RNAi: Pulling Us Toward Finite Therapy

The Science of HBV Cure 2019
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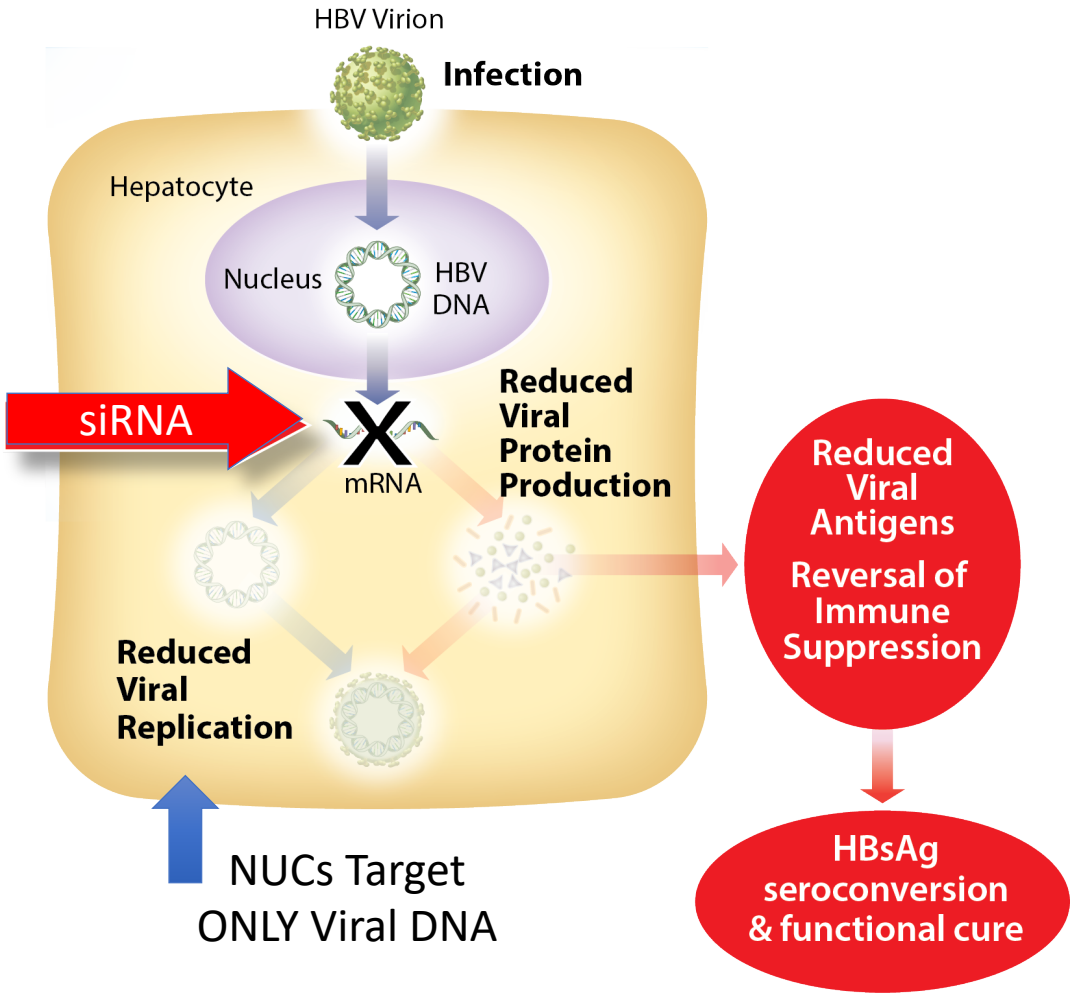
Simplified theories for an HBV RNAi therapeutic



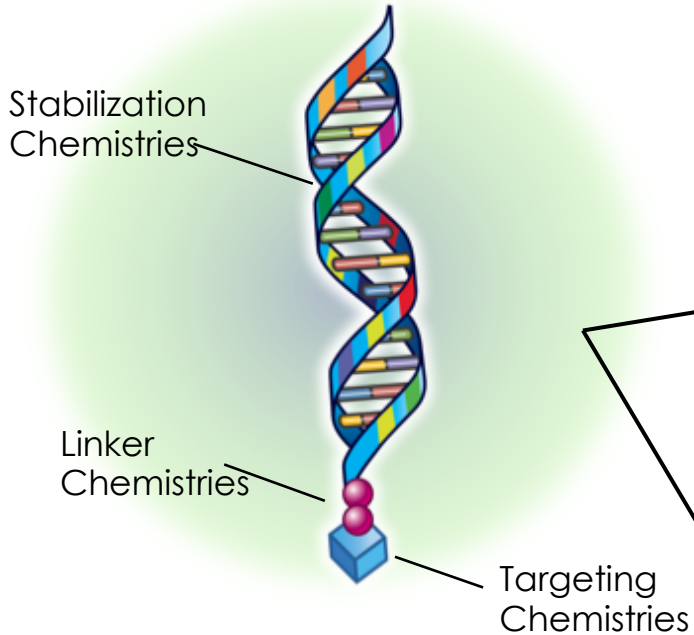
Silence Entire HBV Genome

1. "HBsAg Theory"
   - **Reducing HBsAg** enables host immune system de-repression and long term control of virus
2. Destabilizing Viral Function
   - **Silencing all antigens and reducing pgRNA** could destabilize normal viral function
   - Enable host immune system de-repression and long term control of virus

