

# TUNE-401: a first-in-class epigenetic silencer of HBV demonstrates deep and durable antiviral activity in the phase 1b/2a proof of concept Tune-401-001 study

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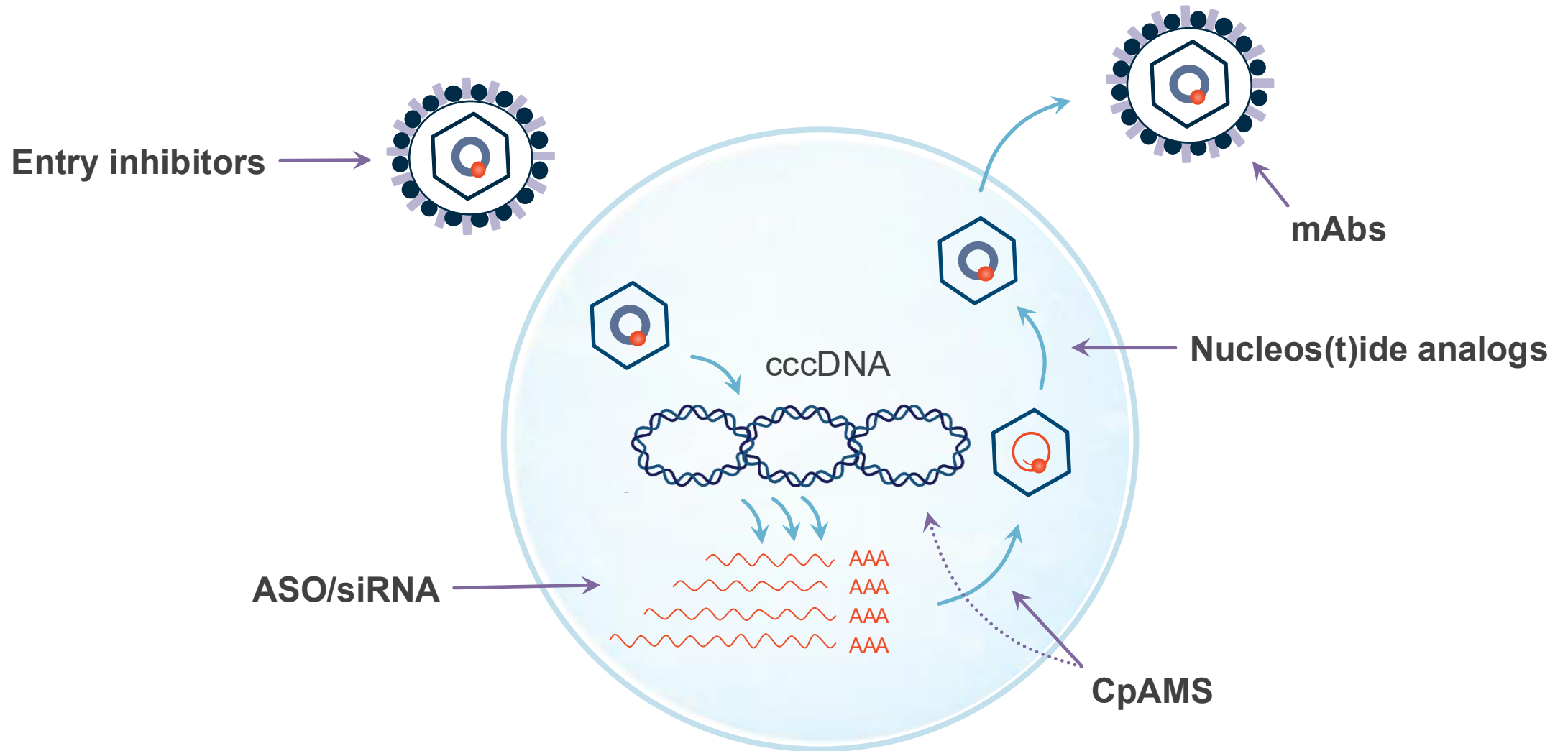
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<sup>7</sup> King's College, London, UK

