Will we need novel combinations to cure HBV?

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Disclosures

- Gilead Sciences
- Janssen
- Arbutus

Combination treatment: Evidence still being gathered

- Limited clinical data to date
- Several steps in the replication cycle of HBV are druggable targets
- Safety of new combinations will be paramount
  - (Given the safety of currently approved nucleoside analogues).

Strategies for HBV eradication

TARGETING HBSAG

TARGETING INTEGRATED VIRAL DNA

HBX PROTEIN

STRATEGIES TO INTERFERE WITH VIRAL ENTRY

CCCDNA REGULATION

RNA INTERFERENCE AGENTS

INNATE IMMUNE AGONISTS

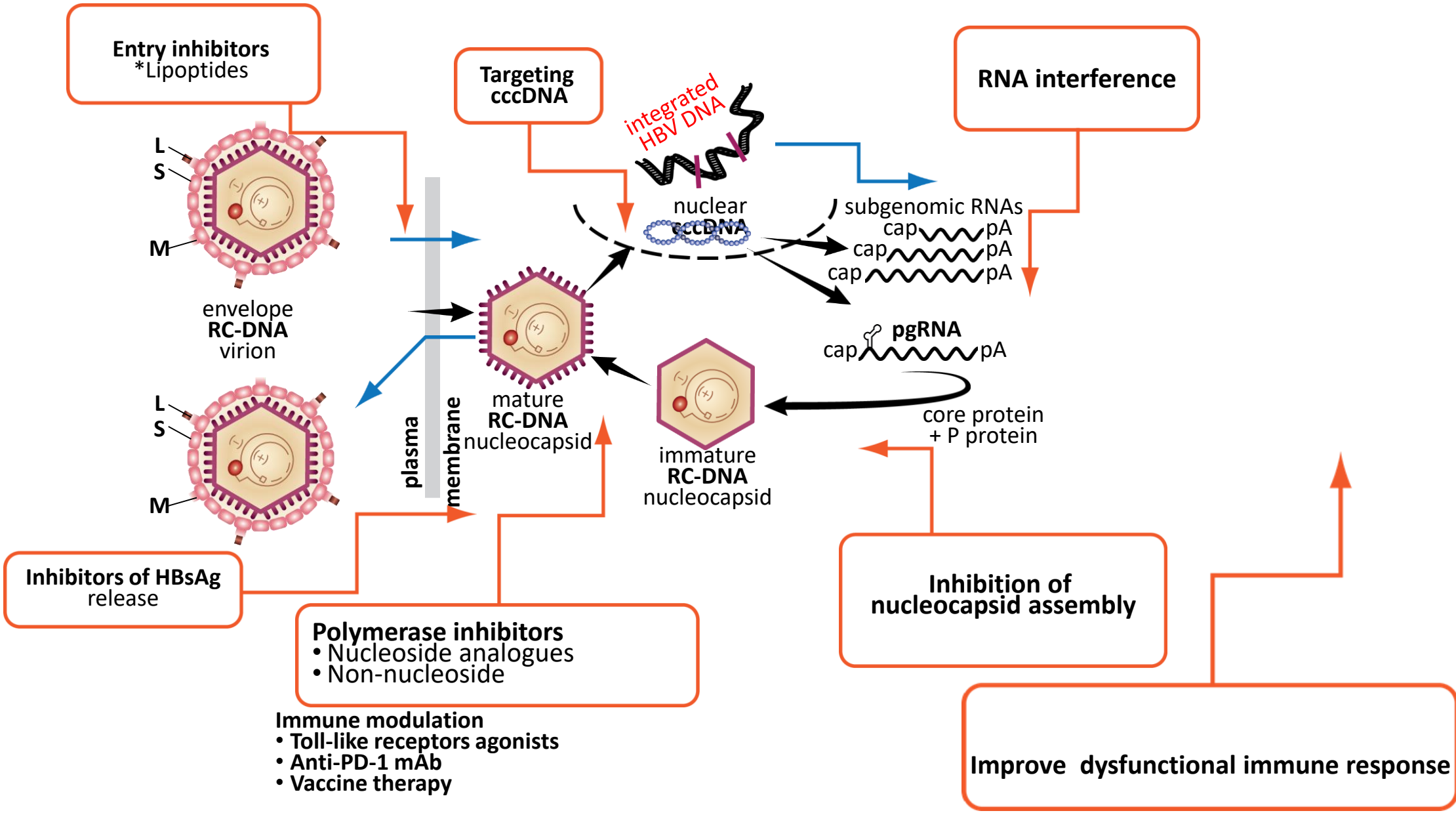
IMMUNE THERAPIES

*CAPSID ASSEMBLY MOD*ULATORS

Virology of HBV poses difficulties for cure

- HBV DNA genomic fragments integrate into the genome of hepatocytes
- The stable episomal cccDNA acts as the template for transcription of HBV mRNAs