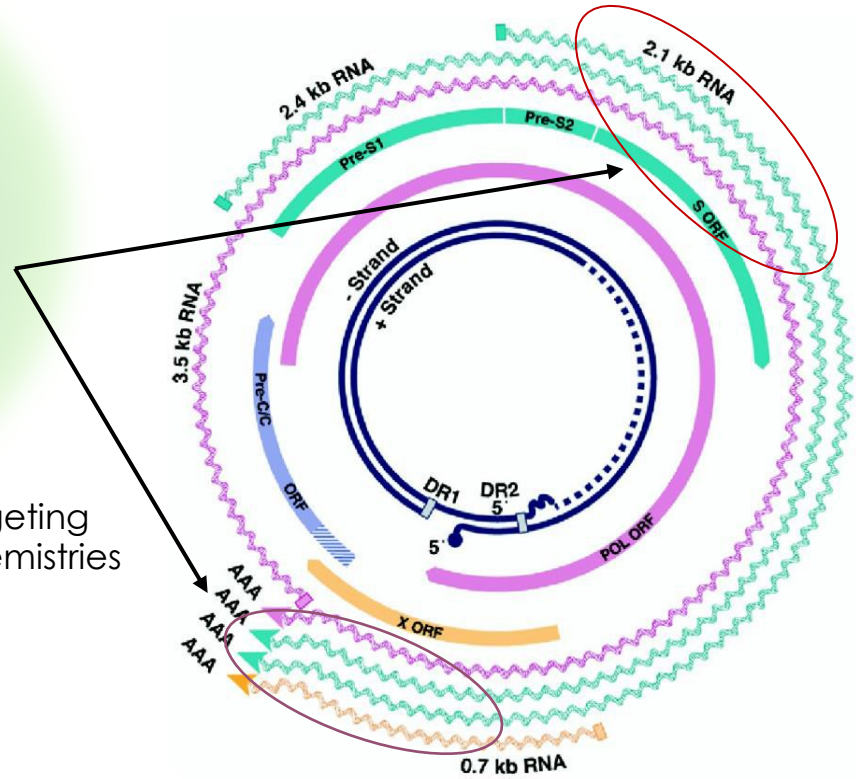
JNJ-3989 (ARO-HBV): Key design elements

- **Addresses full HBV transcriptome**
  - **Two hepatocyte targeted RNAi molecules**
  - **Works for cccDNA and integrated-derived transcripts**
  - **Previously shown to reduce HBV DNA, HBV RNA, HBsAg, HBeAg, & HBcrAg [1,2]**
- **Multiple triggers to avoid resistance development and increase coverage of viral genomes**