<sup>8</sup> Queen Mary Hospital, The University of Hong Kong, Hong Kong, China

# cccDNA: The Barrier to HBV Cure

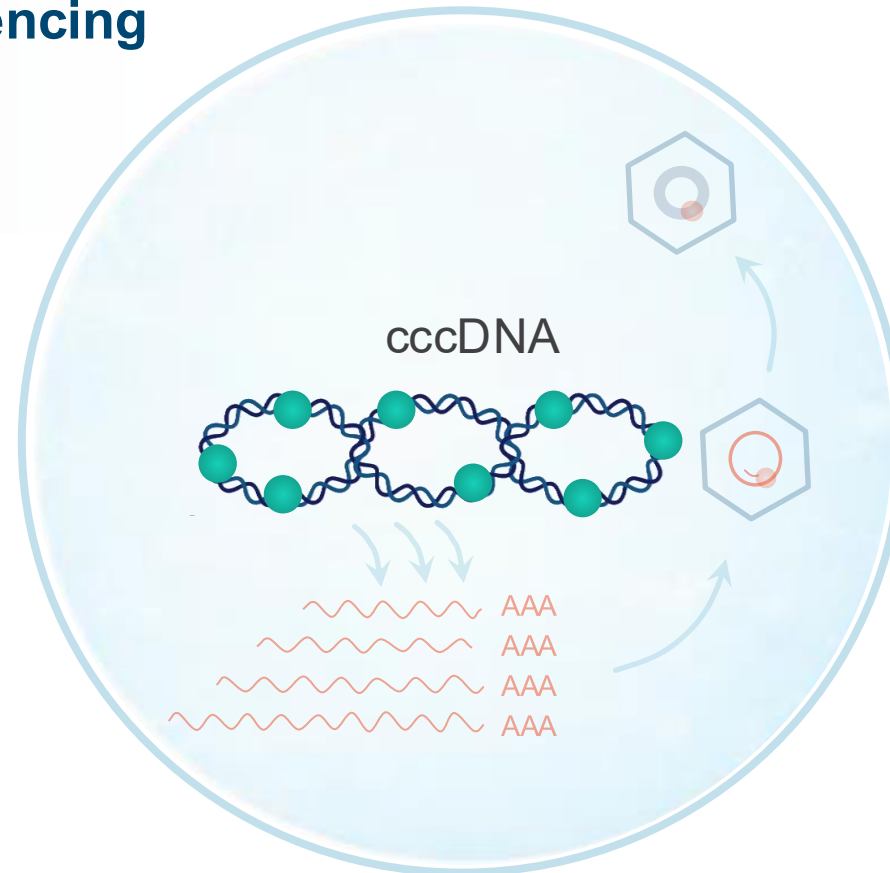
Current HBV antiviral therapies do not directly target the cccDNA reservoir



# cccDNA: The Barrier to HBV Cure

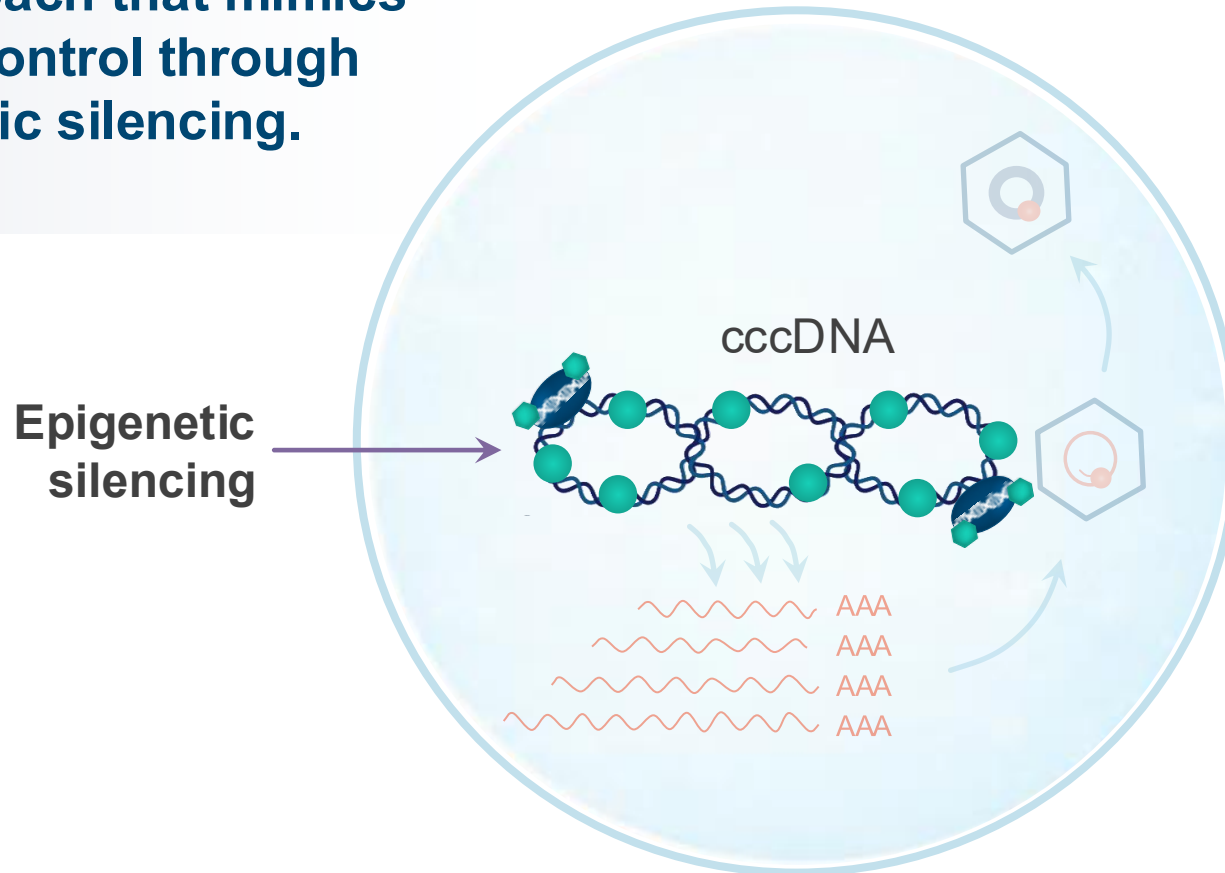
Epigenetic silencing inactivates cccDNA, the source of virus replication