- HBsAg can be transcribed from cccDNA and integrated viral genomes
  - HBeAg negative patients the probable predominant source of HBsAg is from RNAs transcribed from integrant HBV DNA
  - This source of HBsAg is relatively inaccessible without cell loss or DNA editing
- In addition to infectious virions, HBV replication results in the excess production and release of sub-viral empty envelope particles
- HBsAg antigen load may cause profound antigen-specific immune dysfunction and exhaustion.
- Selection of resistant associated substitutions possible with eg CAMs

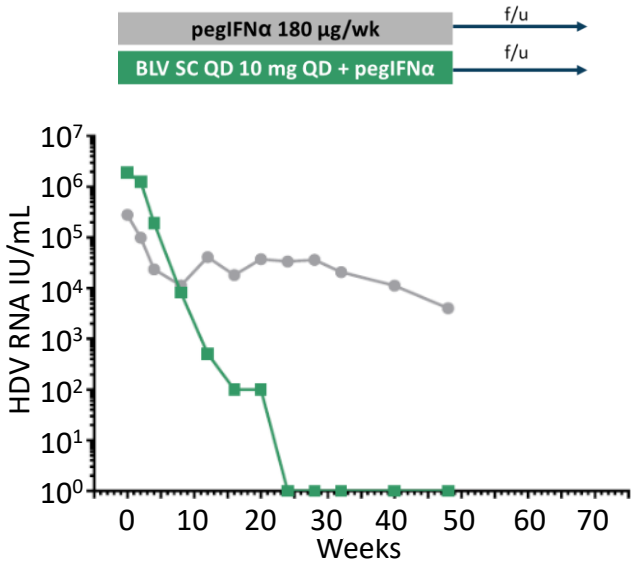
HBV antiviral targets: exploitable targets



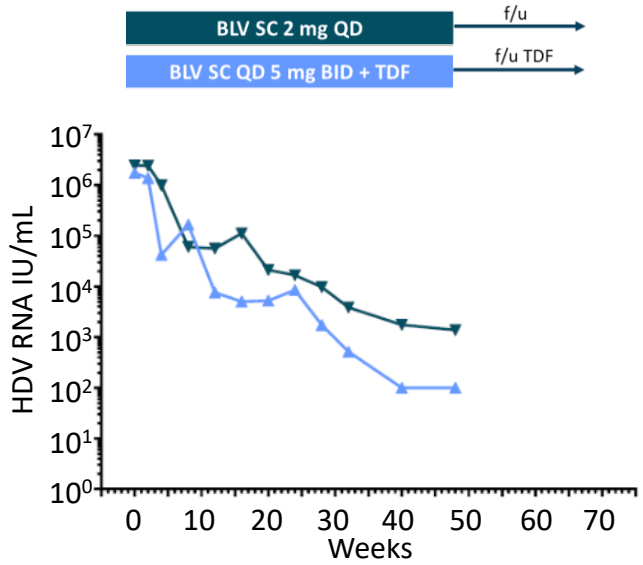
Hepatitis D infection

10 mg bulevirtide (Myrcludex B) in combination with pegIFN-α2a or tenofovir
Chronic HBV/HDV coinfection: Week 24 interim results of the MYR203 extension study

Virologic response (median HDV RNA)