2 Targeted RNAi Molecules



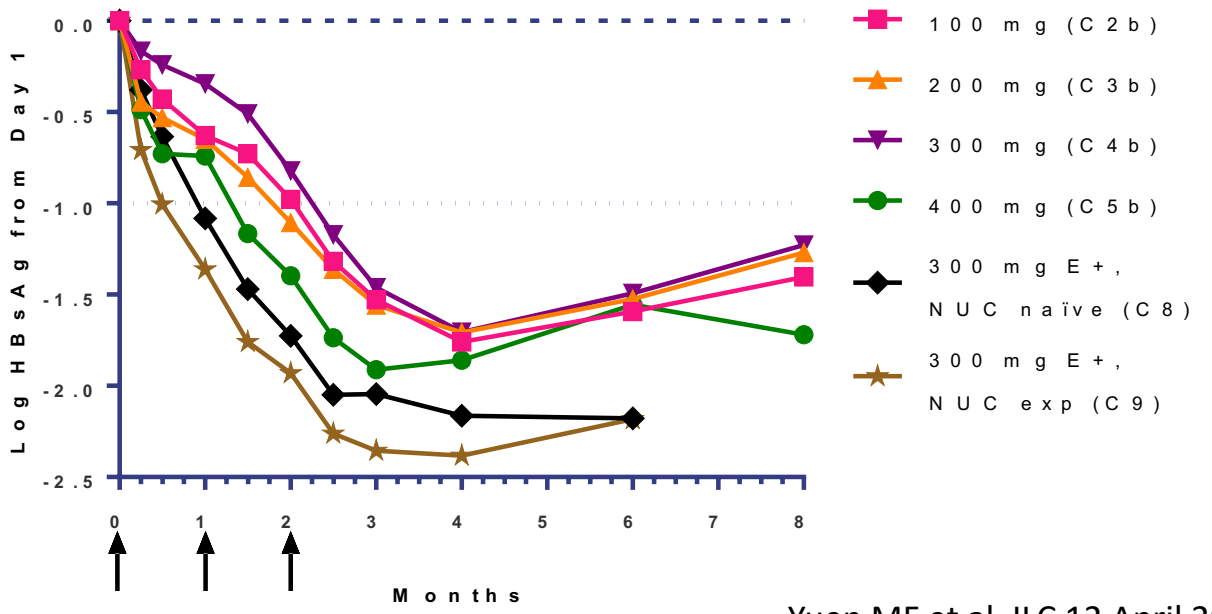
HBV Transcript Map



[1] Gane et al. 2018 Hepatology 68:6 LB-25 [2] Gane et al. 2019 APASL Abstract 638