**Durable HBV inactivation occurs naturally via the epigenetic silencing of cccDNA**



# Tune-401: A first-in-class epigenetic silencer of HBV DNA

**Tune-401 represents a novel therapeutic approach that mimics natural cccDNA control through targeted epigenetic silencing.**



**This approach durably silences transcription without cutting or nicking the underlying DNA.**

# Tune-401: A first-in-class epigenetic silencer of HBV DNA

1

Tune-401 LNP is delivered IV

2

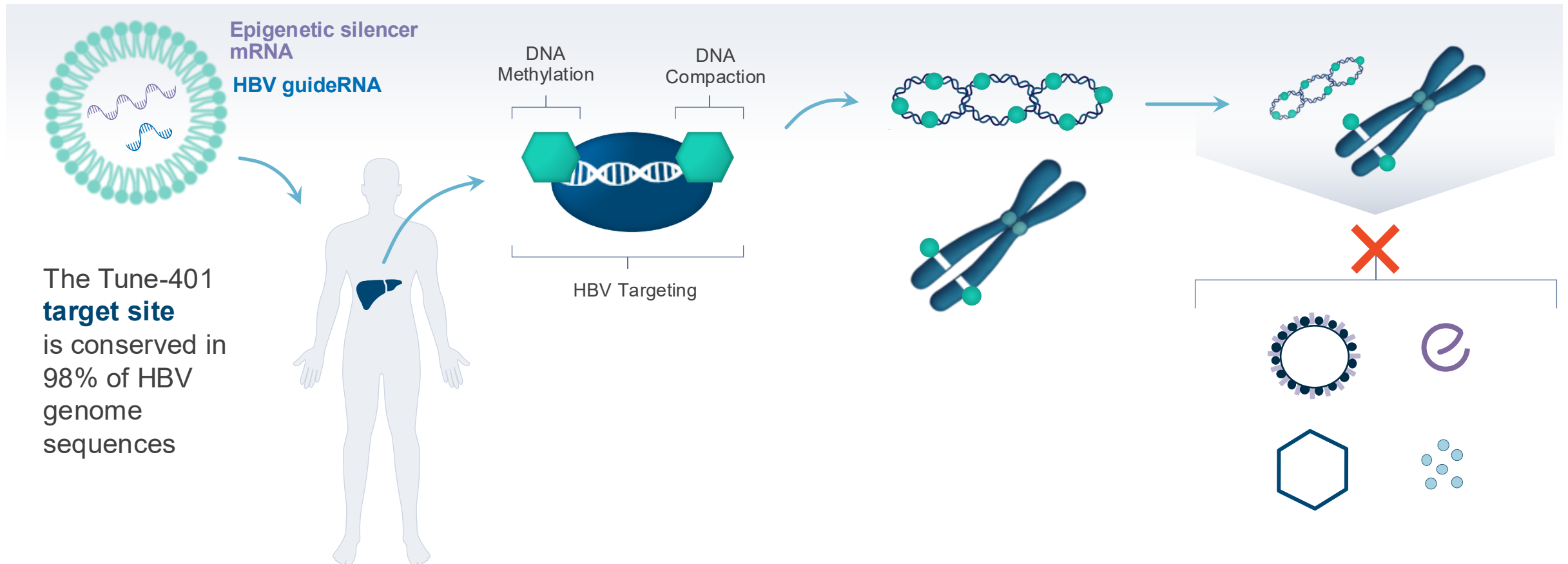
Tune-401 is translated into an HBV silencing protein in liver