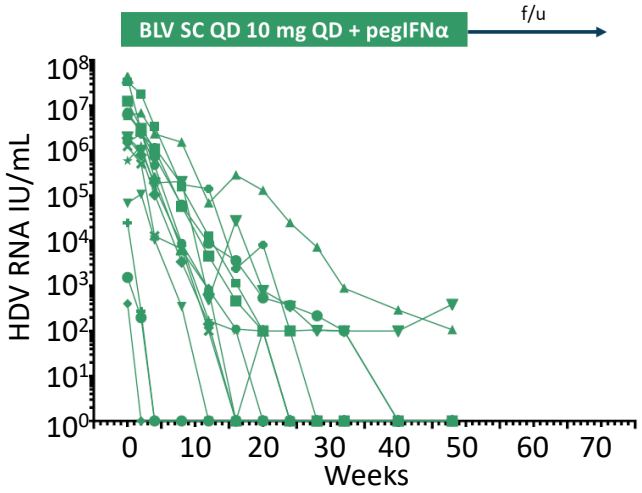


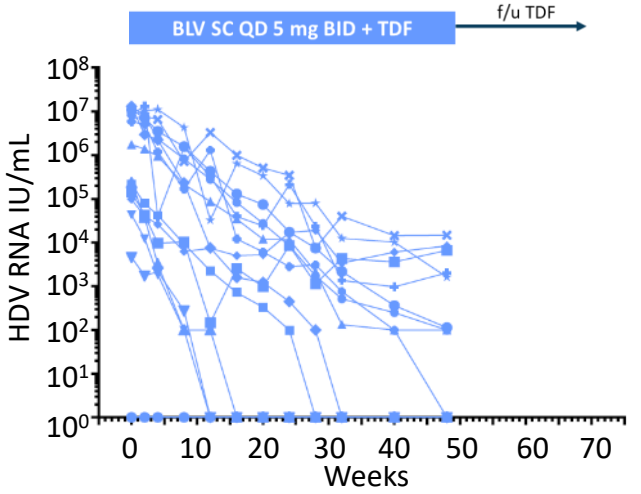
Virologic response: Week 48	Median HDV RNA reduction (log)	Undetectable HDV RNA
pegIFNα	-1.29	13.3%
2 mg BLV + pegIFNα	-5.21	80.0%
5 mg BLV + pegIFNα	-6.13	86.7%
10 mg BLV + pegIFNα	-6.09	86.7%



Virologic response: Week 48	Median HDV RNA reduction (log)	Undetectable HDV RNA
2 mg BLV	-2.84	13.3%
5 mg BLV BID + TDF	-4.58	40.0%

Individual RNA kinetics

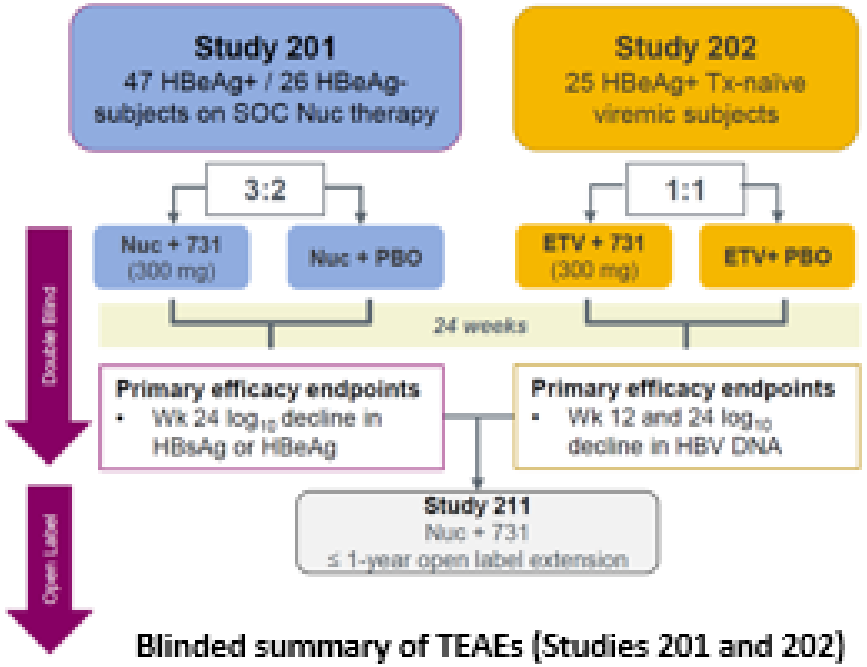




Wedemeyer H, et al. AASLD 2019, Boston, USA. #85

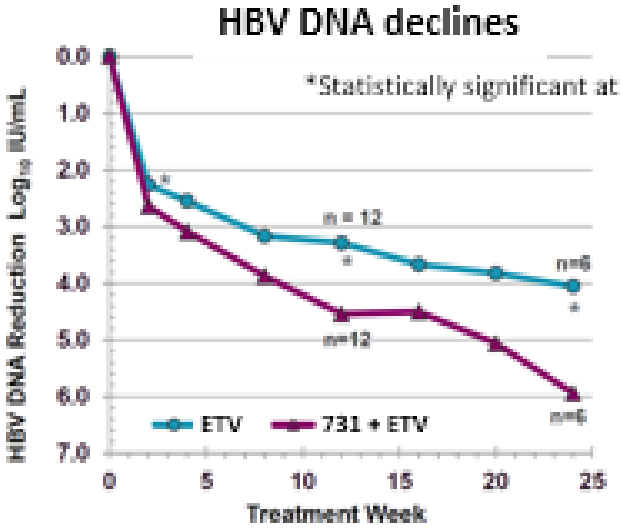
HBV capsid assembly modulators

Interim safety and efficacy results of ABI-H0731 Phase 2a program exploring combination of ABI-H0731 with Nuc therapy in treatment-naive and treatment-suppressed CHB patients



