors (NUCs) unimpressive
- Early generation NUCs were prone to resistance and are not recommended
- Entecavir, tenofovir and now TAF are well tolerated and not prone to resistance
  - Persistent viremia after several years of therapy most likely non-adherence
  - Controlled trials of discontinuation after years of therapy show some potential, although some fatalities and many relapses have been noted
- With the recent success in HCV, there has been a flurry of activity in HBV and drugs against a diverse set of HBV targets have entered development

HBV is Now Exploding with Innovation

The Goal is Finite Therapy

- US FDA, EMA, AASLD and EASL have agreed the general target for approving new agents
  - SVR24 which will be DNA negativity ***and*** HBsAg negativity 24 weeks after cessation of all anti-virals agreed as the primary approval endpoint
- They also agree that combination therapy is likely required as with HIV and HCV
- Some believe that the combinations will include DAAs ***and*** immune boosting agents in at least some patients
- There will be a high safety hurdle because of the efficacy and safety/tolerability of long-term NUCs

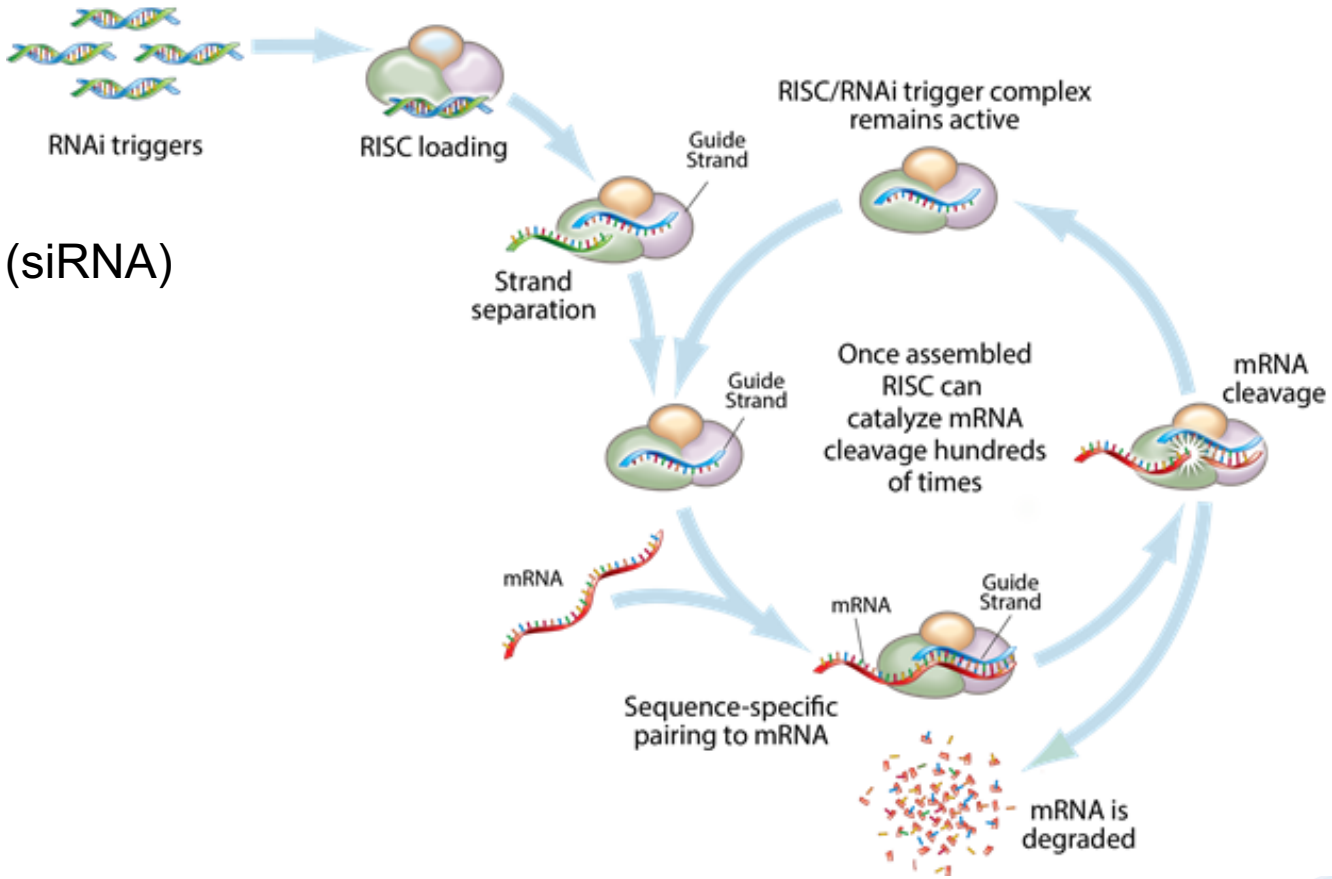
A Very Simplified View of the HBV Lifecycle



Hypothesis: revive host adaptive immune response by reducing HBV proteinemia

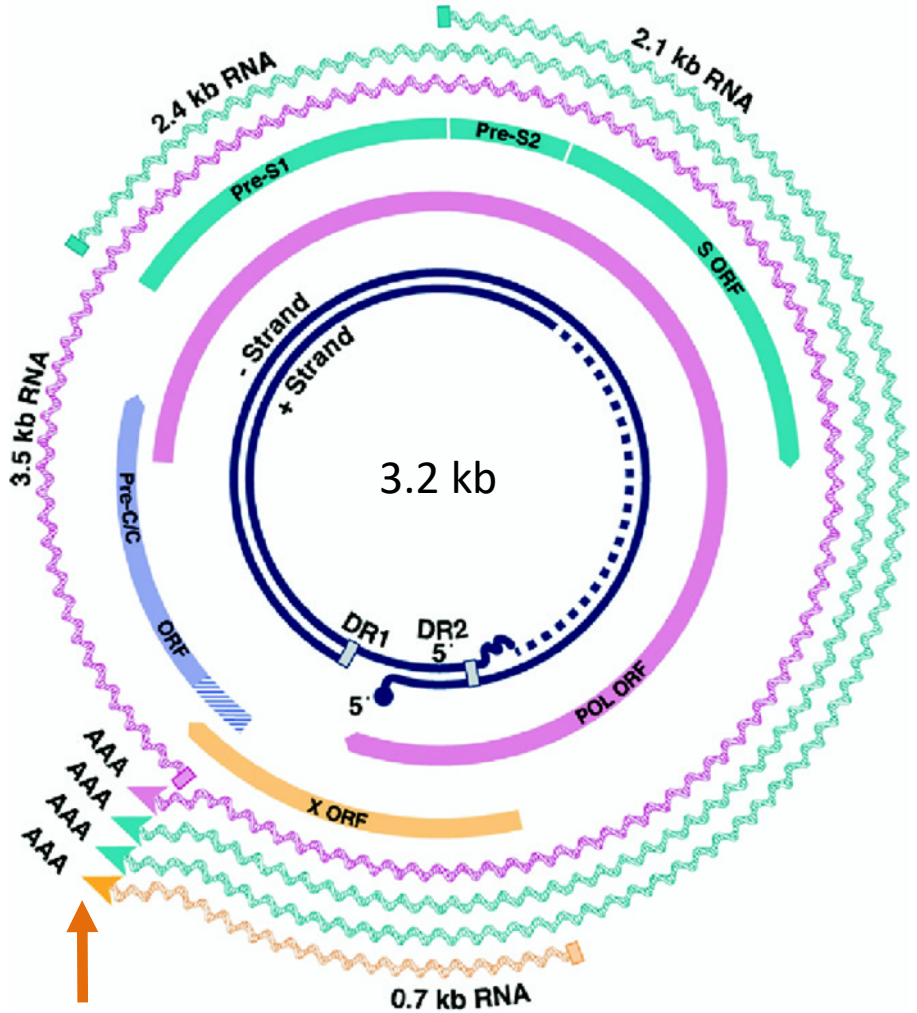
Three Interesting New Classes

RNAi: Target the Gene Silence the Disease



Therapeutic gene silencing with **RNA interference** is highly precise and efficient

Organization of the HBV genome makes it ideal for RNAi



Same polyadenylation signal for all mRNAs

- **5 viral mRNAs**
  - 3.5 kb pre-genomic RNA
  - 3.5 kb pre-core mRNA
  - 2.4 kb pre-S1 mRNA
  - 2.1 kb pre-S2/S mRNA
  - 0.7 kb X mRNA
- **7 major proteins**
  - Polymerase (with reverse transcriptase function)
  - Core (HBcAg), forms capsid
  - e antigen (HBeAg), also called pre-core, a secreted protein
  - Large, medium and small surface proteins (HBsAg), form envelope
  - X protein (Transactivator)