Patients receiving 3 monthly doses have achieved > 1 log reduction in HBsAg

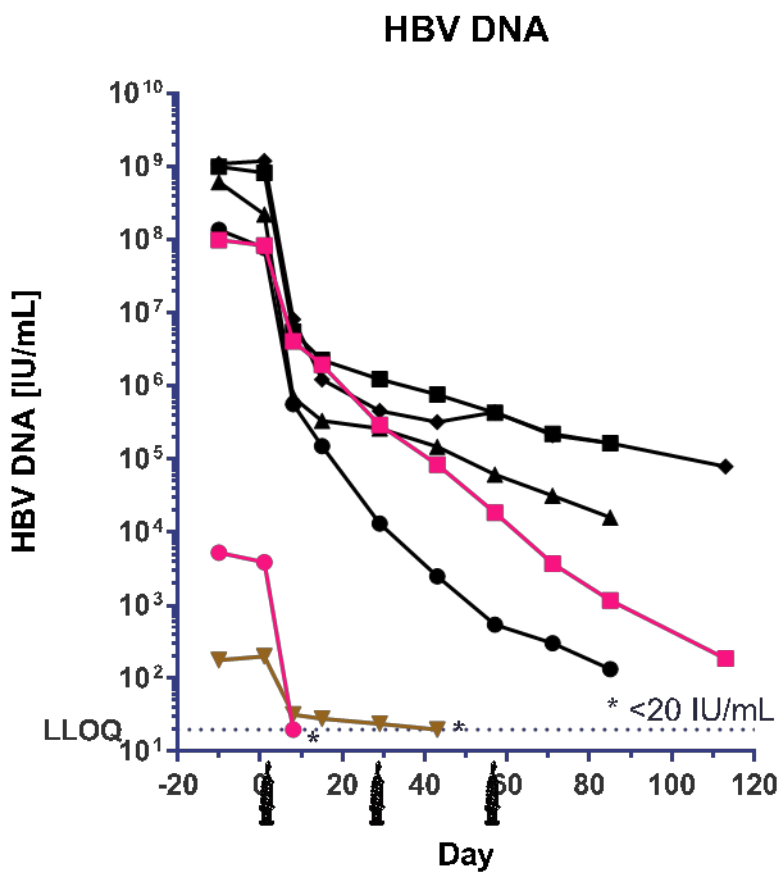
Mean HBsAg reductions from baseline

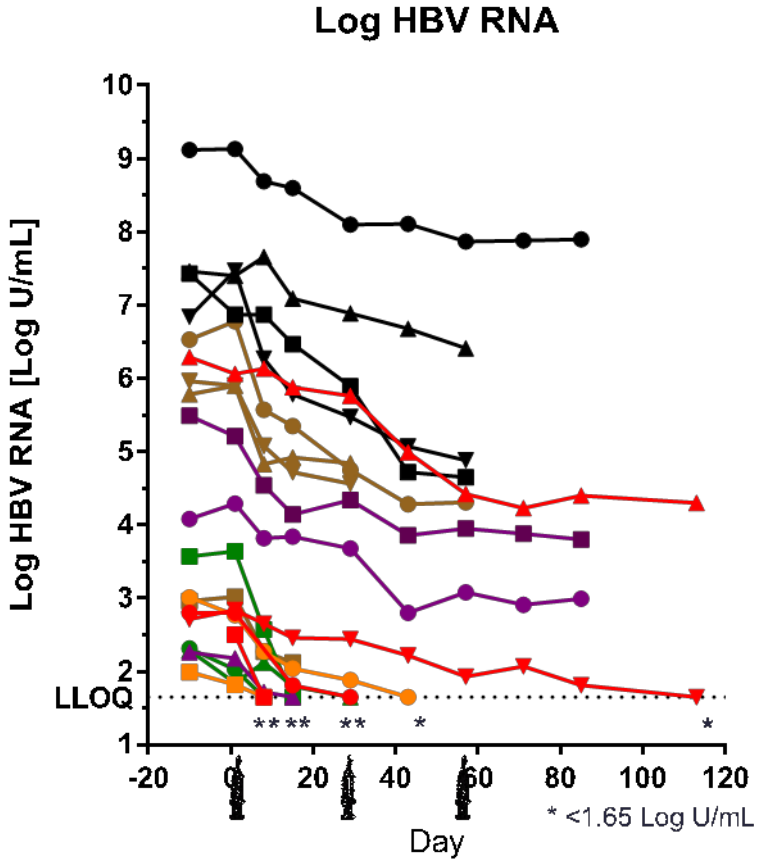


Yuen MF et al. ILC 12 April 2019, PS-080 (as of 2/28/2019)

- NADIR in HBsAg is reached around 4 months post start of therapy
- Duration of pharmacologic effect persisted for > 4 months after last dose