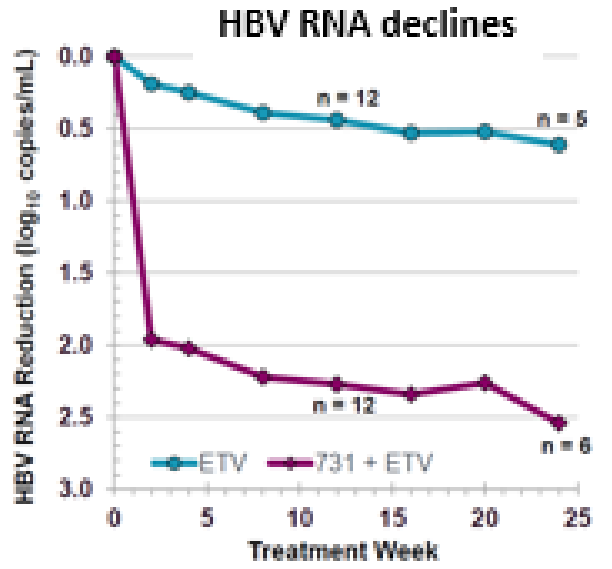
Blinded summary of TEAEs (Studies 201 and 202)

- No SAEs or treatment related d/cs or interruptions
- AEs mostly mild, infrequent, considered unrelated to study drug
- No flares on treatment; no clinical AE > Grade 2
- 3 pts with rash considered "possibly related" (2x Gr 1, 1x Gr 2)
- 1 pt in each study had Gr 2 AE considered possibly related to drug
  - Macular/maculopapular rash–resolved on antihistamine (201)
  - ALT increase–resolved with continued treatment (202)