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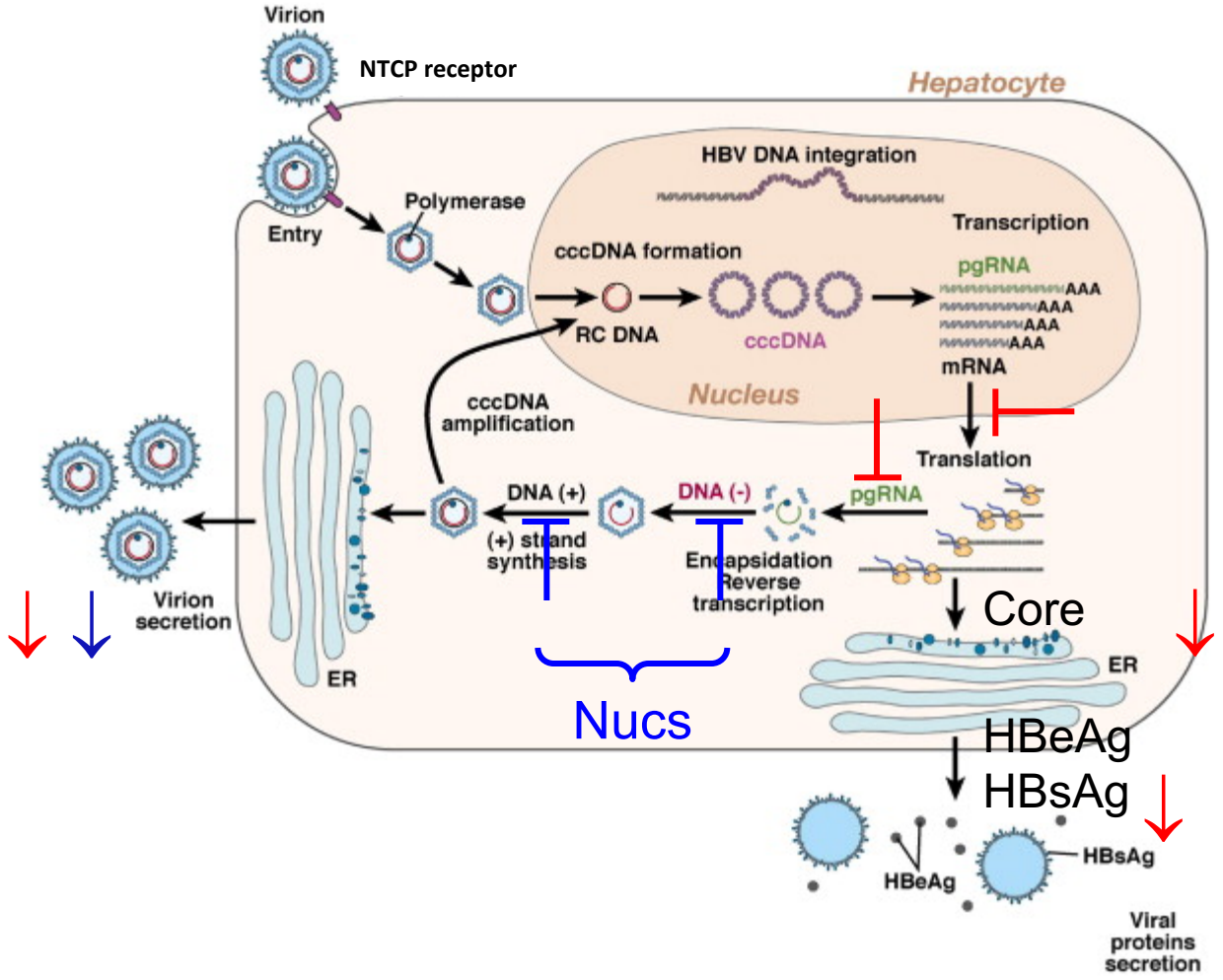
Ghany & Liang (2007), *Gastroenterology* **132**: 1574-1585

RNAi therapeutics to reduce HBV viral RNAs

Differentiation from nucleos(t)ide reverse transcriptase inhibitors



siRNA

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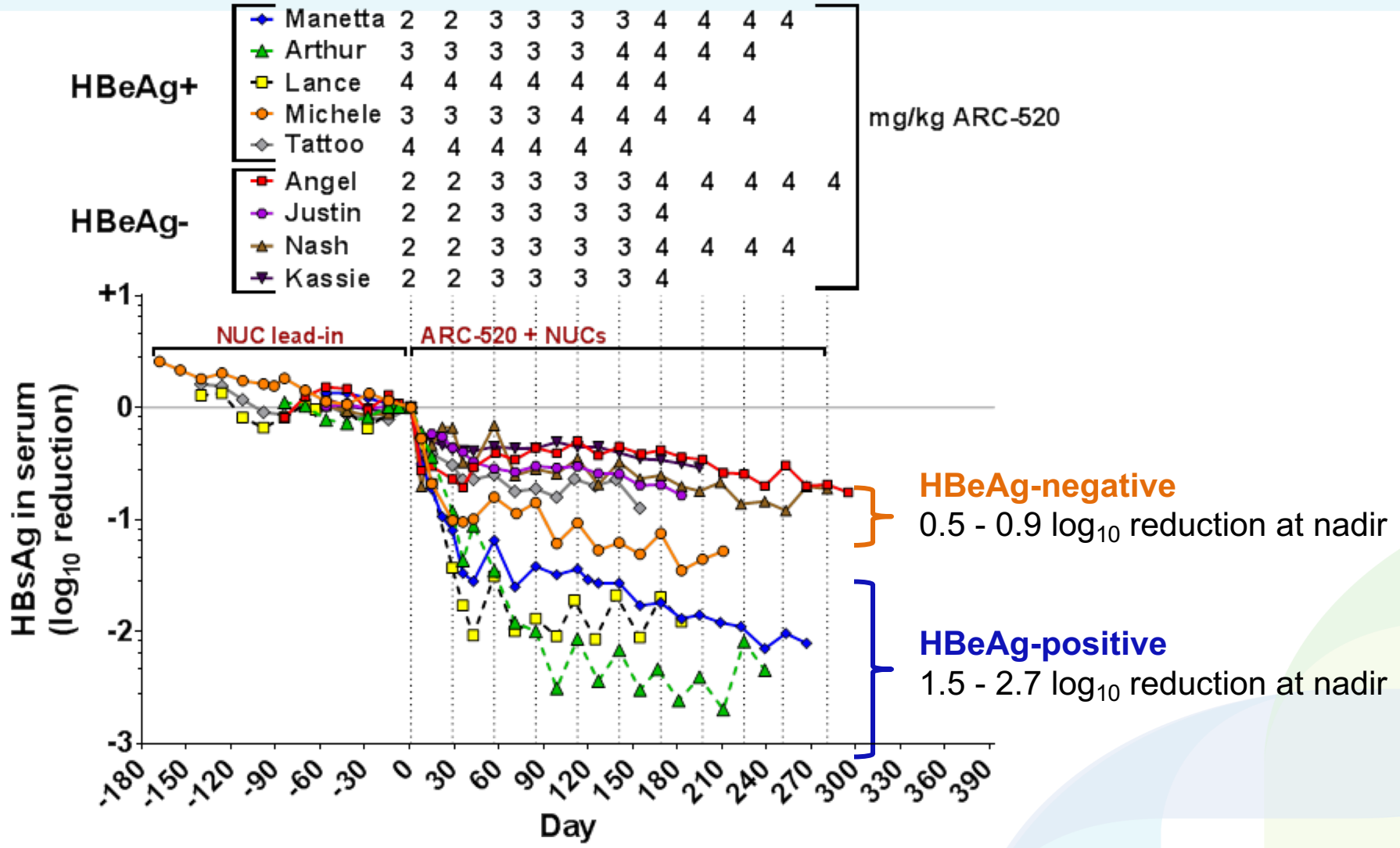
Differences in degree of HBsAg reduction correlated with HBeAg status in chimpanzees