Individual HBV DNA and RNA Responding Well

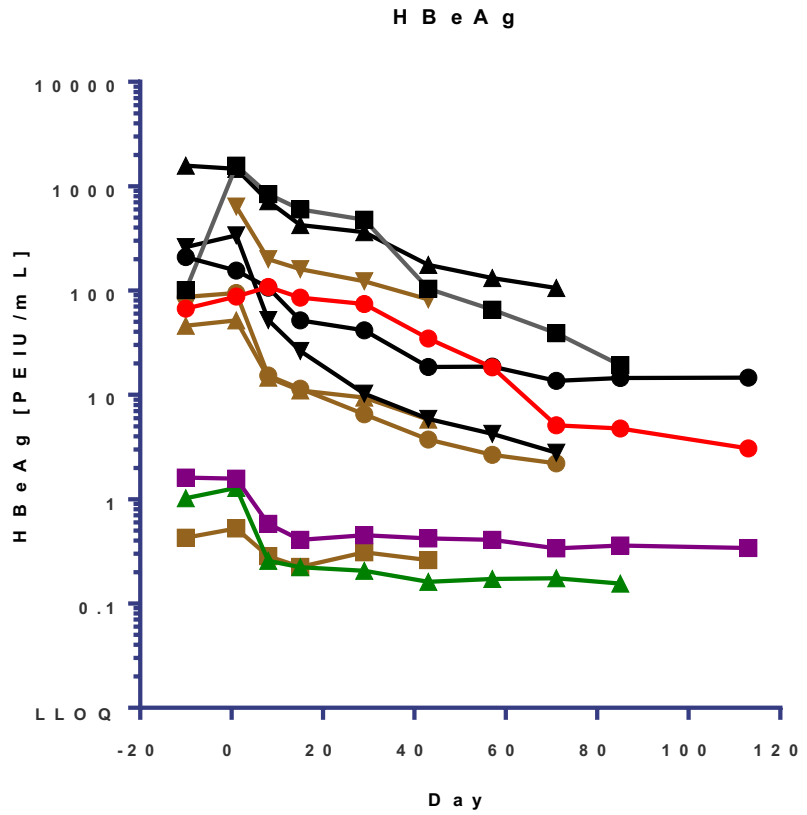


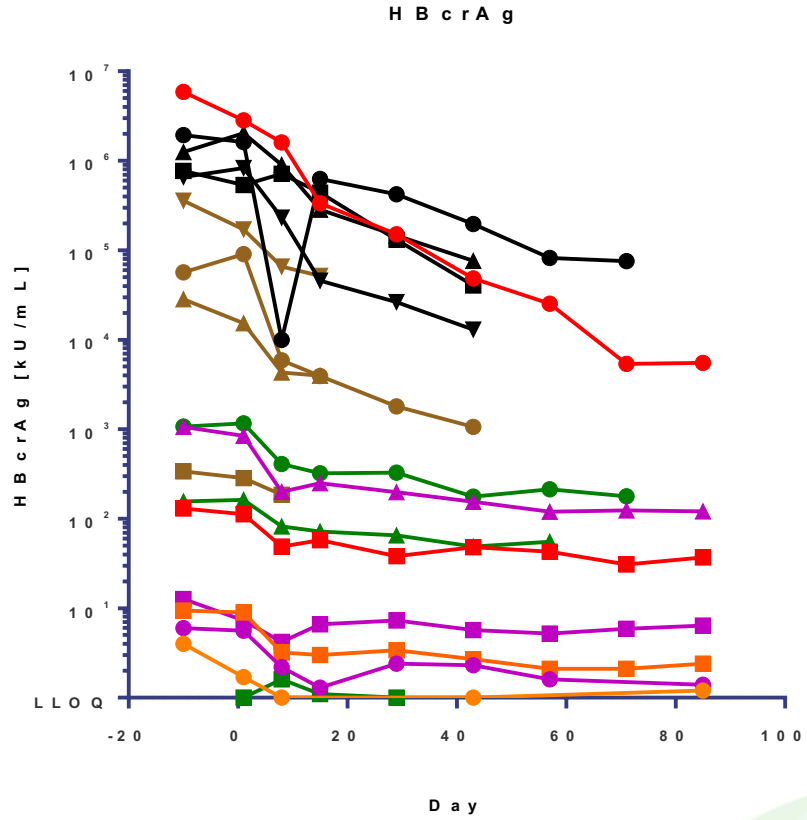


Colors in graphs indicate cohorts as follows: Red (C2b), orange (C3b), purple (C4b), green (C5b), black (C8), brown (C9)

The Search for HBV / HDV Cure 2018

Individual HBeAg and HBcrAg Also Showing Response





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The Search for HBV / HDV Cure 2018

Adverse Events mostly mild without dose related pattern

AEs reported in ≥ 2 CHB patients

AROHBV1001 HBV Patients AE Reported Terms	Cohort 2b Open Label n = 8	Cohort 3b Open Label n = 8	Cohort 4b Open Label n =8	Cohort 5b Open Label n = 8	Cohort 6 Open Label n = 4	Cohort 7 Open Label n = 4	Cohort 8 Open Label n = 4	Cohort 9 Open Label n = 4	Cohort 10 Open Label n = 4	Cohort 11 Open Label n = 4	
Sore Throat, URTI	1	3	3	3	1	1	1	1	2	1	17
Injection Site Erythema/Redness, Very mild Erythema, Injection Site Rash, Injection Site Hematoma/Bruising, IS Pain			3	2		2	2	1		2	12
Headache			2	1		1			1	1	6
Raised or Elevation in Creatine Kinase			2			2	1				5
Lower Back Ache/Pain			1			2	1				4
Acne, Facial Acne							2				2
Bronchitis, Viral Bronchitis						1			1		2
Diarrhea, Intermittent Diarrhea			1	1							2
Pain in abdomen, Intermittent Right Upper Quadrant Pain		1		1							2
Insect Bites ankles, Flea Bites neck	1		1								2
Dizzy, Light headedness	1									1	2
Hot flush				1					1		2
Presence of calcium oxalate crystals in urine		1				1					2
Dry cough				1	1						2
Elevated Blood Pressure, Worsening Hypertension								1		1	2
Other all single occurring terms:											**64 Total**

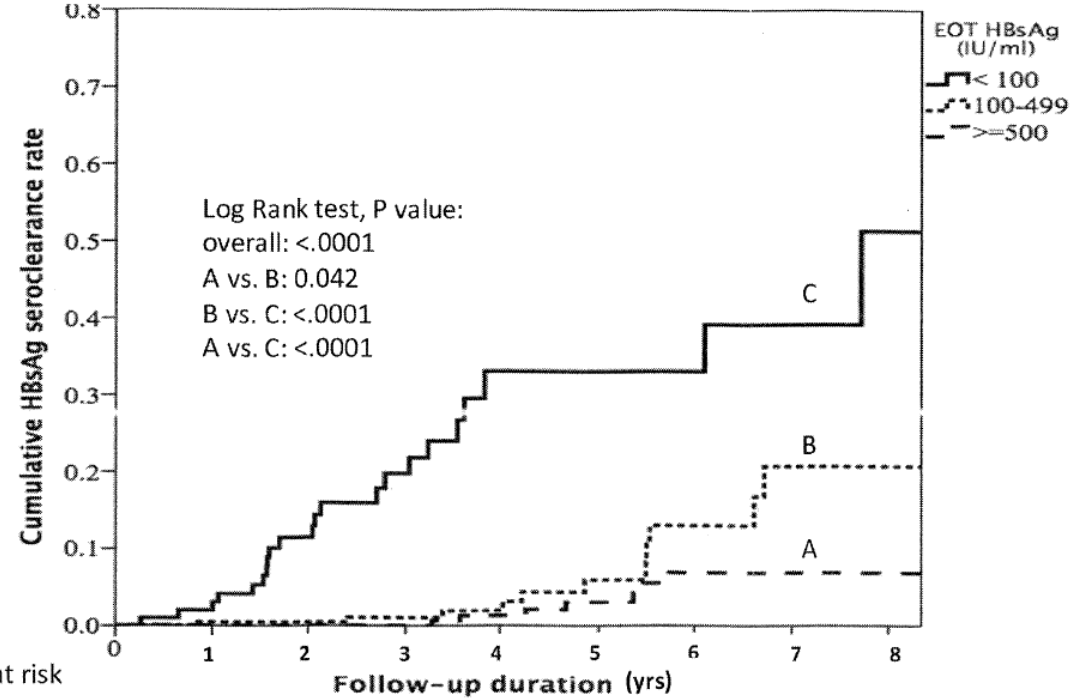
Yuen MF et al. ILC 12 April 2019, PS-080 (as of 3/8/2019)