Week	ETV	ETV + 731	p-value
12	3.29	4.54	<0.011
24	3.99	5.94	<0.005

HBV DNA assessed by Roche CobasqPCR; LOQ = 20 IU

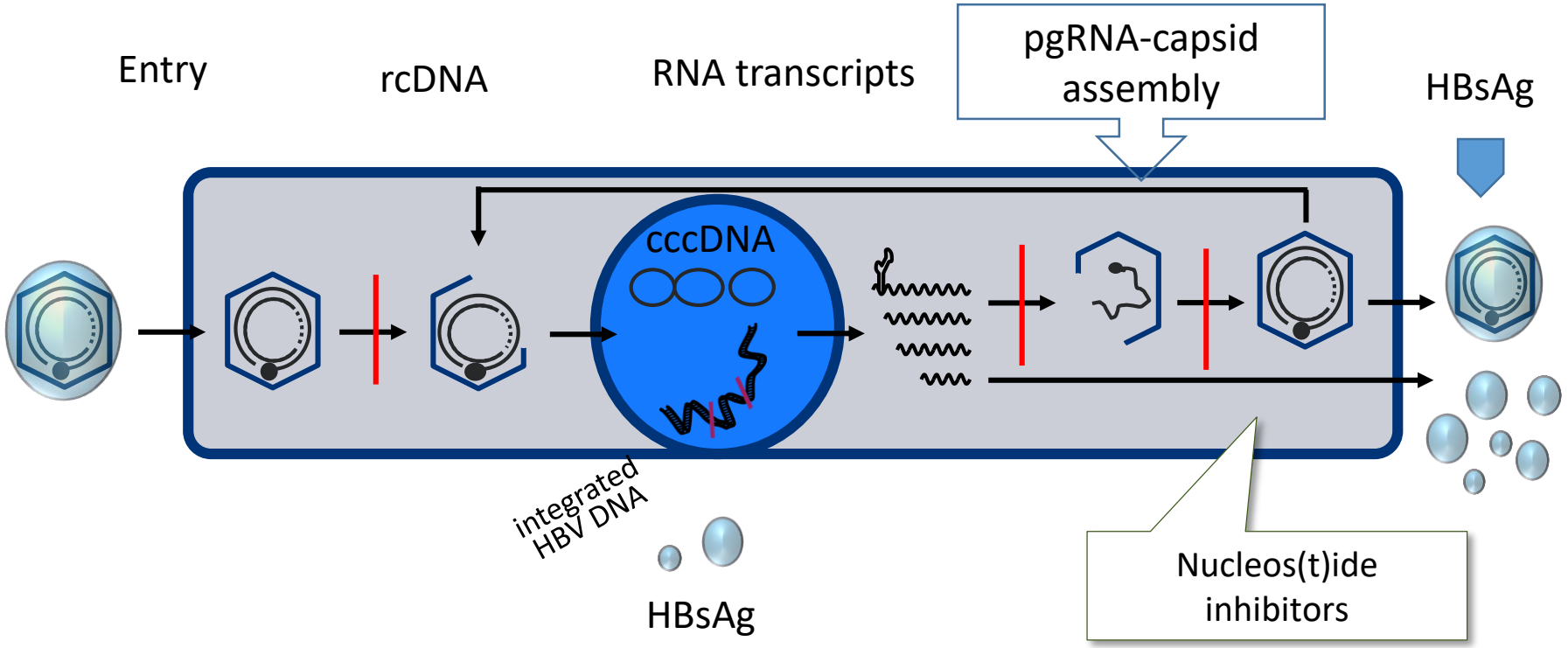


Week	ETV	ETV + 731	p-value
12	0.44	2.27	<0.005
24	0.61	2.54	<0.005

HBV RNA assessed by RT qPCR; LOQ = 200 copies/mL

Capsid Assembly modifier + Nucleoside analogues: effect on HBV replication: effect on cccDNA and HBsAg?

Continued transcription from cccDNA and integrated viral genomes: relatively minor decrease serum HBsAg despite undetectable serum HBV DNA



rcDNA – relaxed circular DNA; cccDNA –covalently closed DNA; pgRNA pre-genomic RNA

RNA therapeutics: RNAi

RNAi-based triple combination therapy in CHB: JNJ-3989 (RNAi), JNJ-6379, (CPAM), and nucleoside analogue

Background

- JNJ-3989 Q4W 3 monthly 100–400 mg with Nuc >1.0 log drop HBsAg and reduced all measurable viral products (EASL 2019)
- JNJ-6379 blocks HBV replication and *de novo* cccDNA pathway achieving significant decline in serum HBV DNA and serum HBV RNA (AASLD 2018)

Aim

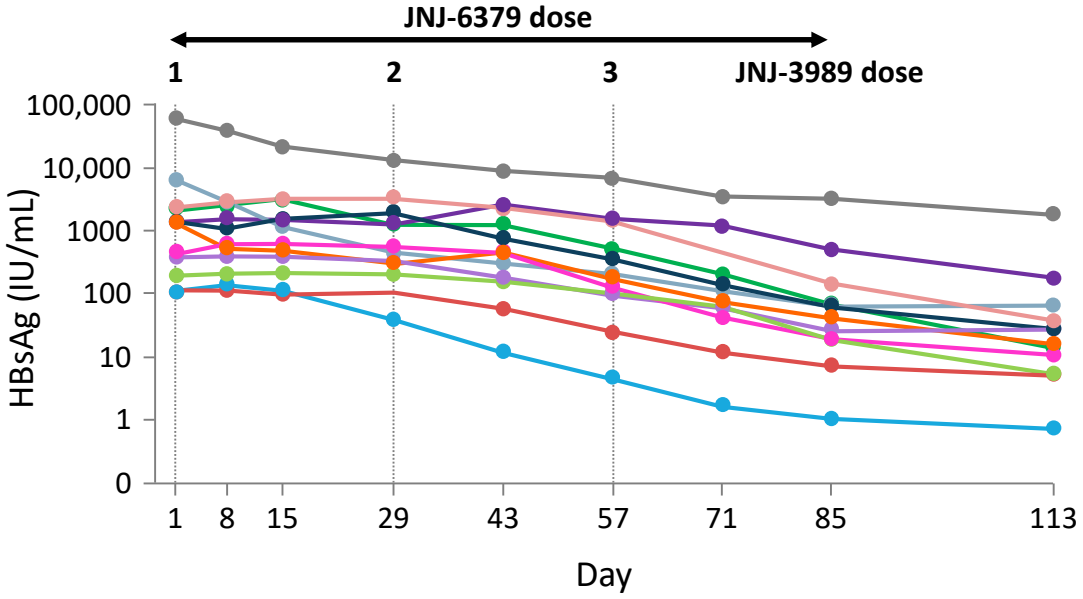
- To help design longer term studies, a cohort added to achieve experimental triple combination of JNJ-3989, JNJ-6379, and NA

