Arrowhead Research
CORPORATION

# AASLD 2015
# Investor Reception Presentation

## San Francisco, CA
## November 16, 2015

# 2015: data-rich year for HBV program

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Long term study in CHB chimps started to read out

Single dose ARC-520 studies in patients read out

Analyst Day September 24, 2015

**ARC-520 de-risked**
**Platform de-risked**
**Changed the HBV textbooks**
**Expanded program: additional candidate**

# Analyst day: summary of emerging story

## Focused on 5 key questions:

- Is ARC-520 safe?
- What did we learn from the chimp study?
- Does the platform work?
- Will ARC-520 work?
- What is the outlook for ARC-520?

AASLD presentations are first opportunities to provide hard data supporting our summary and conclusions

# Is ARC-520 Safe?

- 84 humans have had single doses (or 2x2 mg/kg 2 weeks apart in six patients)
  - No AEs rated as serious or severe
  - No signs of end organ toxicity
  - No discontinuations due to AEs
- 9 chimps received 6 - 11 monthly doses ARC-520
  - No signs of any toxicity

ARC-520 has been well tolerated

# Treatment emergent AEs in Heparc-2001

| Adverse Event | 1 mg/kg n=6 | 2 mg/kg n=6 | 3 mg/kg n=6 | 4 mg/kg n=24 | 2 mg/kg x2; n=6 | PBO n=10 |
|---|---|---|---|---|---|---|
| All | 1 | 5 | 1 | 2 | 1 | 0 |
| Extravasation | | 1 mild | | | | |
| Malaise | | 1 mod | | | | |
| Influenza | 1 mild | | | | | |
| Blood CK increase | | 1 mild | | | | |
| Diabetes Mellitus | | 1 mild | | | | |
| Pain in extremity | | | 1 mild | | | |
| Presyncope | | 1 mod | | | | |
| Headache | | | | 1 mild | | |
| Dizziness | | | | 1 mild | | |
| Fever | | | | | 1 mild | |

All reported AEs were deemed unrelated to ARC-520 by PI

# What did we learn from the chimp study?

**1.** ARC-520 leads to deep HBsAg reduction

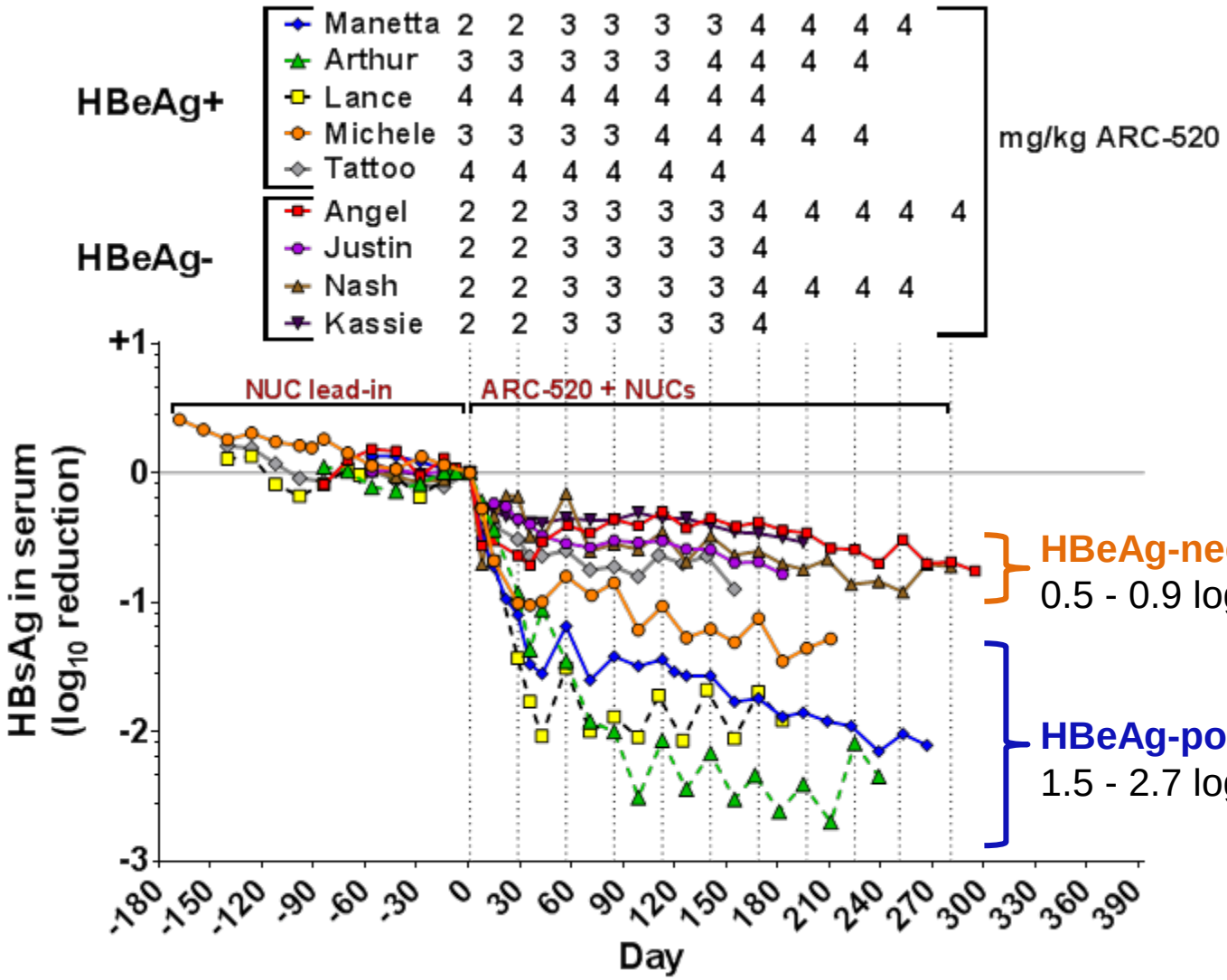
| HBeAg status | HBsAg mean peak KD |
|---|---|
| HBeAg(+): 4 chimps | 99% (2 log) |
| HBeAg(-): 4 chimps | 81% (0.7 log) |
| HBeAg transitional: 1 chimp | 87.4% (0.9 log) |