Early insights for JNJ-3989 plus NUC effects

- Strong activity against HBsAg and other viral products (when measurable)
  - Regardless of HBeAg status, prior NUC exposure or genotype
- Tolerability profile looking favorable
  - Mild injection site reactions most prominent (about 10% of injections)
  - No dropouts due to AEs or severe AEs
  - 2 non-drug related SAEs to date (menorrhagia and anxiety with depression)
- Current data is for 3 doses only
  - Longer treatment durations and combination therapy eagerly awaited

What else merits some discussion / thought?

Is on-treatment HBsAg level important for HBsAg seroclearance?



Patient at risk

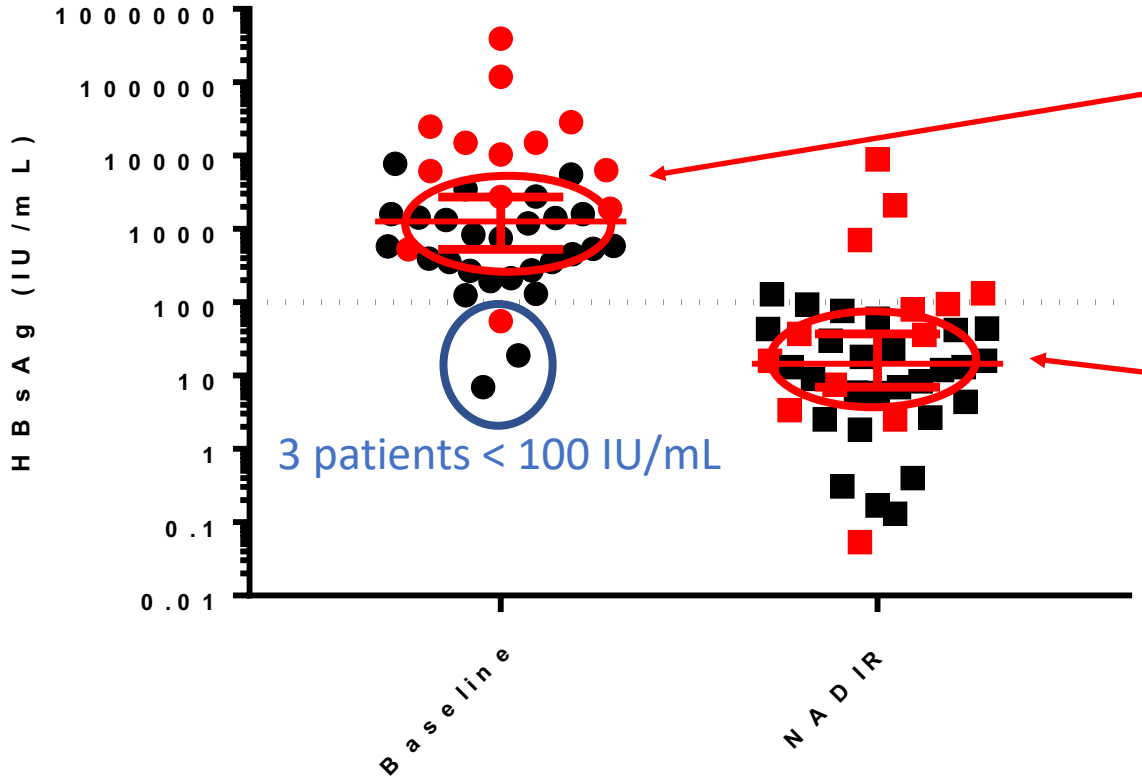
EOT HBsAg (IU/ml)										
A	>=500	303	92	61	39	17	14	12	8	4
B	100-499	274	232	185	129	86	52	30	18	8
C	<100	114	92	61	39	17	13	12	8	4

Yuen MF et al. ILC 12 April 2019, PS-080

HBsAg levels of <100 IU/mL and HBsAg reduction of > 1 Log10 IU/mL have been associated with increased probability of HBsAg seroclearance after cessation of NUCs in HBeAg negative patients [1]