3

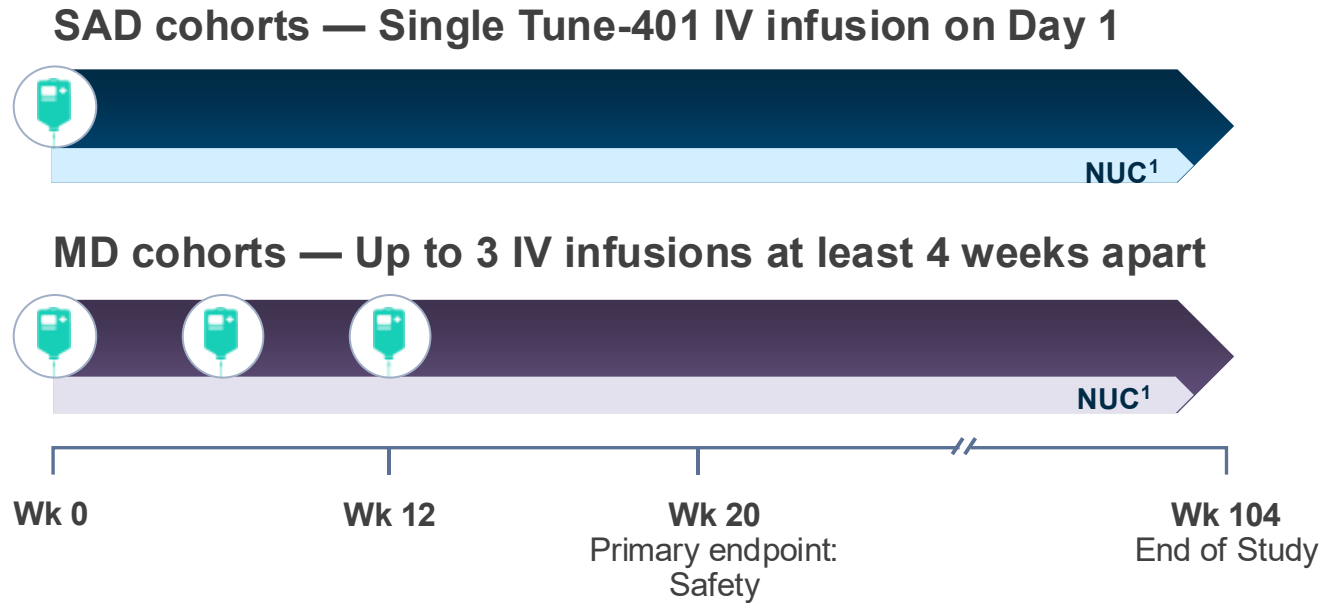
Tune-401 specifically methylates integrated HBV and cccDNA

4

Virus and associated biomarkers are silenced



# Tune-401-001 Phase 1b/2a Study Design



## DOSE ESCALATION

SAD1	0.2 mg/kg
SAD2	0.45 mg/kg
SAD3	0.65 mg/kg
SAD4	0.85 mg/kg
MD3	0.65 mg/kg (x3)

Dose escalation governed by IDMC

**PRIMARY OBJECTIVE:** Safety and tolerability of Tune-401 up to 20 weeks post-dose

**SECONDARY OBJECTIVE:** Antiviral effects of Tune-401

### PREMEDICATIONS:

- Dexamethasone given one day prior to infusion
- Dexamethasone with Paracetamol and H1/H2 blockers immediately prior to infusion
- Intravenous fluids pre- and post-Tune-401 infusion