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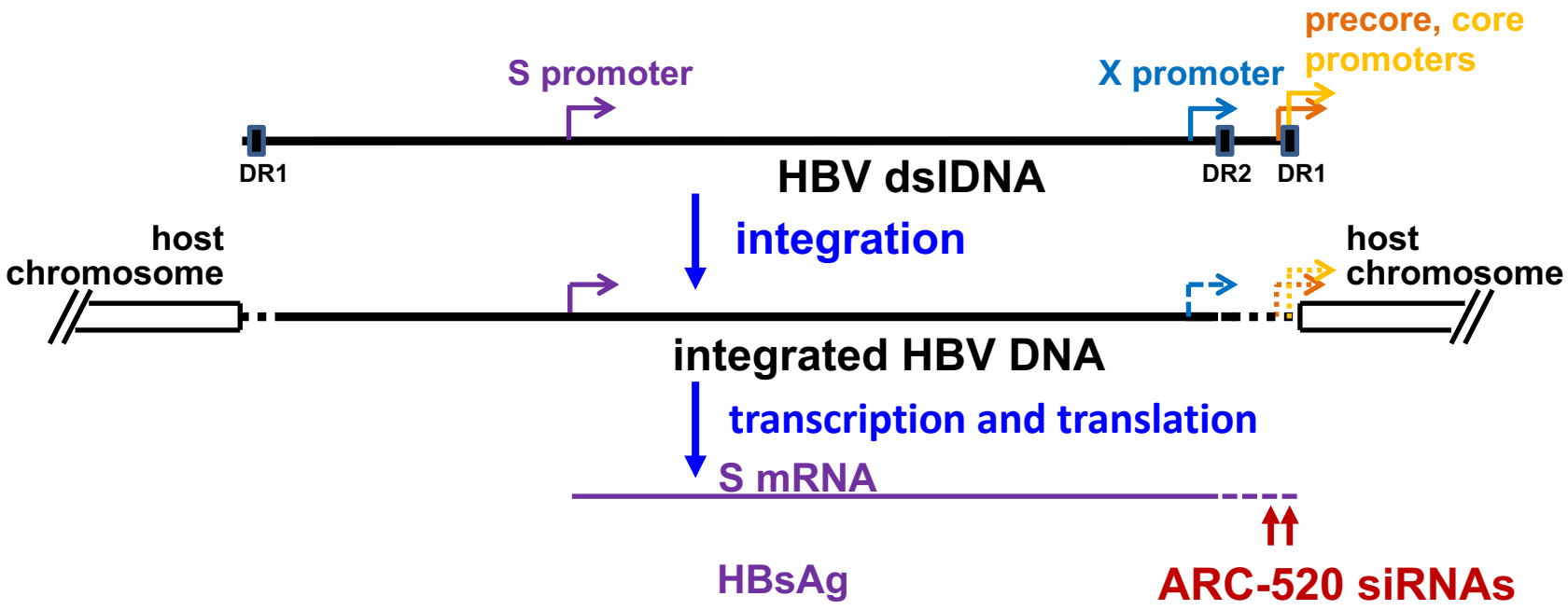
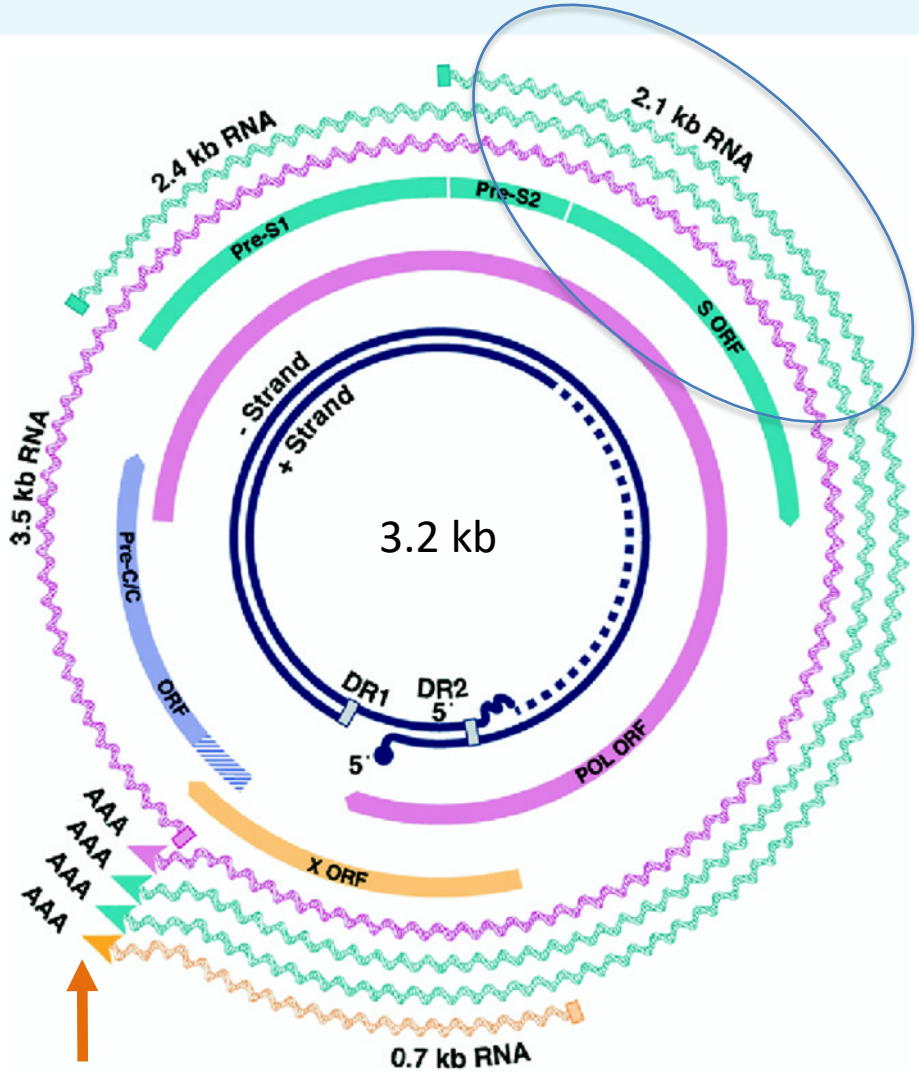
HBV Integration Into the Host Genome Becomes Crucial



1. HBV DNA integrates into host chromosome, during which regions between DR2 and DR1 can be randomly deleted (not new!)

2. Significant HBsAg mRNA can be produced from integrated HBV DNA
   - These S transcripts contain complete HBsAg CDS
   - Expected loss of ARC-520 target sites in many

Addressing integration-derived HBV RNA requires a new target



Same polyadenylation signal for all mRNAs

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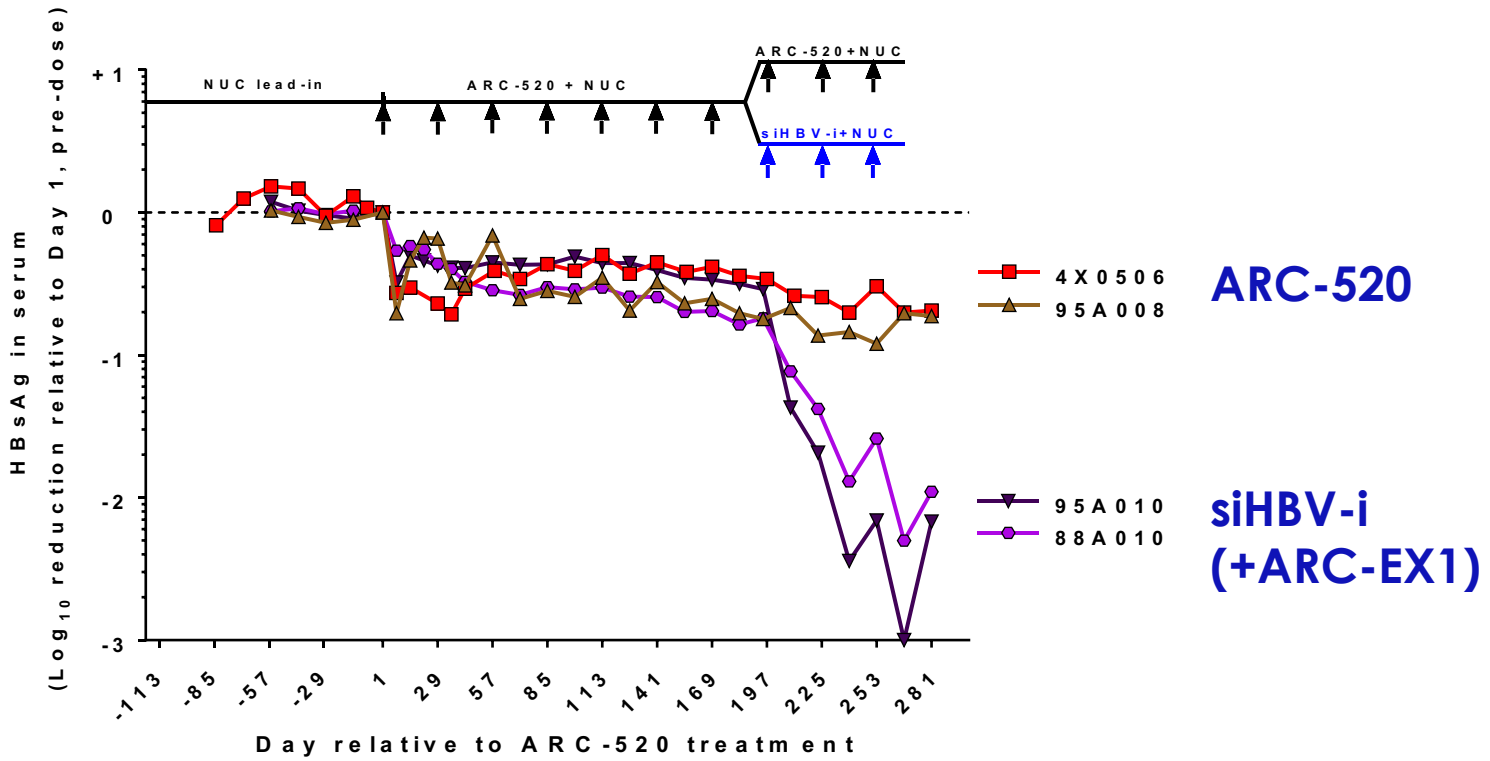
Ghany & Liang (2007), *Gastroenterology* **132**: 1574-1585

siRNA designed to target RNA derived from HBV integration products in HBeAg- chimps increases HBsAg reduction



- siHBV-i targets HBV RNA even if expressed from integrated HBV DNA
- siHBV-i gave deep reductions in HBsAg in HBeAg- chimps, similar to those observed using ARC-520 in HBeAg+ chimps