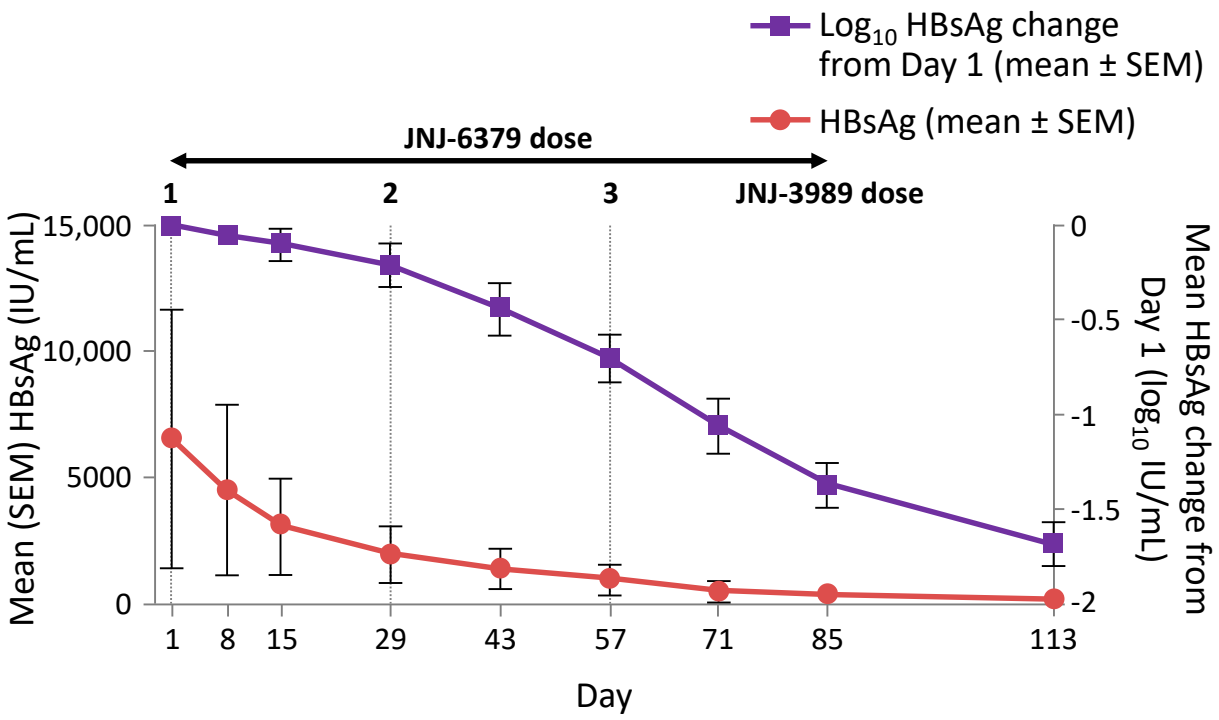
Patients

- 12 patients; 3 doses JNJ-3989 200 mg Day 1, 29, and 57 SC + oral JNJ-6379 250 mg OD for 12 weeks

Results

- Efficacy data to Day 113
  (2 months post-3898 and 1 month post-6378)





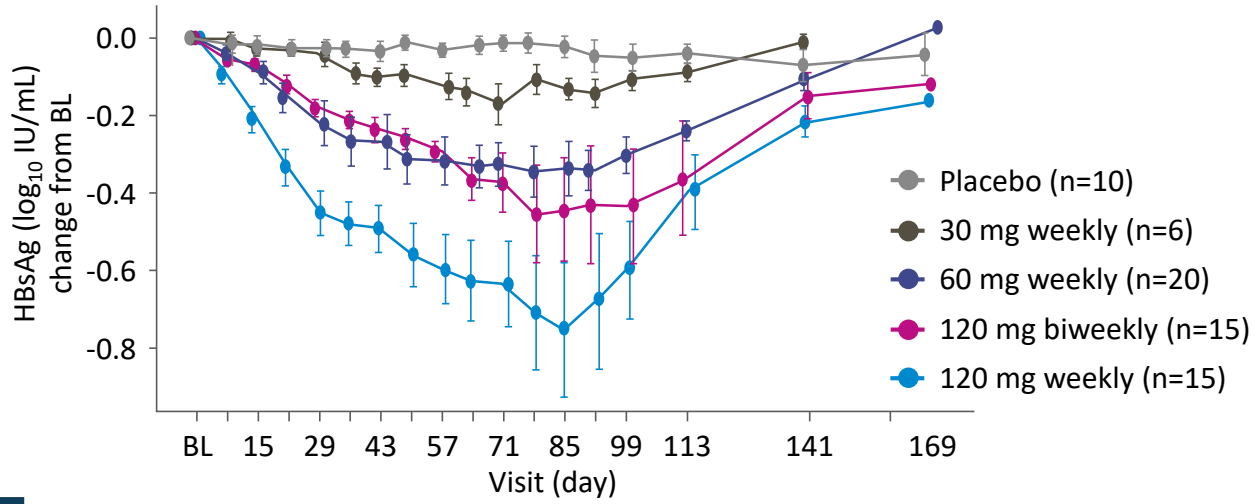
Yuen M-F, et al. AASLD 2019, Boston, USA. #LP4

Antisense oligonucleotides (ASOs)