# Tune-401-001 Phase 1b/2a Inclusion/Exclusion Criteria



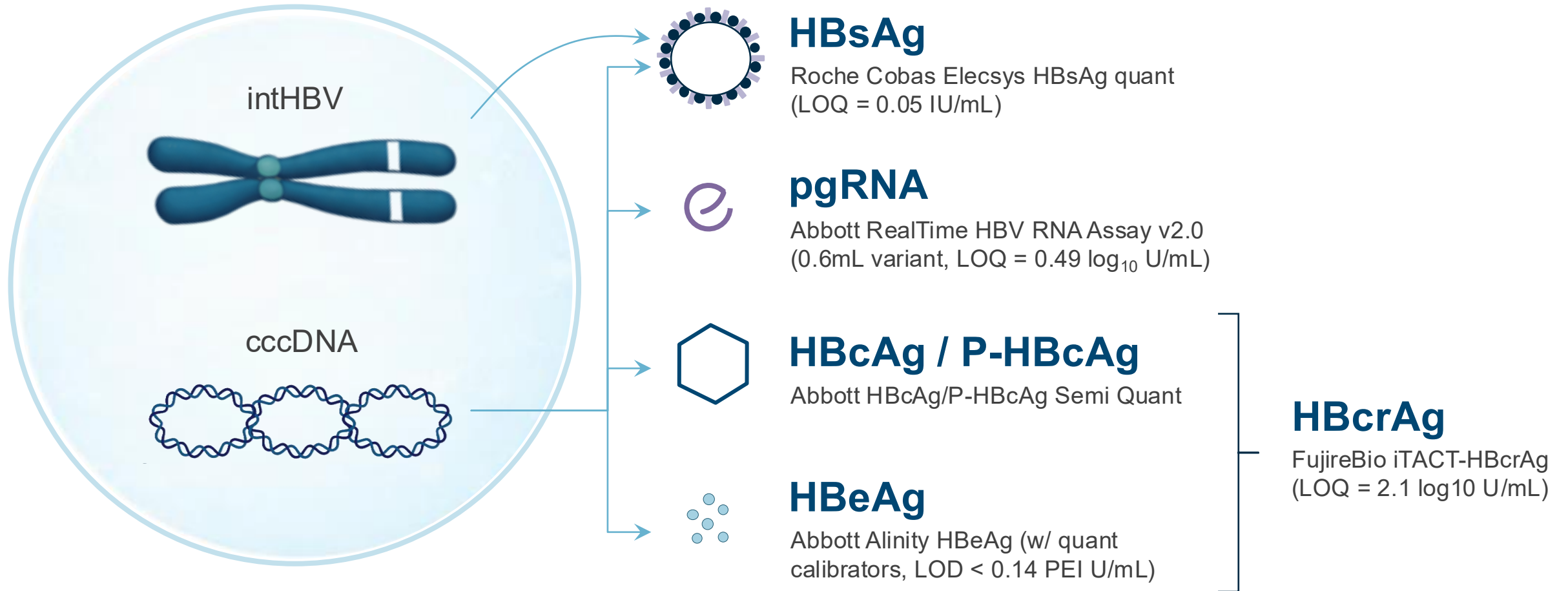
## KEY INCLUSION CRITERIA

- Documented HBV infection > 12 months
- On nucleos(t)ide analogue > 12 months
- HBsAg > 100 IU/ml
- HBV DNA < 90 IU/ml
- HBeAg-negative or positive
- Age 18-75, inclusive
- Body mass index (BMI) > 18.5 kg/m<sup>2</sup>
- Fibroscan ≤8.8 kPa

## KEY EXCLUSION CRITERIA

- Cirrhosis
- Coinfections: HCV, HDV, HIV
- Elevated ALT/AST ≥1.5× ULN
- Elevated bilirubin ≥1.5× ULN
- Low albumin (<3.5 g/dL)
- Recent serious cardiovascular events (MI, stroke, PE, NYHA III/IV HF)
- Recent immunosuppressive therapy
- Experimental HBV therapy within 6 months
- Prior gene therapy