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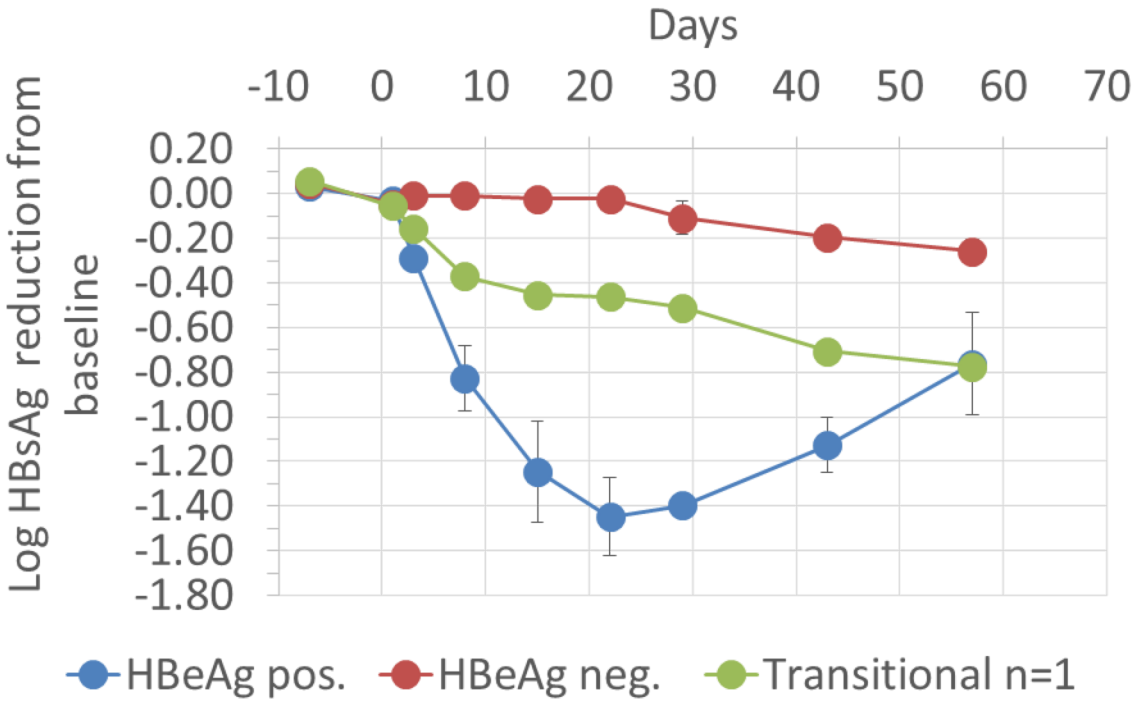
ARC-520 in NUC-naïve chronic HBV patients:
Human HBsAg data reflects chimp data



4 mg/kg ARC-520: NUC-naïve chronic HBV patients

- High level knockdown of HBsAg in HBeAg positive patients
- HBeAg negative patients respond less well
- HBeAg transitional patient is intermediate

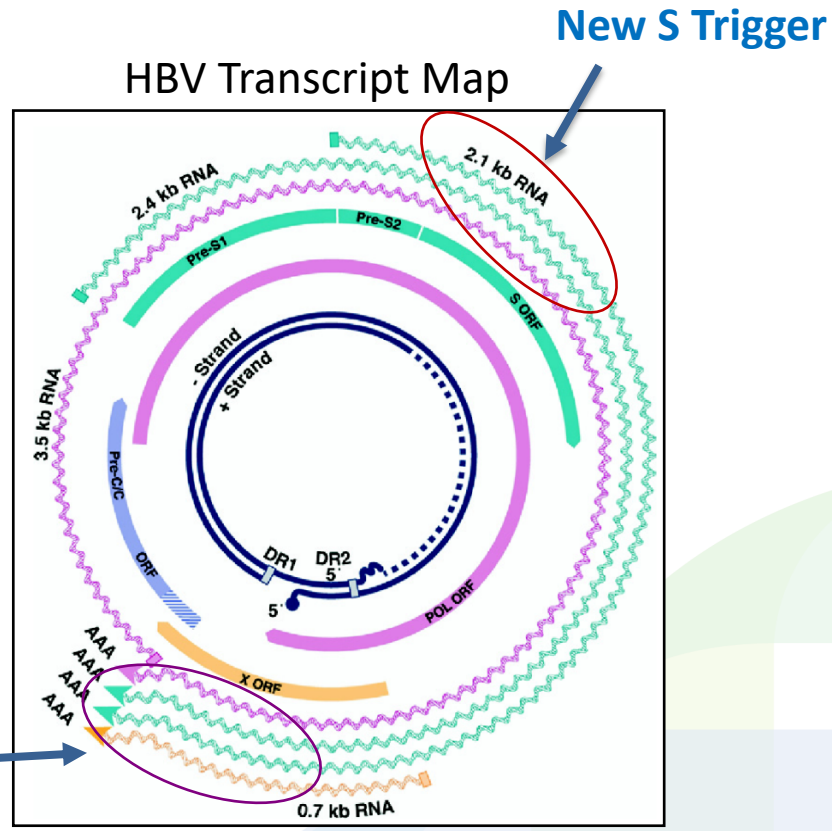
- As in chimps, HBeAg negative patients likely produce significant amounts of HBsAg from integrated DNA not targeted by ARC-520.

ARO-HBV: Key Design Elements

- Subcutaneous dosing, monthly or less frequent
- No need for active endosomal escape agent
- **Addresses full HBV transcriptome**
  - **Works for cccDNA *and* integrated-derived transcripts**
- Multiple triggers to avoid resistance development
- Powerful HBsAg reduction
- Wide therapeutic index
- Efficacy and safety in HBV patients

Importance of integrated HBV DNA as S mRNA source has changed RNAi strategy

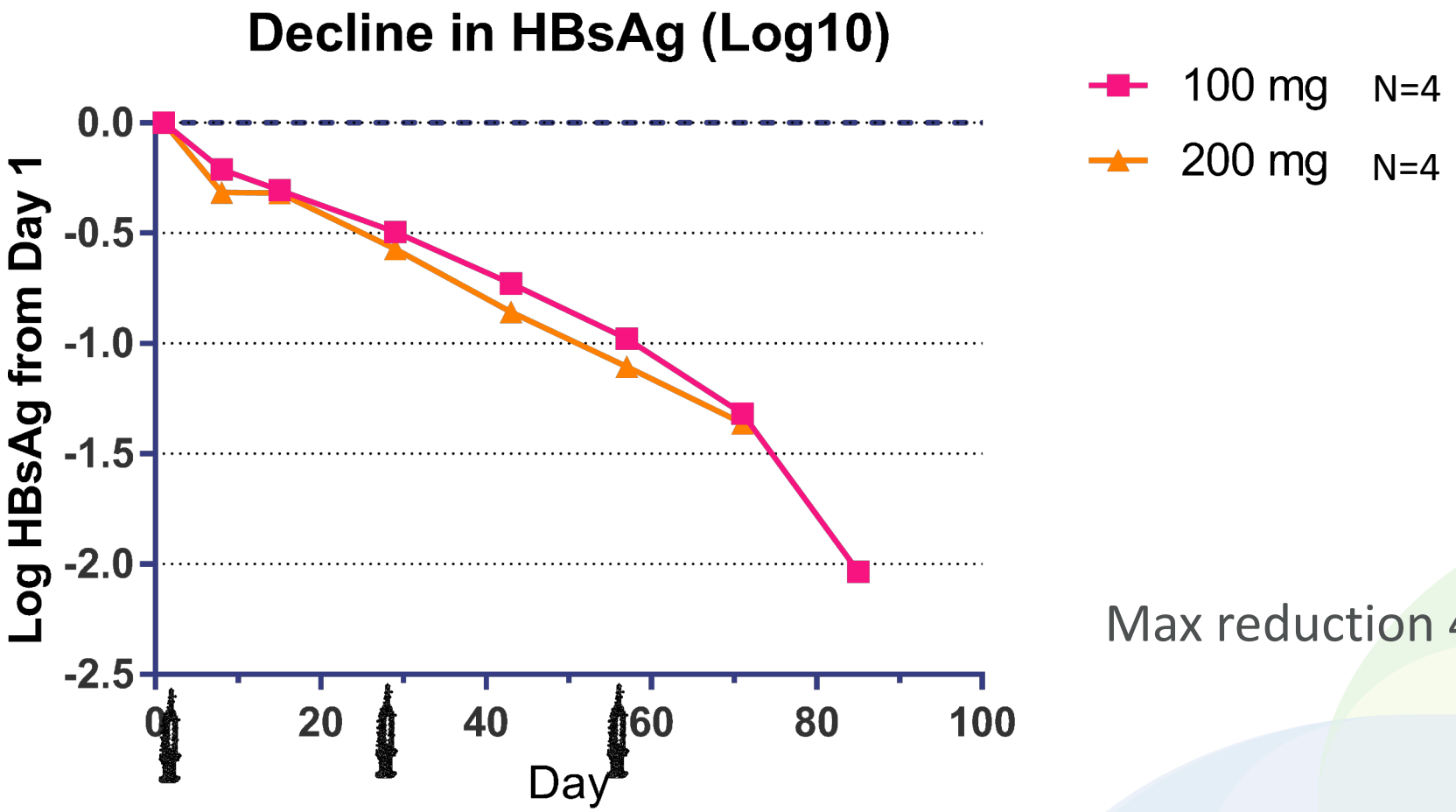
- Single siRNA can reduce all mRNA from cccDNA but can miss integrated HBV-derived mRNA
- Combination of X and S triggers → ARO-HBV
  - Greater genome coverage (99.6% full match of 17mer in ~7000 HBV genomes)
  - Reduce chance of resistance