12 weeks' treatment of multiple doses of GSK3389404 (ASO) in CHB subjects on stable nucleoside therapy
Phase 2a, double-blind, placebo-controlled study

- GSK3389404: 2nd-generation liver-targeted antisense oligonucleotide (ASO) that targets all HBV-derived RNA transcripts
- Phase 2a, multicenter, randomized, double-blind, placebo-controlled study in Asia-Pacific region
- Multiple-dose, 12 weeks SQ injection; study arms:
  - 60 mg weekly
  - 120 mg bi-weekly
  - 120 mg weekly
  - PBO
- HBeAg+/- Nuc-treated non-cirrhotic CHB patients with HBsAg >50 IU/mL and ALT ≤2 x ULN

Mean change from BL in HBsAg (log_{10} IU/mL) over time



	PBO	30 mg weekly	60 mg weekly	120 mg biweekly	120 mg weekly
N	10	6	20	15	15
HBeAg+	30%	17%	40%	13%	27%
Mean HBsAg log_{10}, IU/mL	3.15	2.73	2.96	2.82	3.00
ALT, U/L	22.9	24.5	18.6	21.1	19.1
Platelets, (10^9/L)	214	194	243	200	229

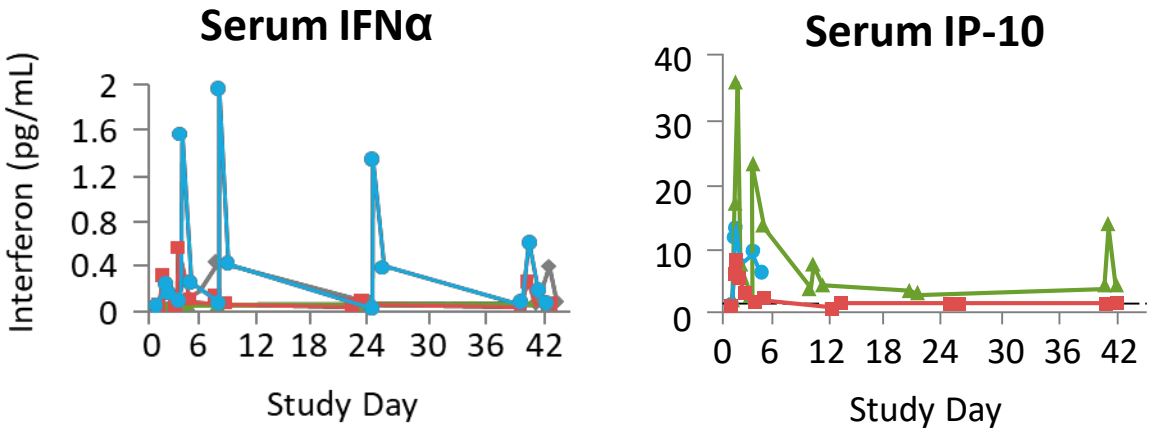
- Dose-dependent declines in mean HBsAg
  - Similar in HBeAg+ and HBeAg- subjects
  - 3 subjects achieved ≥1.5 log_{10} decrease in HBsAg with no ALT flare
    - 1.54 log_{10} in 60 mg weekly arm on Day 85
    - 2.37 log_{10} in 120 mg biweekly arm on Day 92
    - 2.72 log_{10} in 120 mg weekly arm on Day 85
  - Mean HBsAg declines of 0.02 log IU/mL in PBO, 0.13 log IU/mL in 30 mg weekly, 0.34 log IU/mL in 60 mg weekly, 0.44 log IU/mL in 120 mg biweekly, and 0.75 log IU/mL in 120 mg weekly treatment arms by Day 85

Yuen M-F, et al. AASLD 2019, Boston, USA. #695

TLR-7 agonist RO7020531

- Liver targeting specific TLR-7
  - 150 mg QOD dosing for 6 weeks in NA-suppressed CHB patients

PD activity in patients with flu-like symptoms



Relationship between exposure and PD activity (maximum fold of change in individual patients)

	Fraction responding	Geometric mean fold change (range)
Neopterin	6/8	3.13 (1.86–6.08)
IP-10	7/8	3.55 (1.37–36.43)
ISG15	8/8	11.21 (2.31–270.26)
OAS-1	8/8	4.85 (1.71–41.45)
MX1	8/8	6.78 (2.16–87.43)
TLR7	7/8	3.46 (2.04–6.84)

- AASLD 2019 additional 150 and 170 mg cohorts (Yuen #692)
  - full virologic results included a HBsAg decline in qHBsAg
  - Next year planned Phase II platform studies with other agents