# Efficacy Biomarkers Evaluated in the Tune-401 Study

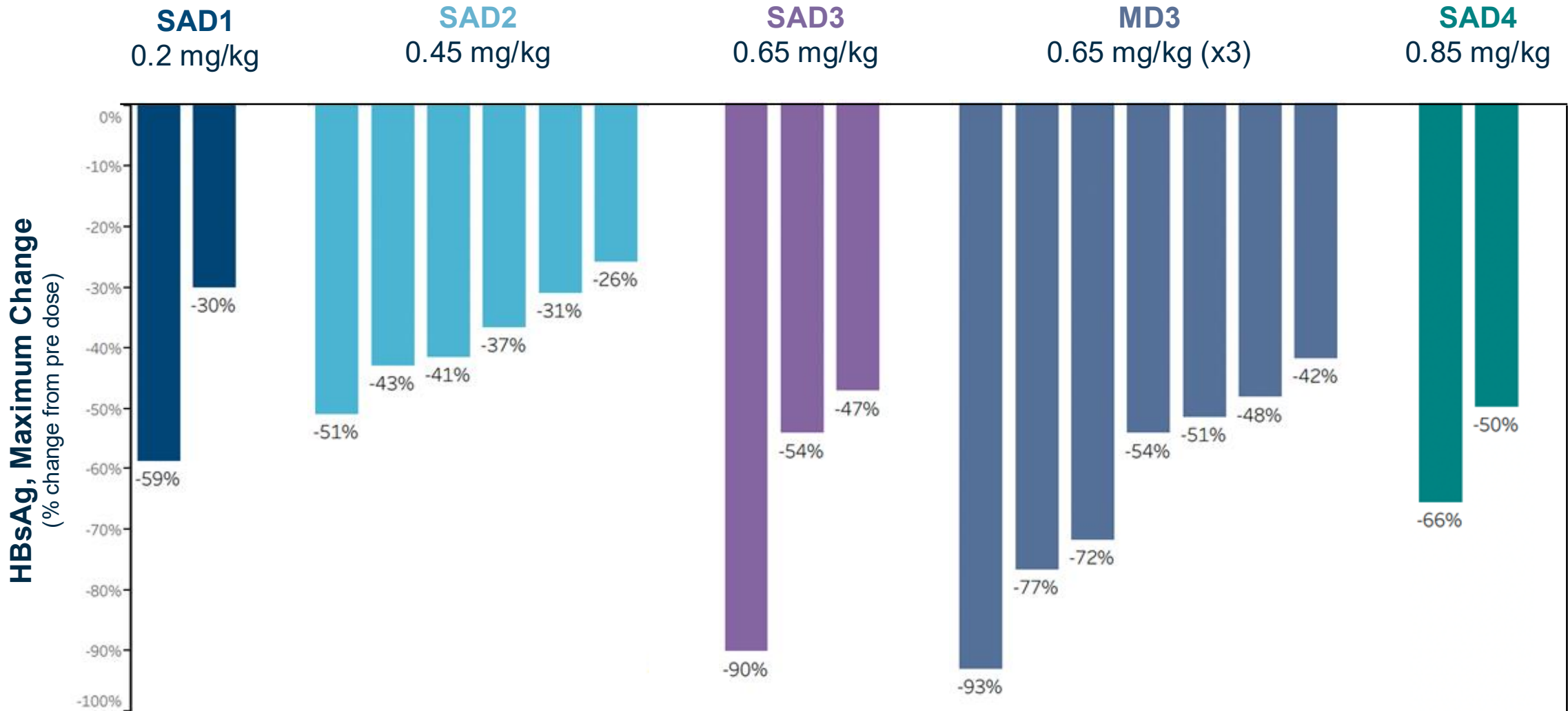


# Results: Baseline Characteristics by Cohort

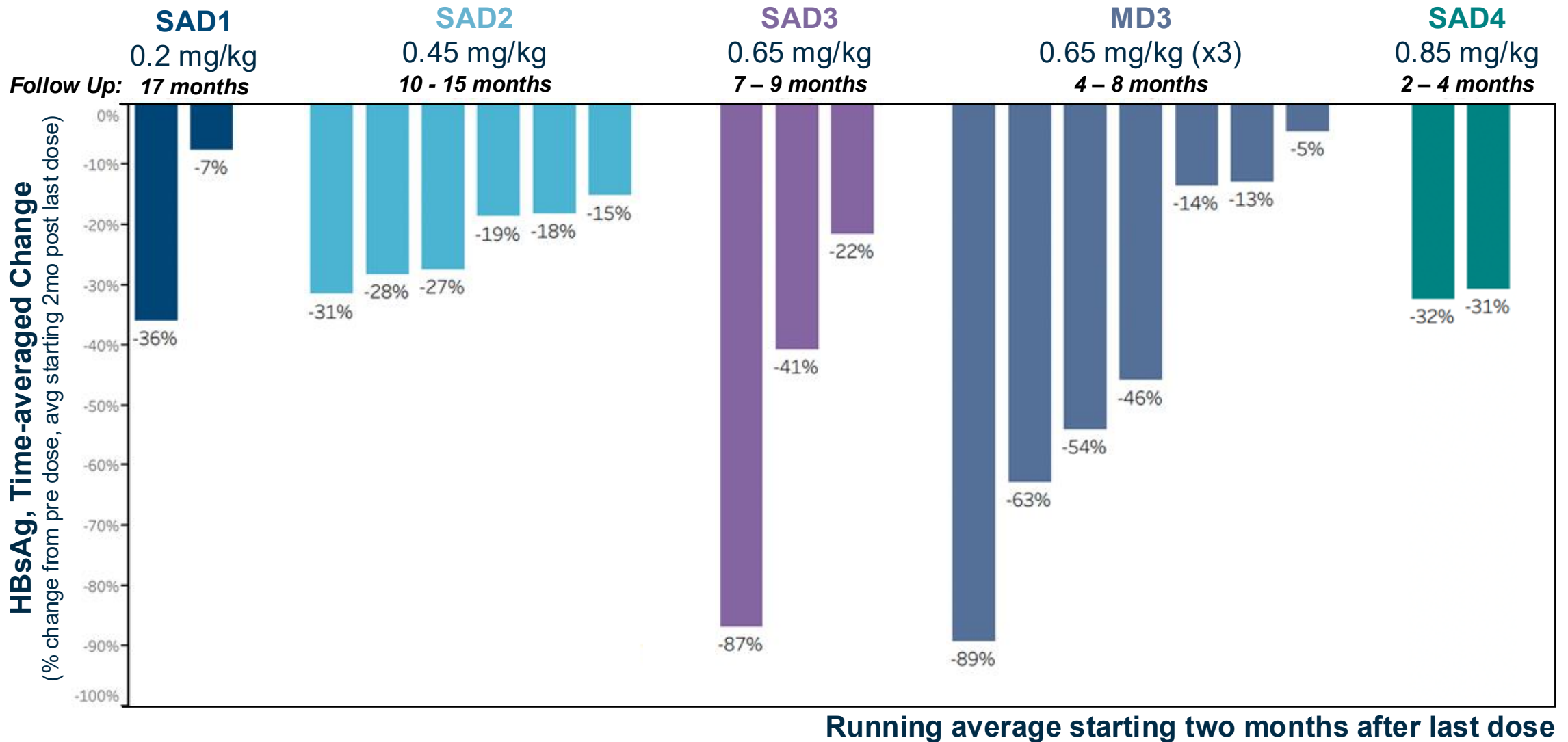


	<b>SAD1</b> 0.2 mg/kg (N=2)	<b>SAD2</b> 0.45 mg/kg (N=6)	<b>SAD3</b> 0.65 mg/kg (N=3)	<b>MD3</b> 0.65 mg/kg x 3 (N=7)	<b>SAD4</b> 0.85 mg/kg (N=8)	<b>Overall</b> (N=26)
<b>(Number of participants)</b>						
<b>Median Age (Range)</b>	<b>53</b> (48 – 58)	<b>51</b> (44 – 60)	<b>54</b> (47 – 56)	<b>47</b> (31– 61)	<b>45</b> (30 – 59)	<b>48.5</b> (30 – 61)
<b>Female, n (%)</b>	<b>0</b> (0%)	<b>3</b> (50%)	<b>1</b> (33.3%)	<b>1</b> (14.3%)	<b>4</b> (50%)	<b>9</b> (35%)
<b>Asian, n (%)</b>	<b>2</b> (100%)	<b>4</b> (66.6%)	<b>1</b> (33.3%)	<b>4</b> (57.1%)	<b>5</b> (62.5%)	<b>16</b> (61.5%)
<b>Median time on NUC, yrs (Range)</b>	<b>5.5</b> (5 – 6)	<b>13</b> (5 – 24)	<b>12</b> (3 – 18)	<b>8</b> (2 – 12)	<b>7</b> (2 – 26)	<b>7.5</b> (2 – 26)
<b>Median ALT at Baseline, U/L (Range)</b>	<b>25.5</b> (11– 40)	<b>20.5</b> (14 – 24)	<b>17</b> (13 – 23)	<b>22</b> (11 – 37)	<b>15.5</b> (12 – 34)	<b>20.5</b> (11 – 40)