[1] Jeng et al. 2018 Hepatology 68:425-434

Distribution of quantitative HBsAg pre and post 3 doses of JNJ-3989



Baseline

Median: 1263 IU/mL
Min: 7.0 IU/mL
Max: 392,800 IU/mL

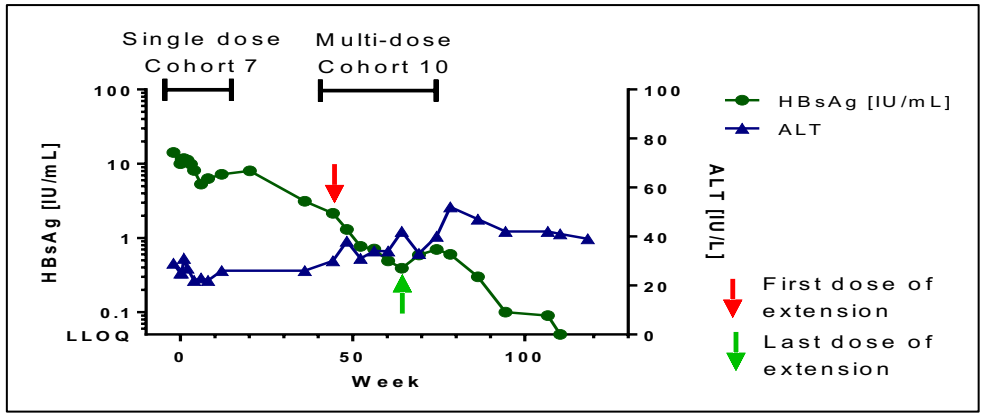
NADIR

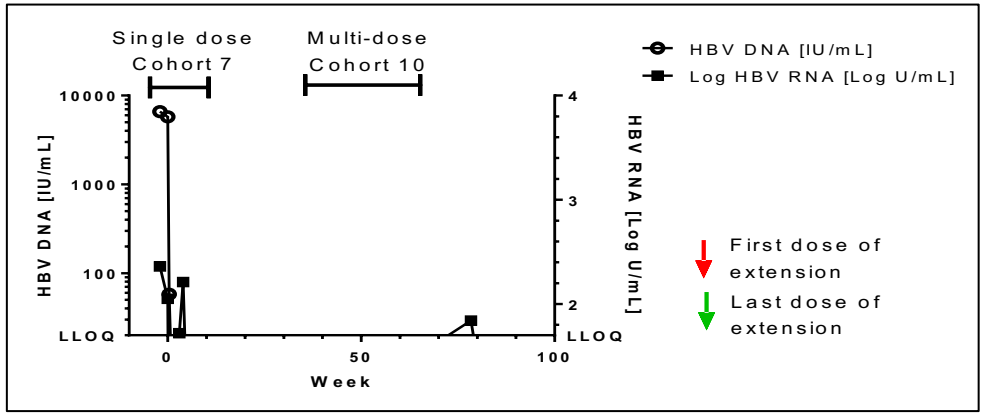
Median: 14.5 IU/mL
Min: 0.05 IU/mL
Max: 8950 IU/mL

Red Points: HBeAg positive patients
Black Points: HBeAg negative patients

Yuen MF et al. ILC 12 April 2019, PS-080

Case study 1: Naïve HBeAg Negative Patient with HBsAg Seroclearance After ARC-520