Ghany & Liang (2007), *Gastroenterology* **132**: 1574-1585

HBsAg Reduction with ARO-HBV After 3 monthly Doses

Includes cohorts with complete data through 14 days after 3rd dose



Max reduction 4 logs

CHB patient AE Table

AEs in >1 subject (data cut 8/24/2018)

AROHBV1001 HBV Patients	Cohort 2b, 100mg X3 Q28 days	Cohort 3b, 200mg X3 Q28 days	Cohort 4b, 300mg X3 Q28 days	Cohort 5b, 400mg X3 Q28 days	Cohort 6, 100mg X3, Q2 wk	Cohort 7, 100mg X3 weekly	Cohort 8, e+ 300mg X3 Q28 day	Cohort 9, e+ 300mg X3 Q28 day	Cohort 10, 200mg X3 Q28 day	Cohort 11, 300mg X3 Q28 day	Total AEs
AE Reported Terms	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	Open Label n = 4	
Insect bites ankles, Flea bites on neck	1		1								2
Upper respiratory tract infection, Sore throat, Laryngitis, Dry cough	1		1		3	1			1		7
Erythema around injection sites, Injection site redness, Haematoma at injection site, Injection Site Bruise			1	2		2	1			1	7
Facial acne, acne							2				2
Headache, headache – intermittent			1			2					3
Raised Creatine kinase			1				1				2
TOTALS	**2**	**0**	**5**	**2**	**3**	**5**	**4**	**0**	**1**	**1**	**23**

Interim AROHBV1001 Findings

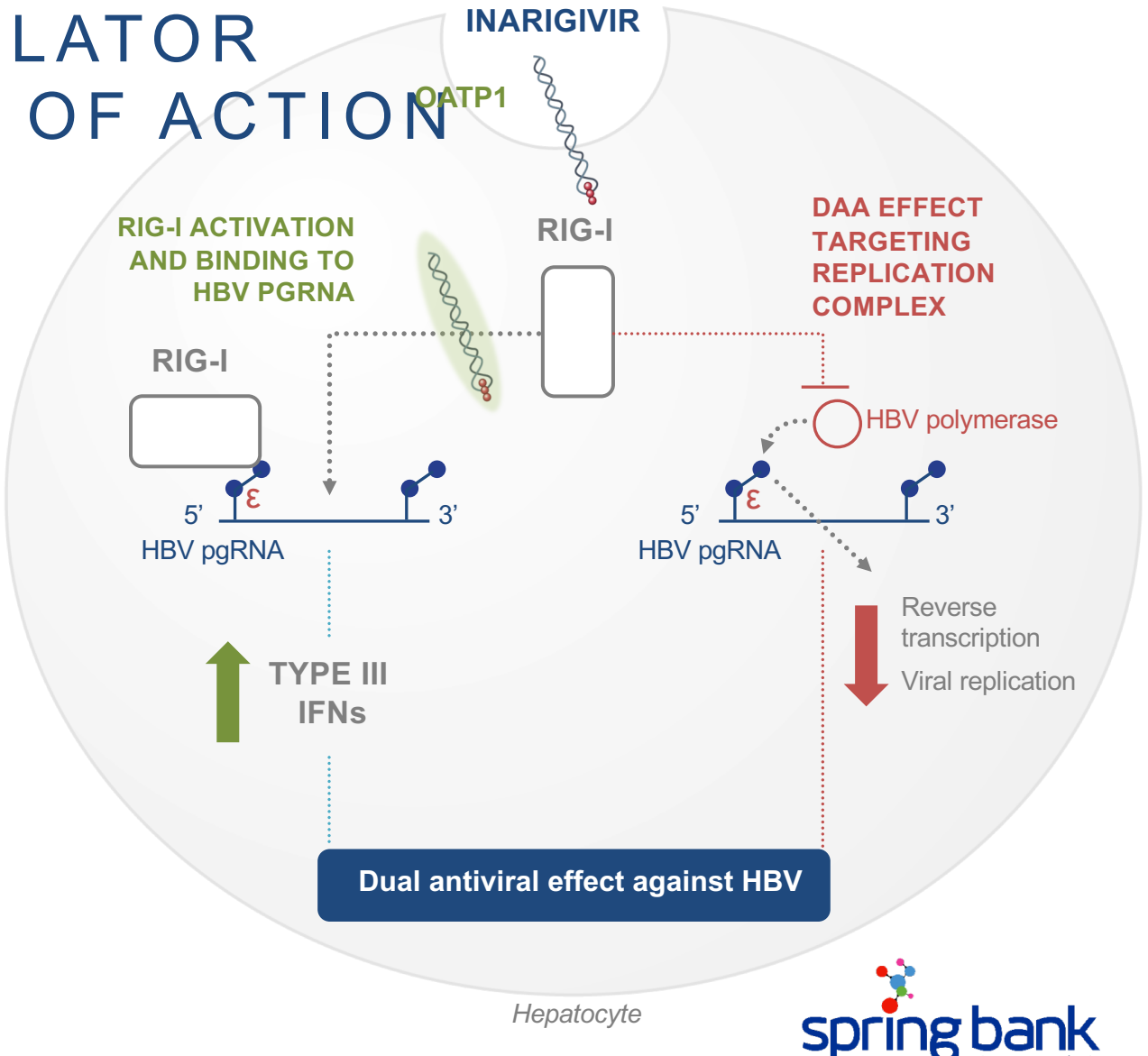
- Mean reduction of HBsAg was 2.0 log10 on day 85 in cohort 2b (100 mg) and 1.4 log10 on day 71 in cohort 3b (200 mg)
  - This may not be the nadir
- Maximum reduction of HBsAg was 4.0 log10
- Activity demonstrated in all patient types (HBeAg pos/neg, NUC naïve/treated)
- Response appeared to be independent of starting HBsAg levels
- ARO-HBV appeared to be generally well-tolerated as of the data cutoff (August 24, 2018)
  - Injection site reactions were observed in approximately 10% of injections

Second Example: Inarigivir

INARIGIVIR: A NOVEL, ORAL SELECTIVE IMMUNOMODULATOR WITH A DUAL MECHANISM OF ACTION

INARIGIVIR is a RIG–I AGONIST which is designed to:

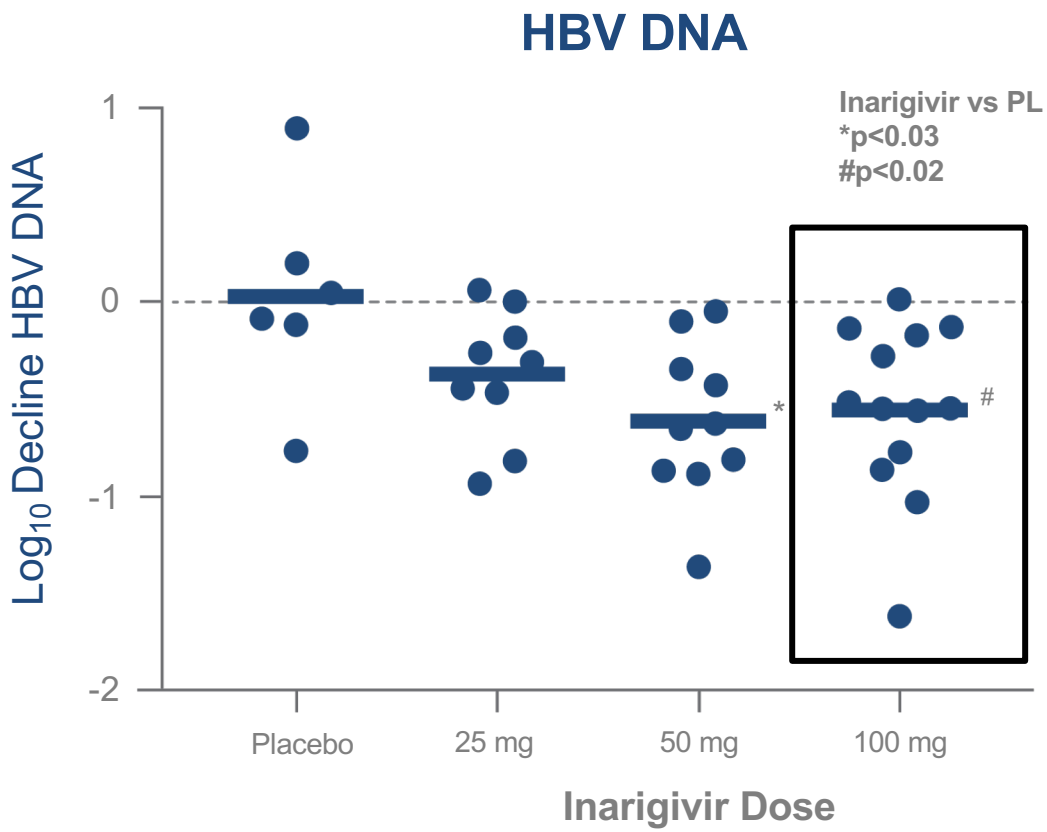
- **Restore hepatic selective innate and adaptive immune response** stimulating the production of type I and III IFNs
- Inhibit the HBV replication complex via a direct acting anti-viral effect
- Result in significant anti-HBV activity with reduction in HBV DNA, HBV RNA, HBsAg and cccDNA