<b>HBeAg(+), n (%)</b>	<b>0</b> (0%)	<b>4</b> (66.7%)	<b>1</b> (33.3%)	<b>2</b> (28.6%)	<b>4</b> (50%)	<b>11</b> (42.3%)
<b>Mean HBsAg Baseline, log 10 IU/mL (Range)</b>	<b>3.60</b> (2.94 – 4.25)	<b>3.03</b> (2.32 – 3.53)	<b>3.11</b> (2.31 – 3.56)	<b>3.36</b> (2.37 – 4.19)	<b>3.22</b> (2.72 – 3.78)	<b>3.21</b> (2.31 – 4.25)
<b>Mean pgRNA Baseline, log 10 U/mL (Range)*</b>	<b>2.05</b> (2.05)	<b>3.61</b> (1.16 – 5.09)	<b>3.38</b> (2.43 – 4.87)	<b>2.92</b> (1.64 – 6.21)	<b>3.31</b> (1.65 – 5.88)	<b>3.23</b> (1.16 – 6.21)
<b>pgRNA &gt;LOQ at Baseline, n (%)</b>	<b>1</b> (50%)	<b>6</b> (100%)	<b>3</b> (100%)	<b>7</b> (100%)	<b>7</b> (100%)	<b>24</b> (96%)
<b>Mean HBcrAg Baseline, log 10 U/mL (Range)*</b>	<b>3.3</b> (3.3)	<b>4.52</b> (2.8 – 5.5)	<b>4.6</b> (2.1 – 7.5)	<b>4.70</b> (2.4 – 7.0)	<b>4.6</b> (2.2 – 6.0)	<b>4.54</b> (2.1 – 7.5)
<b>HBcrAg &gt;LOQ at Baseline, n (%)</b>	<b>1</b> (50%)	<b>6</b> (100%)	<b>3</b> (100%)	<b>6</b> (85.7%)	<b>5</b> (100%)	<b>21</b> (91%)