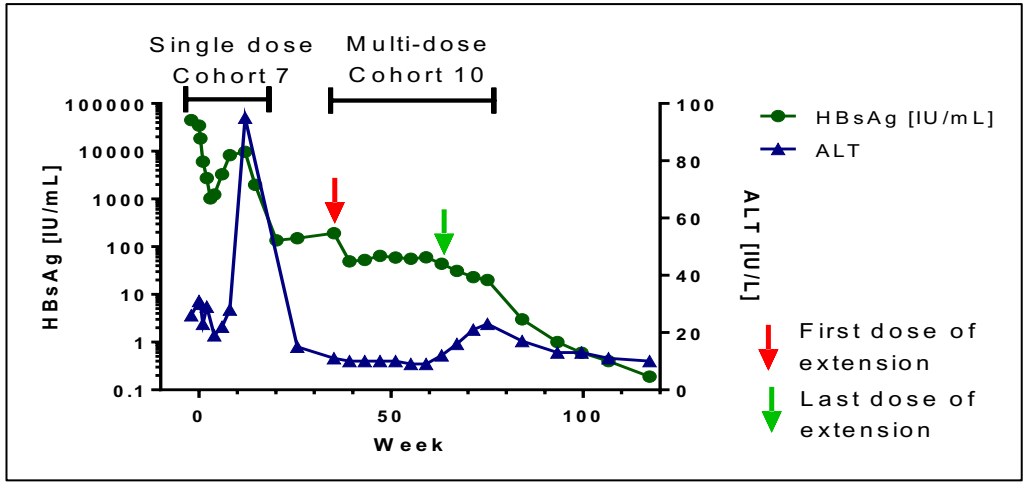


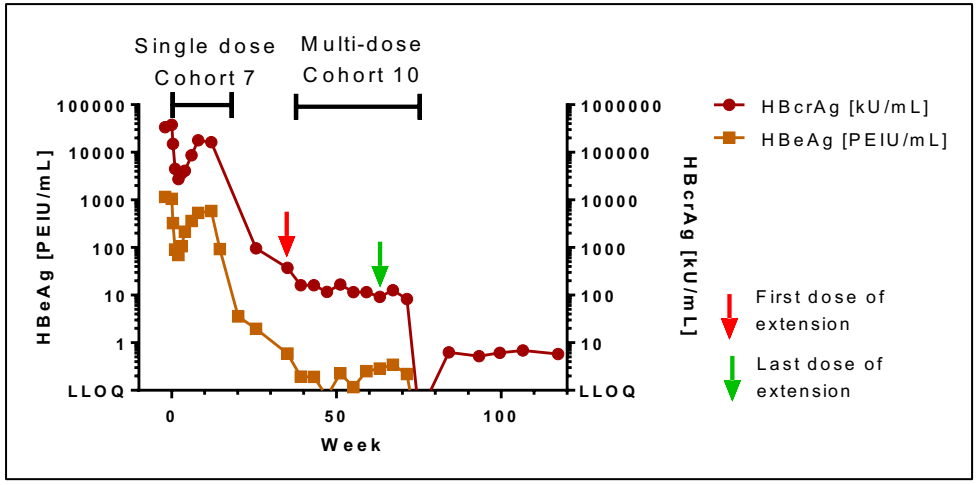


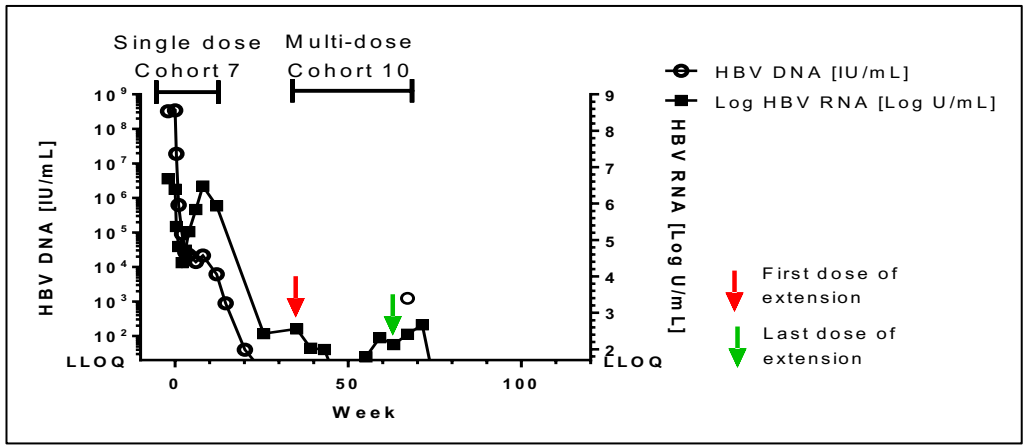
Genotype: B2 adw

- **>2.4** Log10 HBsAg reduction from baseline to BLOQ (HBsAg seroclearance)
- HBcrAg BLOQ throughout the study
- HBV RNA decreased rapidly from a low baseline to BLOQ after single dose of ARC-520 and then remained at or below LLOQ throughout the study
- Rapid reduction of HBV DNA to undetectable levels with ARC-520 plus entecavir
- **Antigen decrease and seroclearance off ARC-520** coincided with a doubling of ALT, consistent with increased host response to virus

Case study 2: Naïve HBeAg Positive Patient with HBsAg Seroclearance After ARC-520







- HBsAg, RNA, HBeAg, HBcrAg all respond to a single dose of ARC-520
- Withdrawal of RNAi associated with host ALT response and reductions in viral parameters
- **This patient ultimately serocleared 26 months after withdrawal of ARC-520**

Some Informed Speculation (My Opinion Only)

- Finite therapy with Interferon and now NUCs has been associated with HBsAg seroclearance rates beyond spontaneous background
  - Often after a few years
- ARC-520 data even with background NUCs continuing looks similar to my eye
- JNJ-3989, representing the current generation of RNAi agents, can reduce all viral components and importantly might get HBsAg in most patients below 100 IU/ml
- True finite therapy, including stopping background NUCs, will be fascinating to watch in the next few years
  - Adding immune stimulation at this point only adds to the anticipation

Acknowledgements

- Patient volunteers
- Investigators, especially MF Yuen for long-term ARC-520 data
- Our Scientific Advisory Board (R. Gish, S. Locarnini, C. Ferrari, C.L. Lai)
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- Our Janssen colleagues