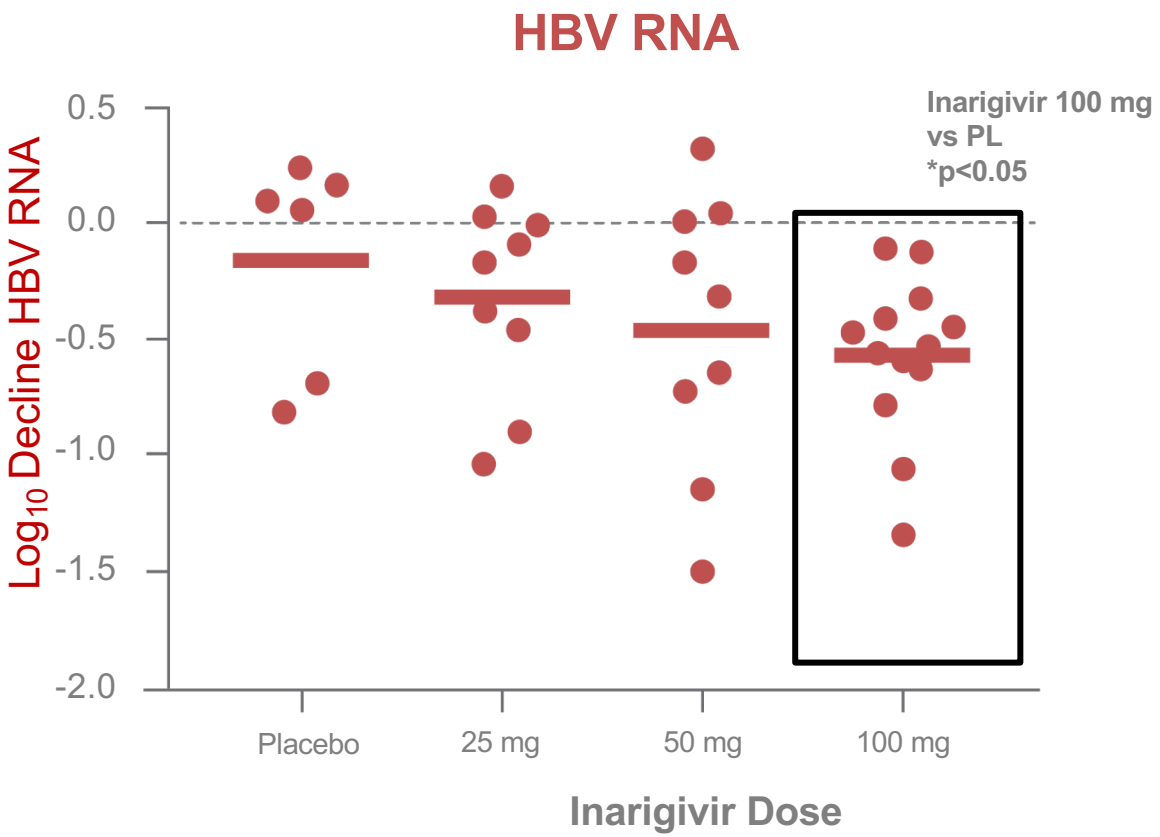


HBV, hepatitis B virus; IFN, interferon; pgRNA, pregenomic RNA; RIG-I, retinoic acid-inducible gene-I.

Sato et al. *Immunity*. 2015;42:123-132.