**2.** Evidence of immune reactivation in 2 of the 4 HBeAg(+) chimps and 1 achieved sustained virologic response (SVR) off therapy

**3.** We concluded that different responses due to decrease of cccDNA during lifecycle of virus: HBsAg increasingly expressed by integrated DNA

Deep KD with ARC-520 and new paradigm for lifecycle of virus

# Deep reductions in HBsAg correlate with HBeAg status




**HBeAg-negative**
0.5 - 0.9 $\log_{10}$ reduction at nadir

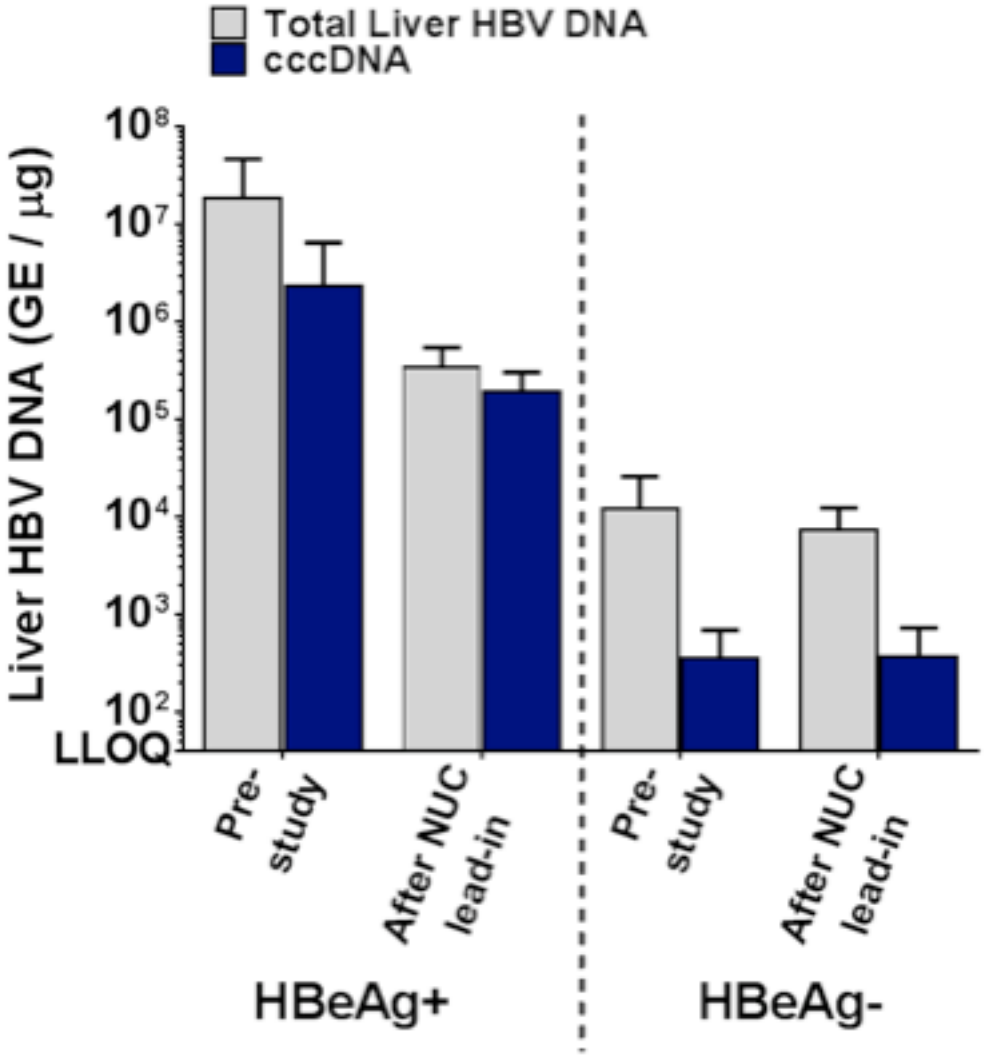
**HBeAg-positive**
1.5 - 2.7 $\log_{10}$ reduction at nadir

# Evidence for immune re-activation in two chimps with chronic dosing

- 2 of 4 HBeAg positive chimps developed evidence on biopsy of cytokine activation in the pattern expected for immunological de-repression
- One of these chimps had an on-treatment flare and shows ongoing viral suppression following withdrawal of all therapy