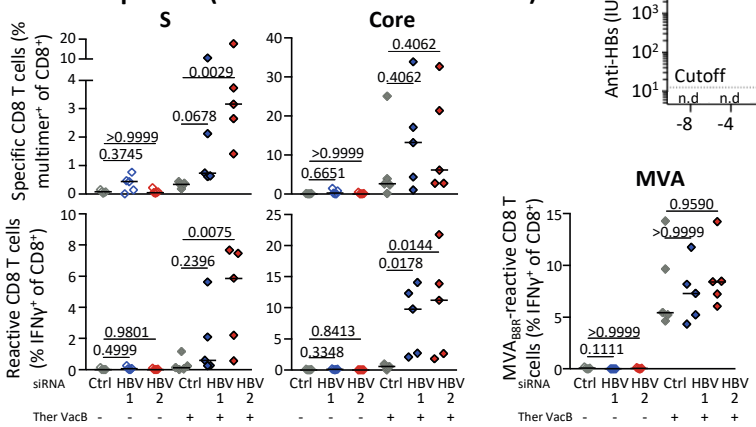
Gane E, et al. AASLD 2018, San Francisco, USA. #LB-33 Yuen M-F, et al. AASLD 2019, Boston, USA. #692

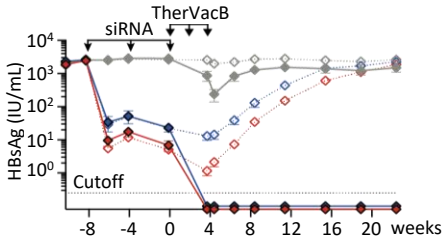
Experimental mouse models

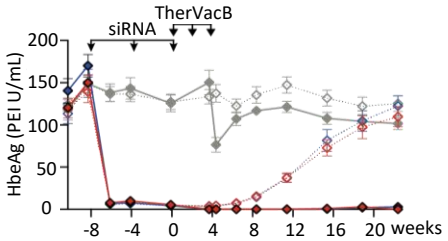
Combinatorial RNAi/vaccination therapy for chronic hepatitis B achieves long-term functional cure in preclinical mouse model

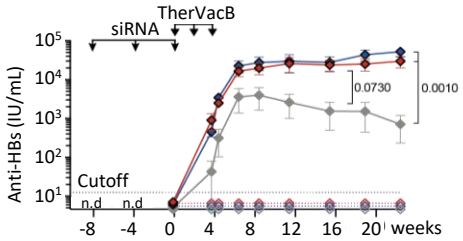
- Heterologous therapeutic hepatitis B vaccine (**TherVacB**) consisting of a protein prime / Modified Vaccinia Ankara Virus (MVA) boost vaccination
- N-acetylgalactosamine-coupled siRNA enables hepatocyte-specific delivery of siRNA targeting the common 3' end of HBV transcripts to suppress all viral transcripts and proteins

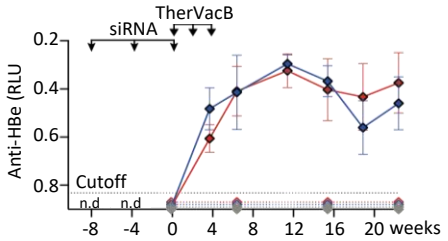
T cell responses (5 months after MVA-boost)

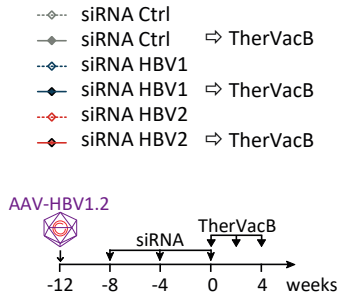












AAV-HBV1.2: 2x10^{10} geq i.v.
GalNAc-siRNAs: 3 mg/kg bw s.c.

n.d. not determined

- Functional cure in all 12 mice treated with HBV siRNA ⇨ TherVacB
- 3/12 animals showed mild and transient HBeAg relapse 4 months after stop of treatment

- Combinational siRNA/vaccination therapy achieved functional cure through induction of virus-specific CD8+ T cell response
- Proof of concept on suppression of all viral antigens but not HBV DNA alone is needed for immune induction by therapeutic vaccine

Michler T, et al. EASL 2018, Paris. #PS-025

Conclusions: Will we need novel combinations to cure HBV?

Synergistic mechanisms need to incorporate a decrease in HBV transcription, loss of cccDNA or altered epigenetic regulation of cccDNA and immune modulation or immunologically stimulated hepatocyte cell turnover.

Nucleoside analogue suppressed patients being included in many current trials. Trials are progressing to combination therapy as additive or synergistic effects are sought.

Trials will provide insights into the biology of HBV and perturbations of the immune response, required to effect HBsAg loss at different stages of the disease.