INARIGIVIR DEMONSTRATES A CONTINUING POSITIVE DOSE RESPONSE IN HBeAg +VE PATIENTS AT WEEK 12





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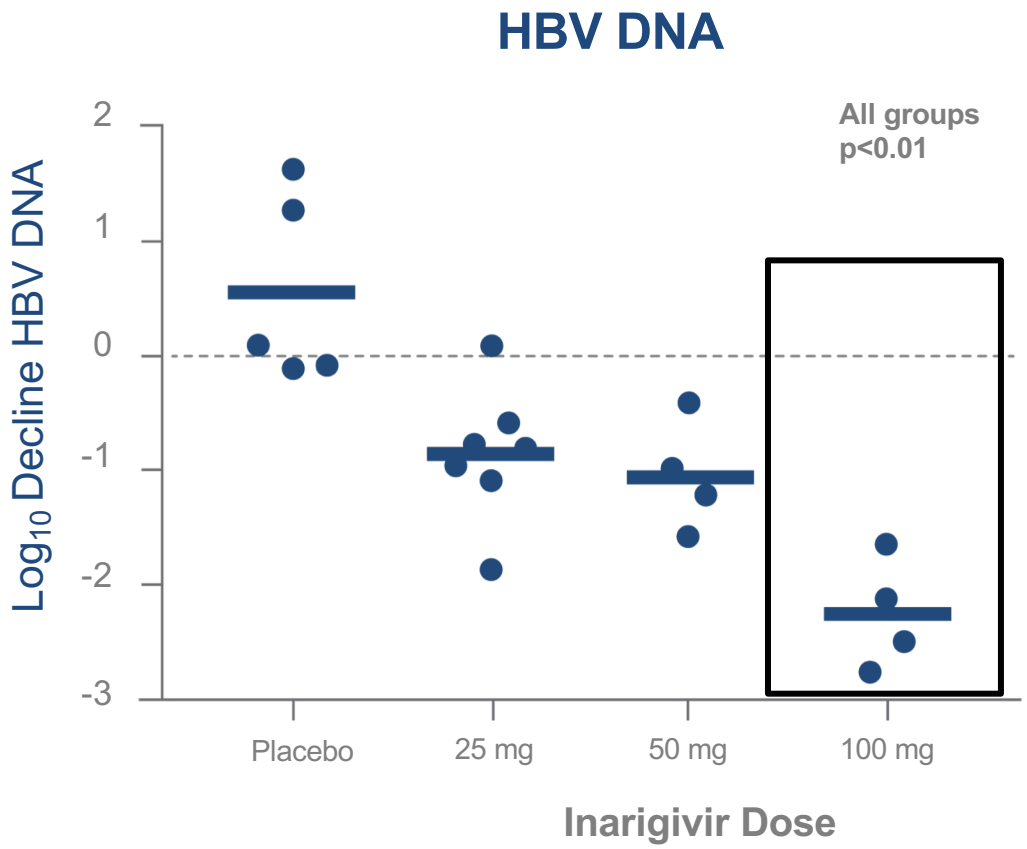
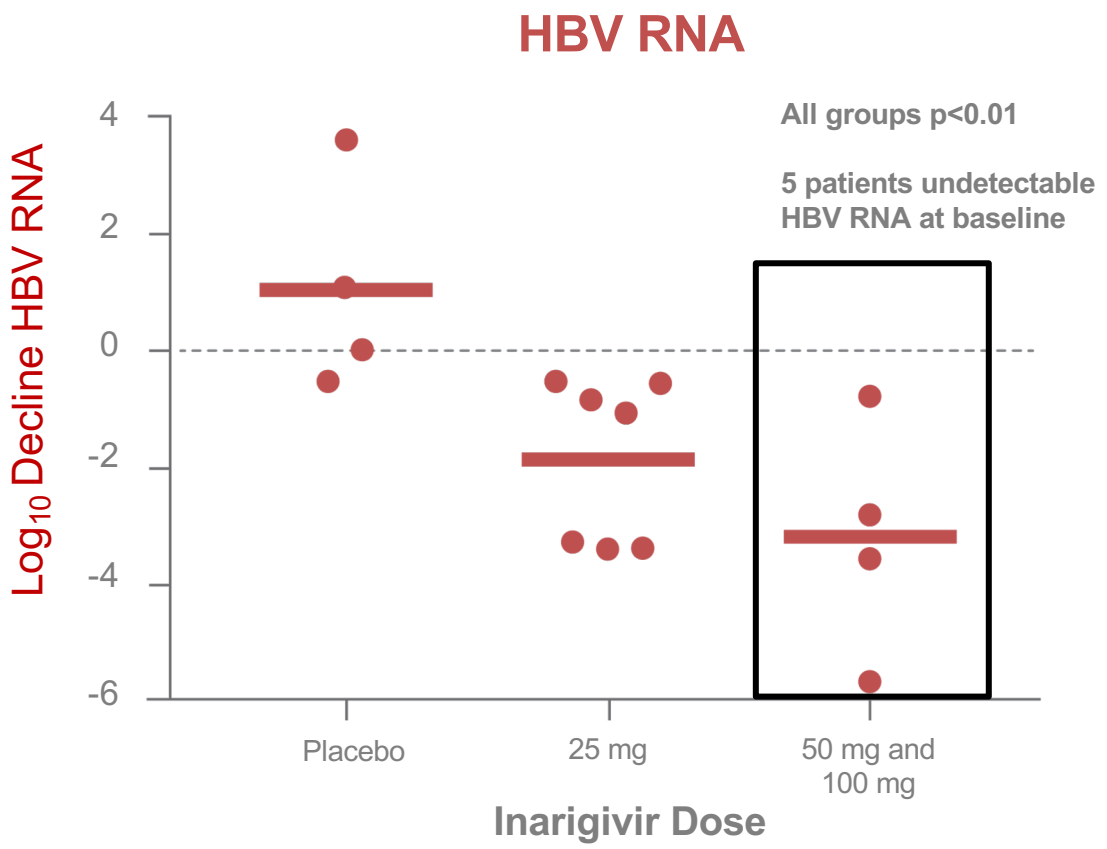
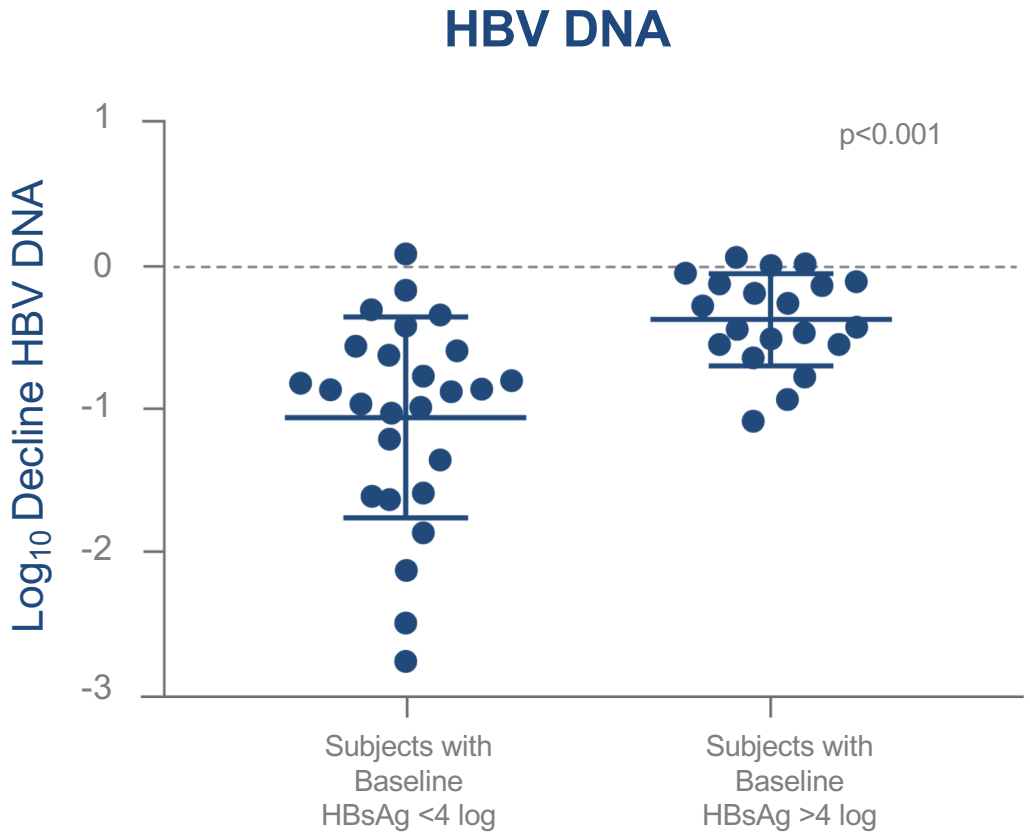
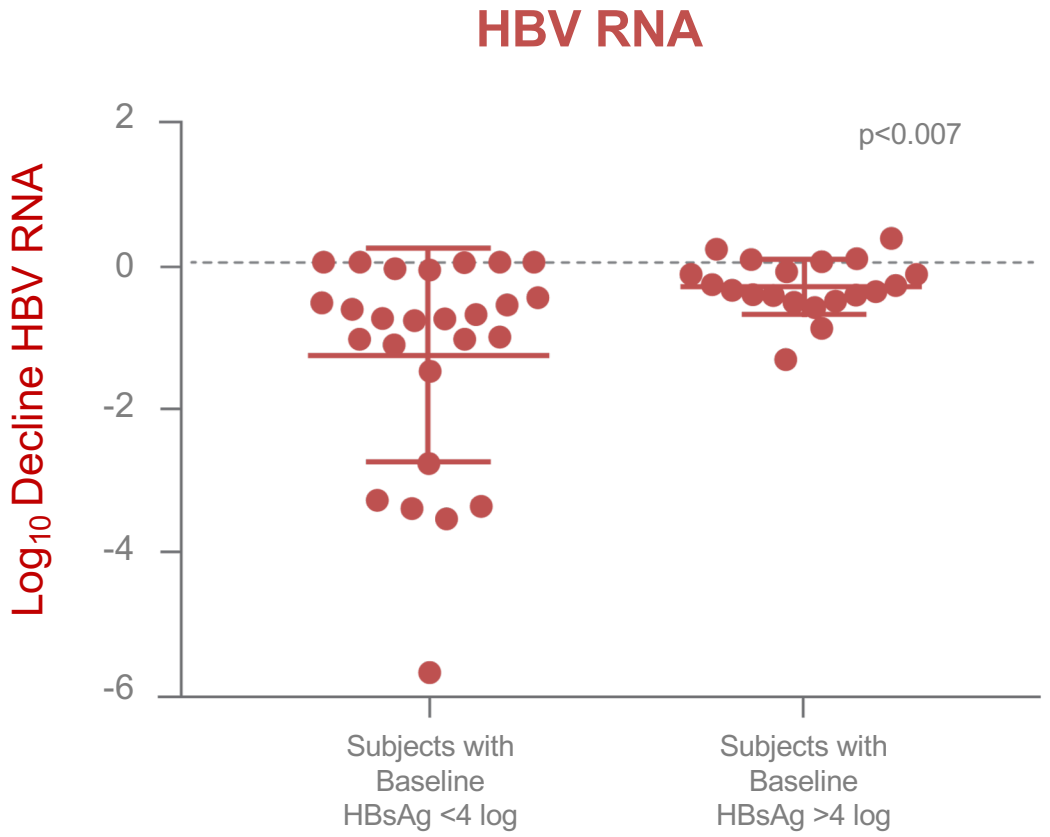




IN ALL COHORTS: BASELINE HBsAg PREDICTS RESPONSE OF BOTH DNA AND RNA TO INARIGIVIR





Patients: **HBsAg <4 log: 16 HBeAg –ve, 10 HBeAg +ve**

HBsAg >4 log: 1 HBeAg –ve, 19 HBeAg +ve

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Third Example: JNJ-6379

Capsid Assembly Modulator (CAM)

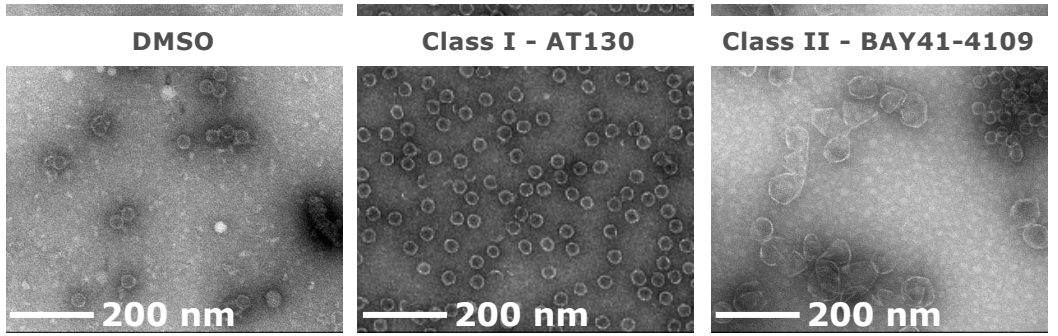
Also known as core protein allosteric modulator (CpAM), core (protein) inhibitor or capsid assembly effector/inhibitor