Immune re-activation will be presented in detail at HepDart in December

# Predominant form of liver HBV DNA differs in HBeAg- vs. HBeAg+




- On NUCs, most of HBV DNA of HBeAg+ chimps is cccDNA
- 500-fold less cccDNA in HBeAg- compared to HBeAg+
  - Only 5% of total HBV DNA in liver of HBeAg- was cccDNA
  - Liver DNA levels in HBeAg- were negligibly affected by NUCs

**Conclusion:**

**DNA profile in HBeAg- chimps is consistent with a high proportion of HBV DNA existing as integrated copies in the host genome**

# HBeAg- chimps have fewer pre-core/core transcripts than HBeAg pos chimps

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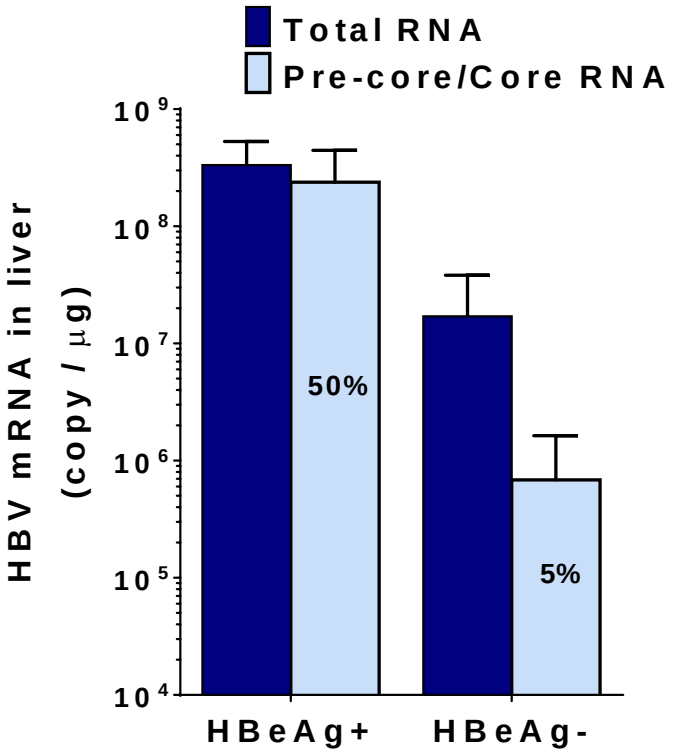
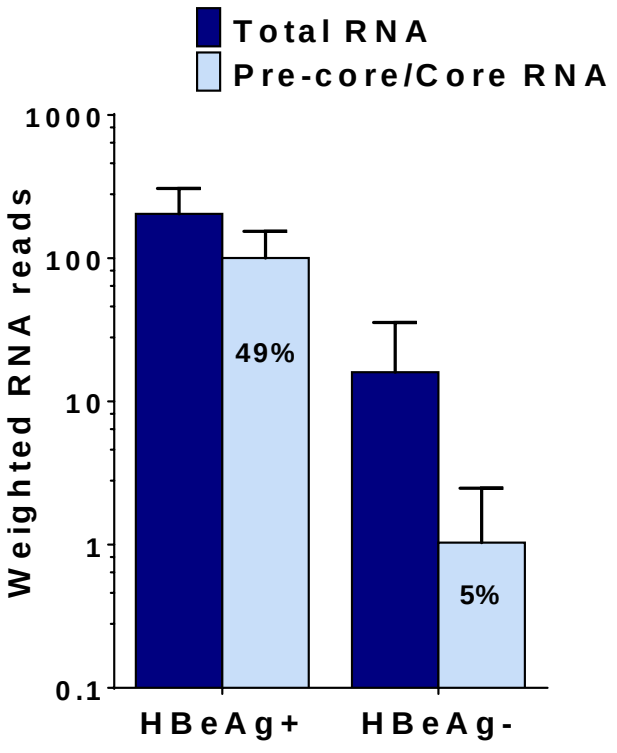
## RT-qPCR analysis