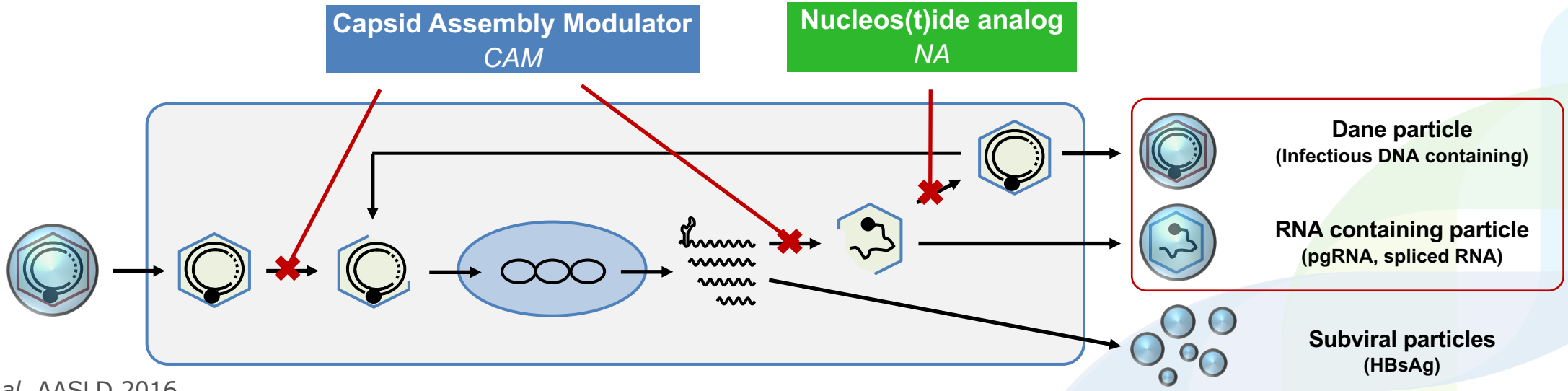
Influence assembly kinetics

Induce two types of empty capsids *in vitro*

Class I - Normal geometry & size

Class II - Abnormal geometry & size





Berke JM, *et al*. AASLD 2016

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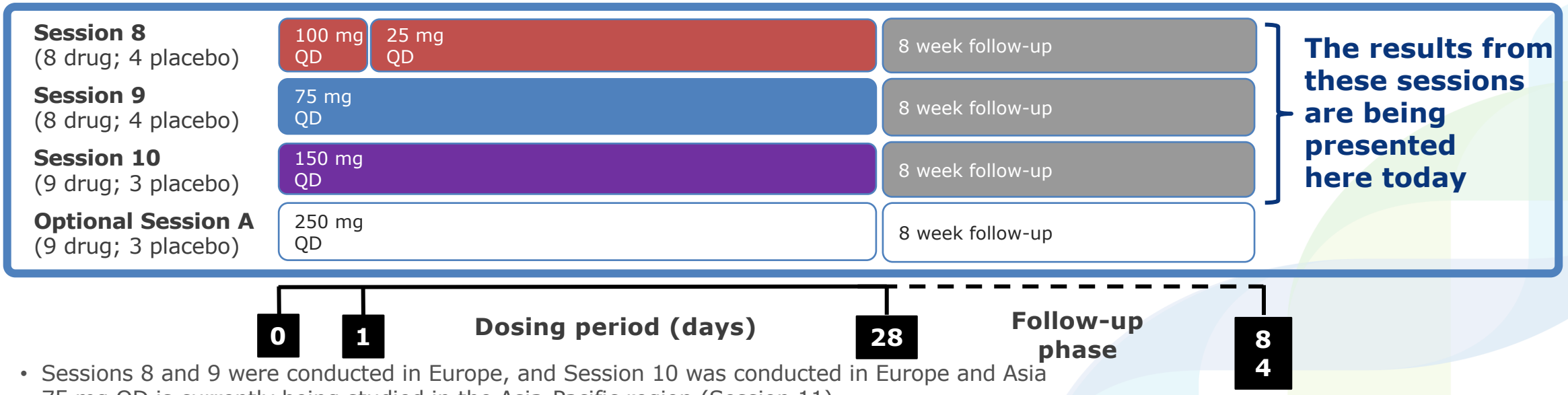
HPB1001 Part 2: Chronic Hepatitis B patients
Objective and study design

The objective of **Part 2** is to evaluate antiviral activity, safety and PK for 28-day oral treatment of JNJ-6379 in adult, treatment-naïve, chronic hepatitis B (CHB) patients meeting the following criteria:

- HBeAg-positive or -negative
- Plasma HBV DNA >2,000 IU/mL
- Non-cirrhotics (F0–F2)
- ALT less than 2.5x ULN



- Sessions 8 and 9 were conducted in Europe, and Session 10 was conducted in Europe and Asia
- 75 mg QD is currently being studied in the Asia-Pacific region (Session 11)

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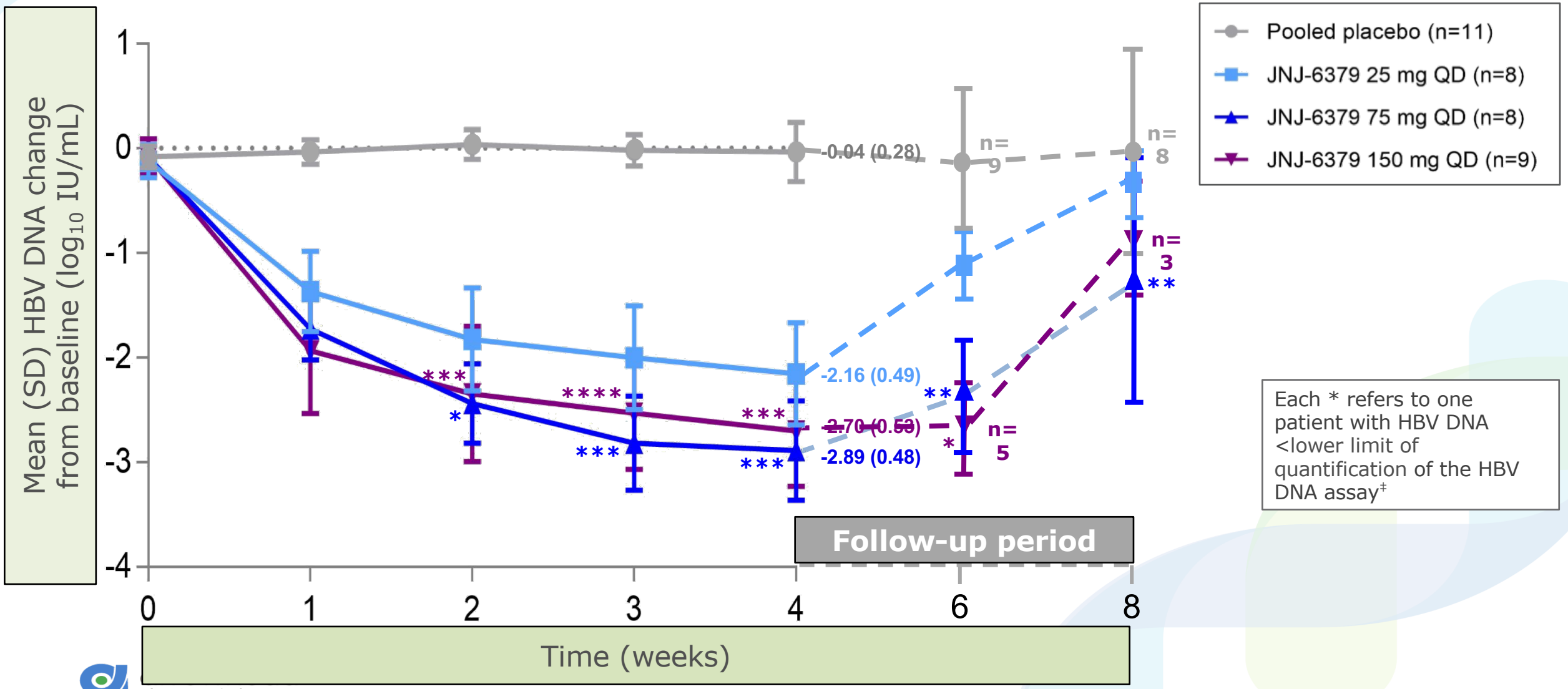
Zoulim F, *et al*. EASL 2018

Mean HBV DNA change from baseline up to 4 weeks follow-up



‡Roche COBAS AmpliPrep/COBAS TaqMan HBV Test, V. 2.0

Zoulim F, *et al*. EASL 2018

Mean HBV DNA and HBV RNA change from baseline after 4 weeks of treatment

	HBV DNA				HBV RNA			
	Baseline		Day 29		Baseline[a]		Day 29	
Treatment arm	N	Mean (SD) log_{10} IU/mL	Mean (SD) Change from Baseline log_{10} IU/mL	<LLOQ n (%)	N	Mean (SD) log_{10} cp/mL	Mean (SD) Change from Baseline log_{10} cp/mL	Not detected n (%)
Session 8 (25 mg QD)	8	6.90 (1.91)	–2.16 (0.49)	0	8	5.59 (2.37)	–2.30 (0.59)	3 (38%)
Session 9 (75 mg QD)	8	5.26 (1.50)	–2.89 (0.48)	3 (38%)	8	3.39 (2.21)	–1.85 (1.42)	6 (75%)
Session 10 (150 mg QD)	9	5.10 (1.56)	-2.70 (0.53)[b]	3 (38%)[b]	9	3.37 (1.66)	-1.67 (0.99)[c]	4 (80%)[c]
Pooled placebo	11	5.10 (1.64)	-0.04 (0.28)	0	11	3.33 (2.58)	0.02 (0.86)	3 (27%)

No relevant changes in HBsAg were observed

[a] Two patients in the 75 mg JNJ-379 group, one patient in the 150 mg JNJ-6379 group and three patients in the placebo group had undetectable HBV RNA at baseline
[b] HBV DNA at Day 29 is available for eight patients
[c] HBV RNA at Day 29 is available for five patients
LLOQ = Lower limit of quantification

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Zoulim F, *et al*. EASL 2018

Where to Next……

- The next frontier is combination therapy with NUCs (usually), with Interferon (maybe to rarely) - but most importantly combining new classes
- Our bias is that RNAi will be at the center of many/most/?all combos due the ability to affect the entire HBV transcriptome, including integrated DNA-sourced RNA
- The bar will be very high for activity (functional cure) and safety/tolerability
- Immuno-oncology agents (PD1/PDL1) monoclonals may play a role but safety concerns may dominate. In the meantime, other immune stimulation approaches are being tried

Thank you !

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