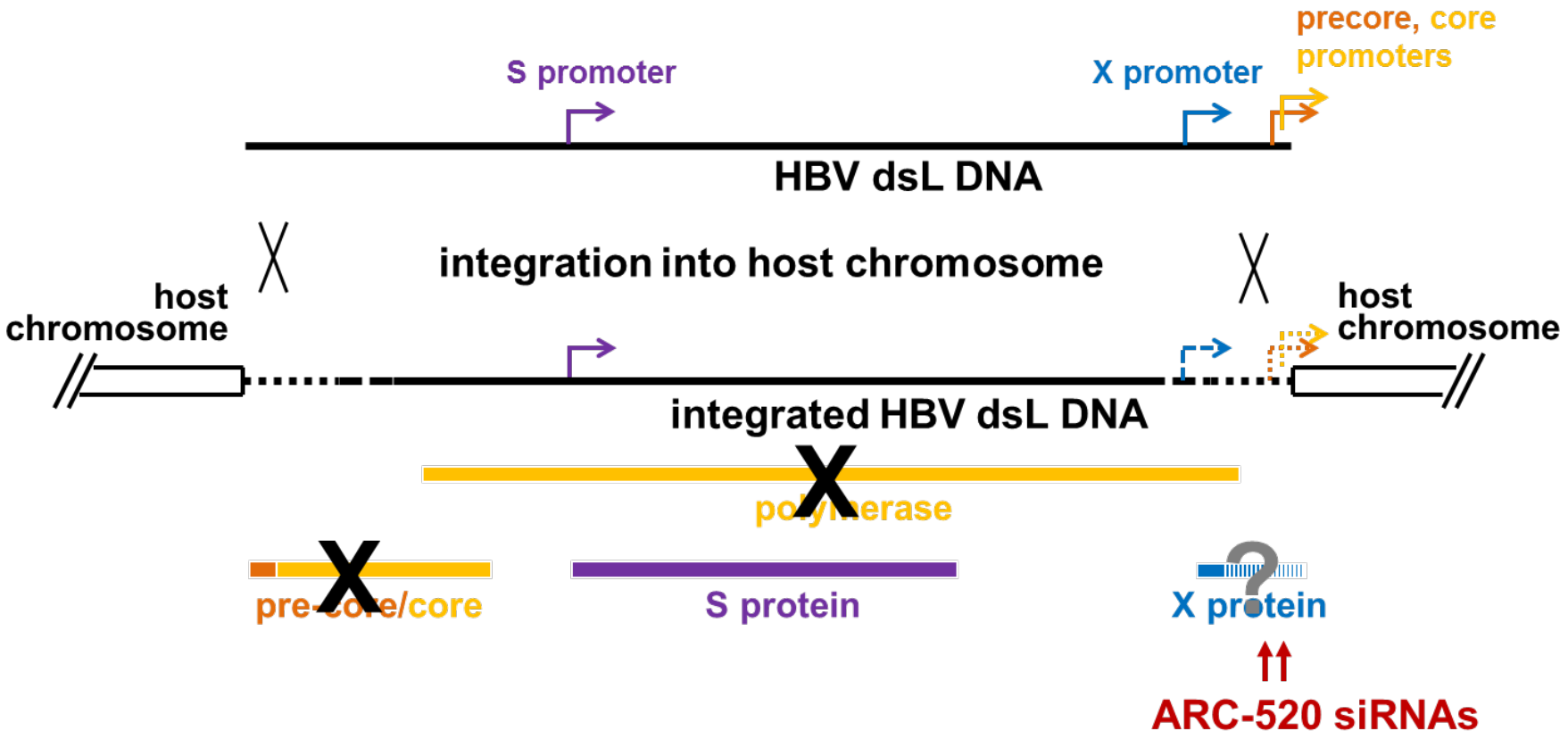



## mRNA deep sequencing



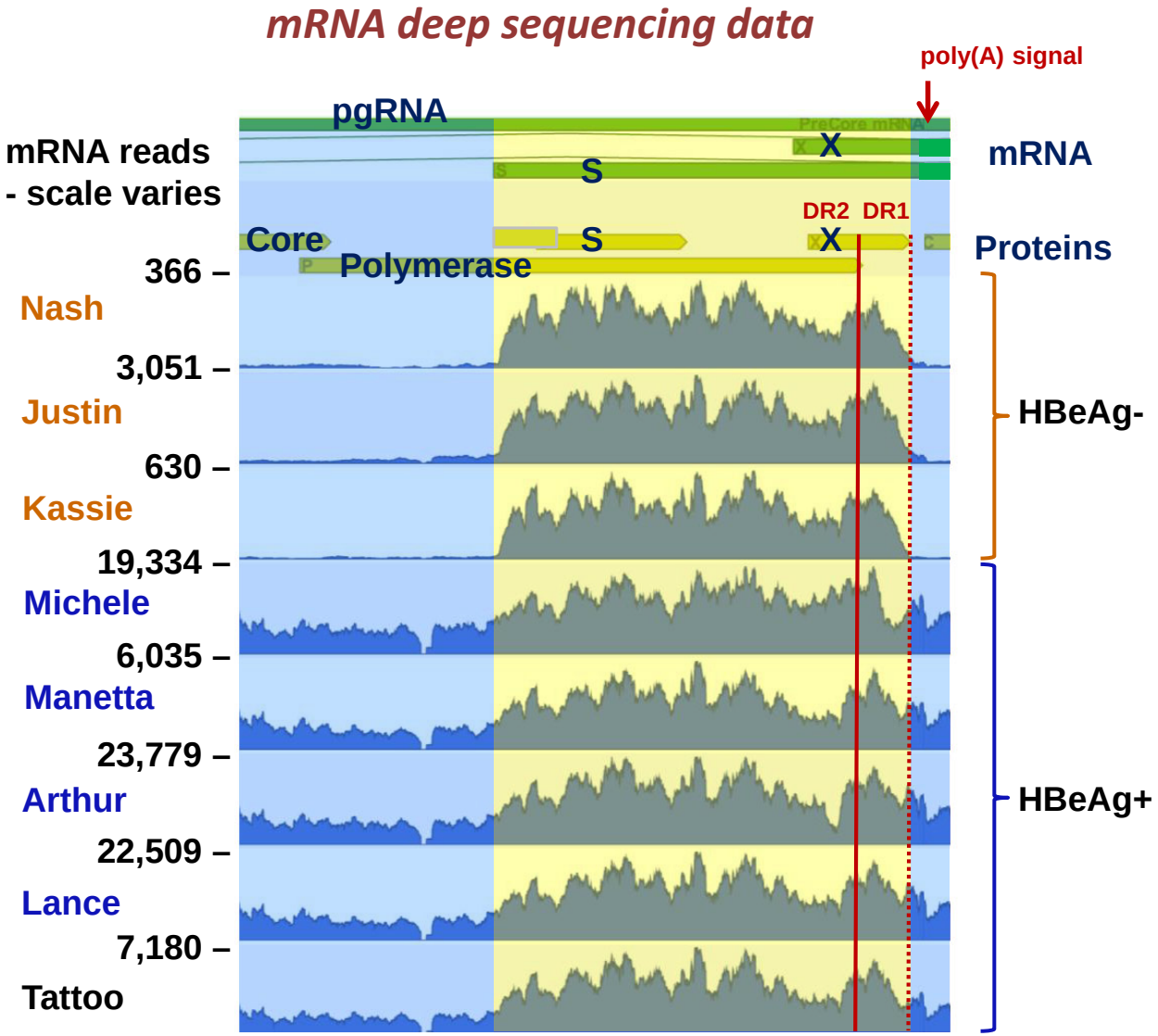

10-fold more transcripts in HBeAg+ than HBeAg-

# Process of HBV dsL DNA integration and theoretical production of HBsAg

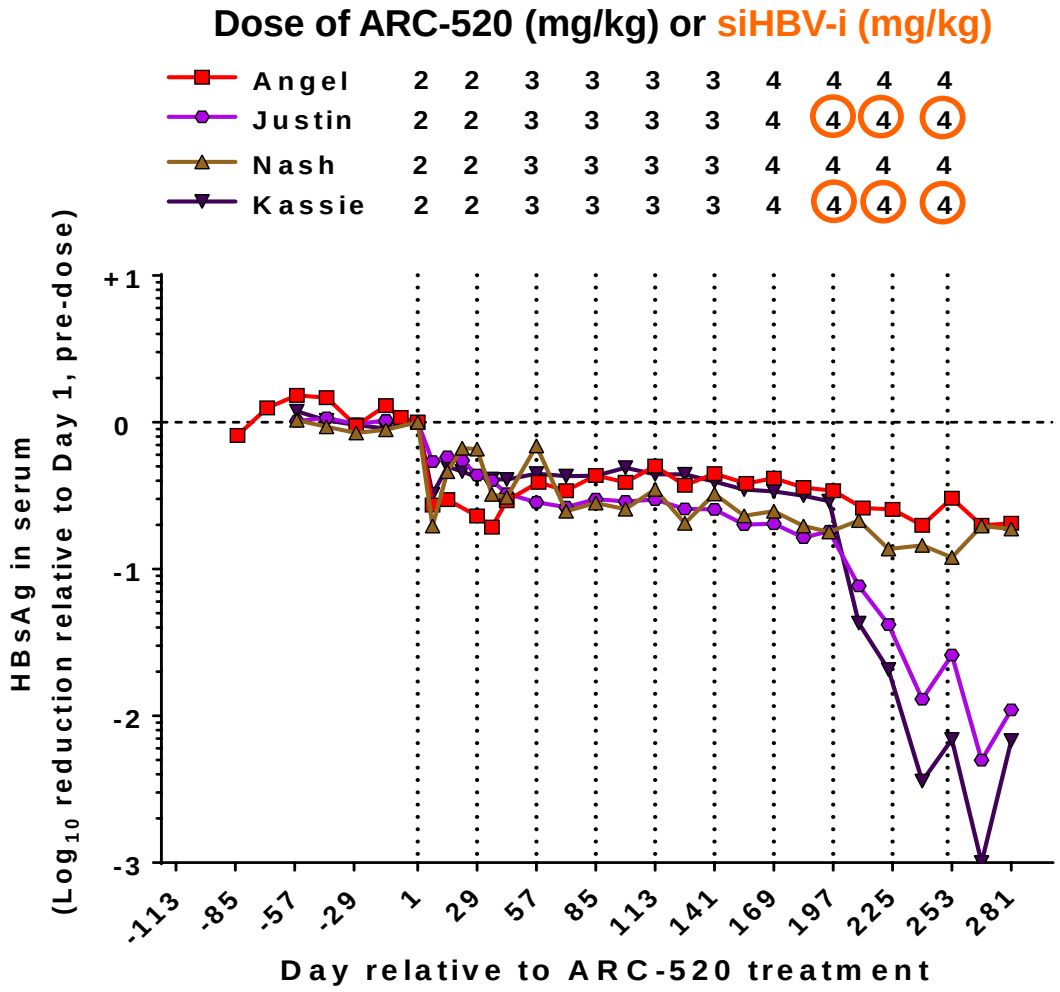



- Integrated DNA allows for expression of primarily HBsAg
  - Expression of truncated X protein also possible
- Explains persistent HBsAg expression despite low cccDNA in HBeAg- chimps
- Loss of ARC-520 target sites explains lower HBsAg KD in HBeAg- chimps

# HBV transcript profiles differ between HBeAg- and HBeAg+ chimps



# RNAi triggers directed to expression from integrated DNA in HBeAg- chimps




- siRNA with target sequence outside of DR1-DR2 (siHBV-i) was designed to target HBV RNA expressed from integrated HBV DNA.
- siHBV-i was administered to two HBeAg- chimps once a month for 3 months following ARC-520 therapy.
- siHBV-i gave deep reductions in HBsAg in HBeAg- chimps, similar to those observed using ARC-520 in HBeAg+ chimps.

RNAi triggers targeting expression from integrated DNA produce deep KD in HBeAg- chimps

# Back to the clinical program
# Does the platform work in HBV patients?

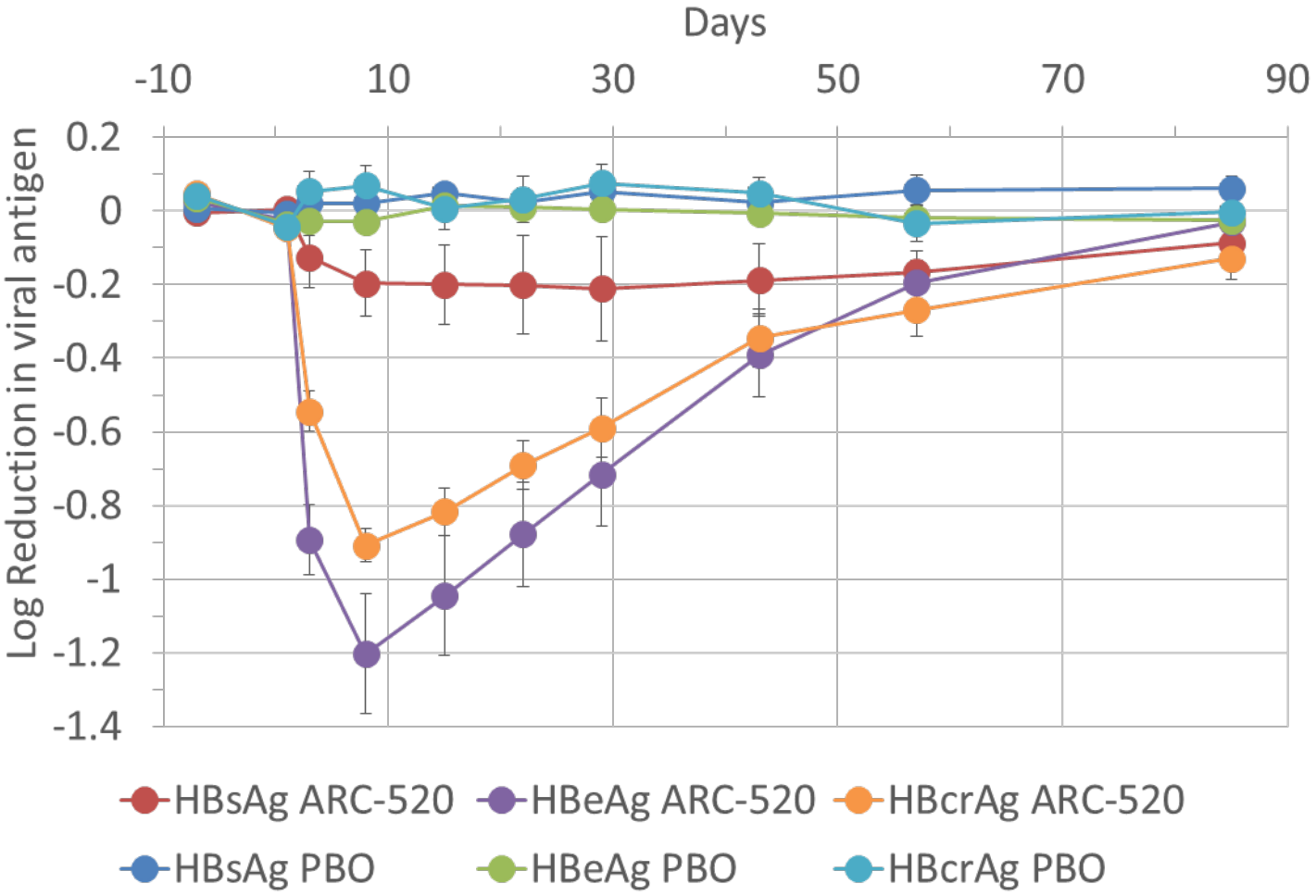
- The integrated DNA story made this question unanswerable with HBsAg in treatment experienced patients
- The answer in humans came from looking at HBeAg and HBcrAg levels in treatment experienced patients and HBsAg in naïve, HBeAg positive patients

# Heparc-2001 explored four HBV groups

- Treatment experienced (2-8 years prior entecavir)
  - HBeAg negative
  - HBeAg positive
- Naïve to prior treatment
  - HBeAg negative
  - HBeAg positive

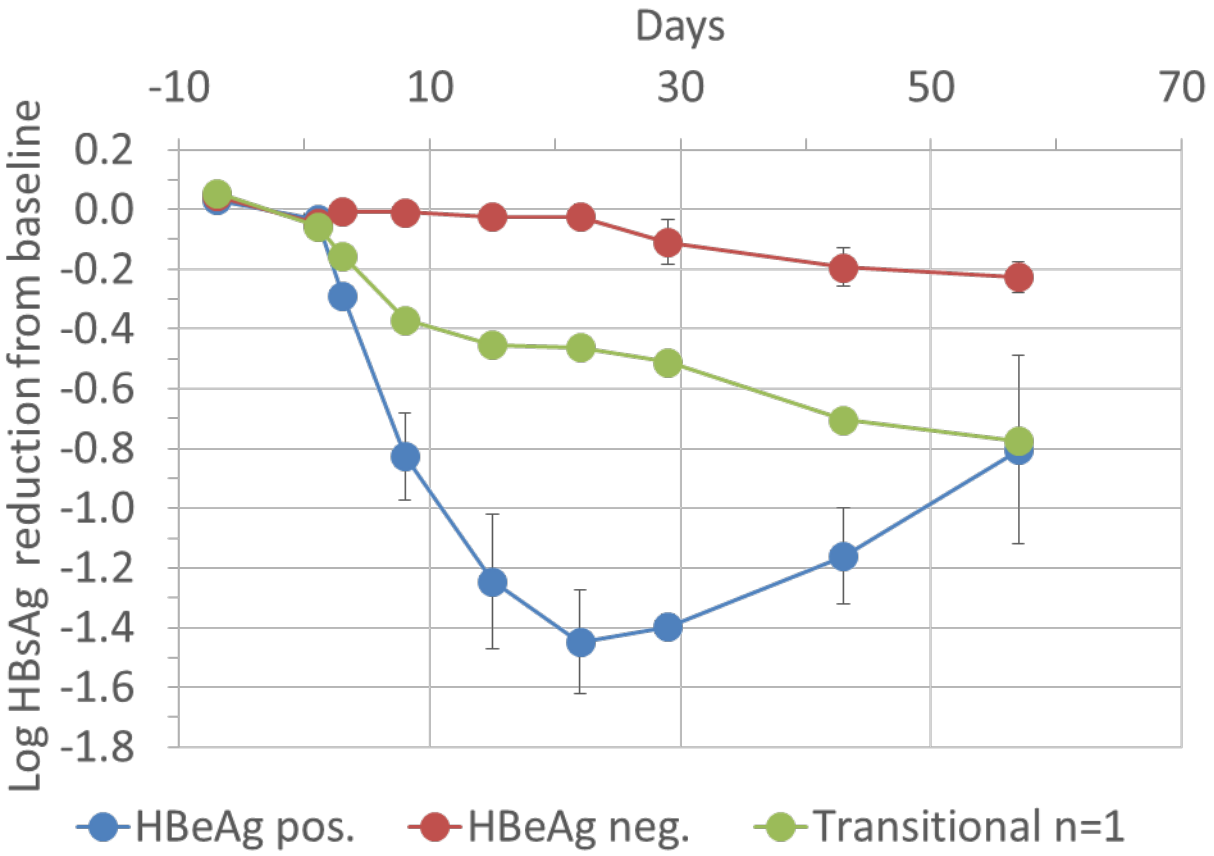
| Cohort | Prior ETV | Pat Type | ARC-520 dose | Active / PBO | Baseline HBsAg mean (range)‡ | Status |
|---|---|---|---|---|---|---|
| 1 | Yes** | HBeAg neg | 1.0 mg/kg | 6/2 | 3.4 (3.0-4.2) | Complete/Unblinded |
| 2 | Yes** | HBeAg neg | 2.0 mg/kg | 6/2 | 3.5 (3.2-4.3) | Complete/Unblinded |
| 3 | Yes** | HBeAg neg | 3.0 mg/kg | 6/2 | 3.6 (3.1-4.0) | Complete/Unblinded |
| 4 | Yes** | HBeAg neg | 4.0 mg/kg | 6/2 | 3.4 (3.2-4.0) | Complete/Unblinded |
| 5 | Yes** | HBeAg pos | 4.0 mg/kg | 6/2 | 3.6 (3.1-4.2) | Complete/Unblinded |
| 6* | Yes** | HBeAg pos | 2 x 2.0 mg/kg | 6/0 | 3.3 (3.0-3.6) | Complete/Open label |
| 7 | No | HBeAg pos<br>HBeAg neg | 4.0 mg/kg | 6/0<br>6/0 | 4.4 (3.1-4.9)<br>2.9 (0.8-3.6) | Ongoing / Open label |

# Deep HBeAg and HBcrAG KD in cohort 5




The platform works

# Deep and durable HBsAg KD in treatment naïve patients




Transitional patient was HBeAg-pos. at baseline and HBeAg negative at days 3 to 43

Consistent with our hypothesis that HBeAg-pos, treatment naïve patients would be cccDNA driven

# Max reductions in viral antigens

| | | | | Log reduction from baseline Mean (max) | | |
|---|---|---|---|---|---|---|
| Cohort | Dose [mg/kg] | HBeAg status | Prior ETV | HBsAg | HBcrAg | HBeAg |
| 1 | 1 | Neg | Y | -0.2 (-0.3)* | -0.2 (-0.2) | N/A |
| 2 | 2 | Neg | Y | -0.2 (-0.3)* | -0.5 (-0.5) | N/A |
| 3 | 3 | Neg | Y | -0.3 (-0.4)* | -0.4 (-0.7) | N/A |
| 4 | 4 | Neg | Y | -0.4 (-0.5)* | -0.9 (-1.1) | N/A |
| 5 | 4 | Pos | Y | -0.3 (-0.7)* | -0.9 (-1.1) | -1.2 (-1.7) |
| 6‡ | 2x2 | Pos | Y | -0.5 (-0.8)+ | -0.7 (-1.2) | Pending |
| 7‡,† | 4 | Pos | N | -1.5 (-1.9)+ | Pending | Pending |
| 7‡ | 4 | Neg | N | -0.2 (-0.4)+ | Pending | N/A |

- Best HBsAg reduction was seen in naïve HBeAg-pos patients
- HBeAg-pos, ETV experienced patients had substantially higher reductions in HBeAg and HBcrAg compared to HBsAg
- HBeAg-neg., ETV experienced patients showed a dose response in HBcrAg; qHBsAg dose response was less pronounced
- Divided doses at 4 mg/kg were similar to a single dose

# ARC-520 key points

- Well tolerated
- Deep KD in treatment-naïve HBeAg+ patients
  - Max 99% HBsAg KD (1.9 log); mean nadir 97% (1.5 logs)
  - Highest single dose KD ever reported in humans using RNAi
- Clearly disrupts virus in NUC-experienced and HBeAg- patients
  - >1 log KD of HBeAg, HBcrAg, and presumably others
  - ARC-520 intended for multi-dose therapy: sustained measurable HBsAg KD and very deep KD of **all** other antigens could be important to reaching functional cure

ARC-520 is very potent at silencing cccDNA: could be key component in achieving functional cure

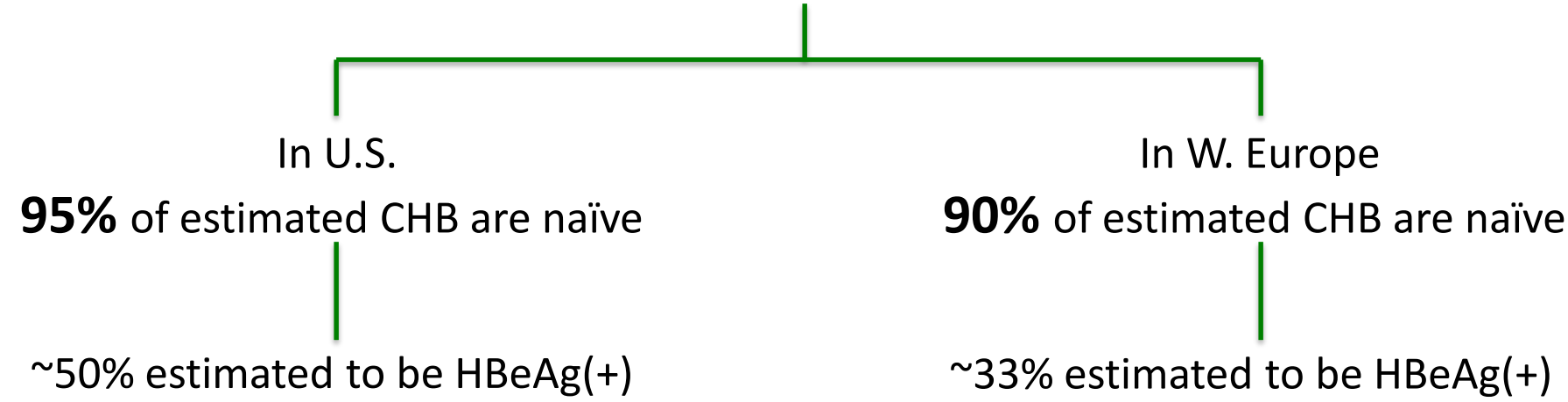
# What is the outlook for ARC-520?

## As expected, HBV will have subpopulations that will respond differently to different treatments

- We identified cccDNA / integrated DNA as determinant of a subgroup
  - ARC-520 is well tolerated and deeply silences cccDNA
  - NUC-naïve HBeAg(+) patients are richest in cccDNA

Is that a small slice of a huge market?

No, it is a large segment of the chronic HBV (CHB) population






*Proprietary data from Clarion Healthcare, LLC*

# What about the rest of the market?

We have developed an additional candidate to:

(1) Ensure broader coverage of entire market;
(2) Provide 2 shots on goal

| ARC-520 | ARC-521 |
| --- | --- |
| • Optimized for cccDNA KD<br>  • Clarity on KD and safety<br>• >1log KD in all antigens studied<br>• Began multi-dose studies<br>• Combo studies starting in Q4 with first IRB/regulatory approvals in hand | • Safety expected = ARC-520<br>• Optimized to include integrant KD<br>• Validated in chimps<br>  • Multi-log KD<br>• Complement to ARC-520<br>• IND or equivalent by June 2016 |

De-risked program with safety/activity of ARC-520, increased exposure to additional patient populations

# Basic Take Home Points

- So far, single doses in humans and multiple doses in chimpanzees have been well tolerated
- Deep (even single dose record) knockdown has been demonstrated against multiple HBV viral antigens
- Immune awakening has been observed in 2 of 4 HBeAg positive chimps
- ARC-520 will be studied in four subgroups, under multiple doses and in combinations looking for a recipe to produce HBsAg seroclearance
- ARC-521, optimized against cccDNA *and* integrated DNA is in active development with regulatory submissions mid-2016