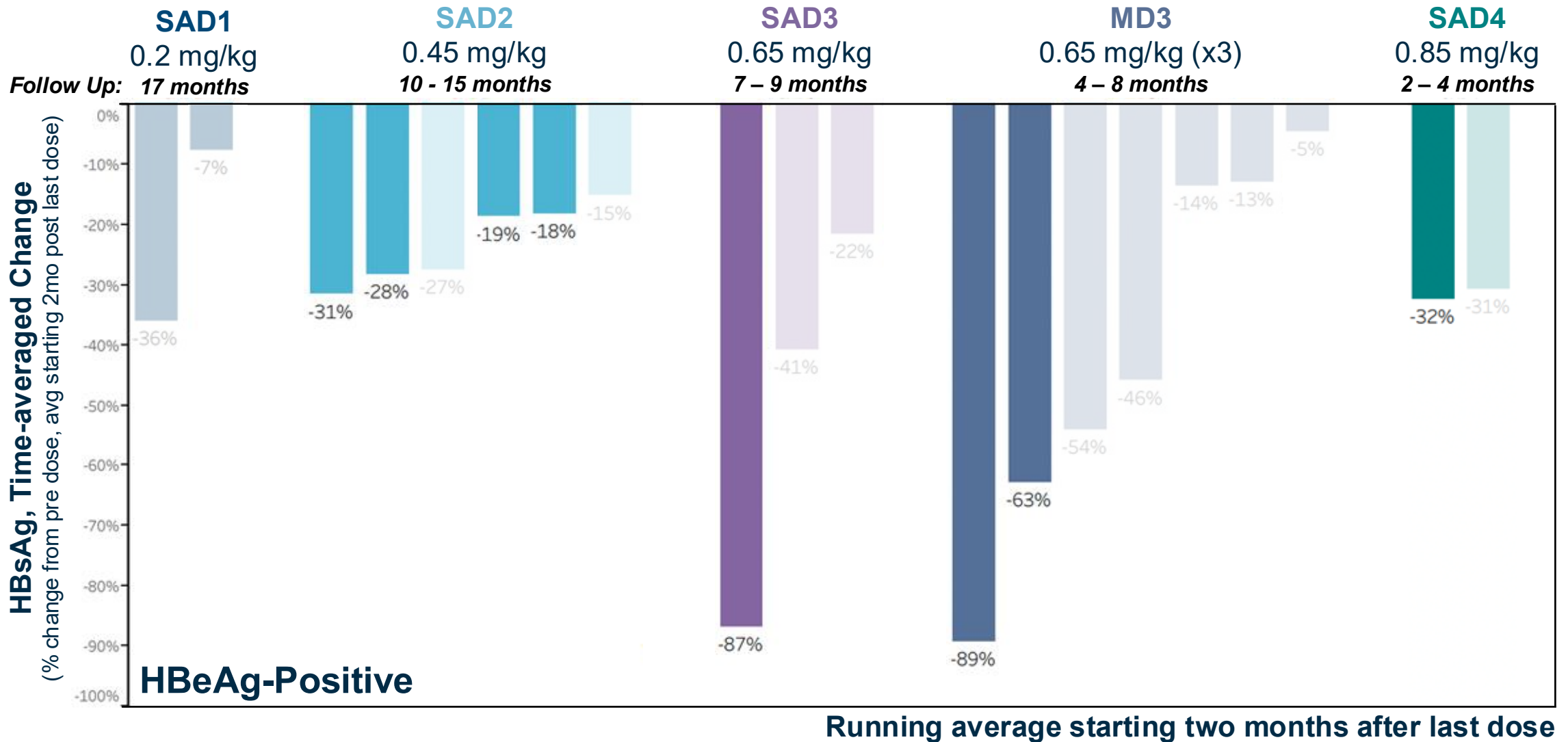
# HBsAg: Maximum Change by Cohort



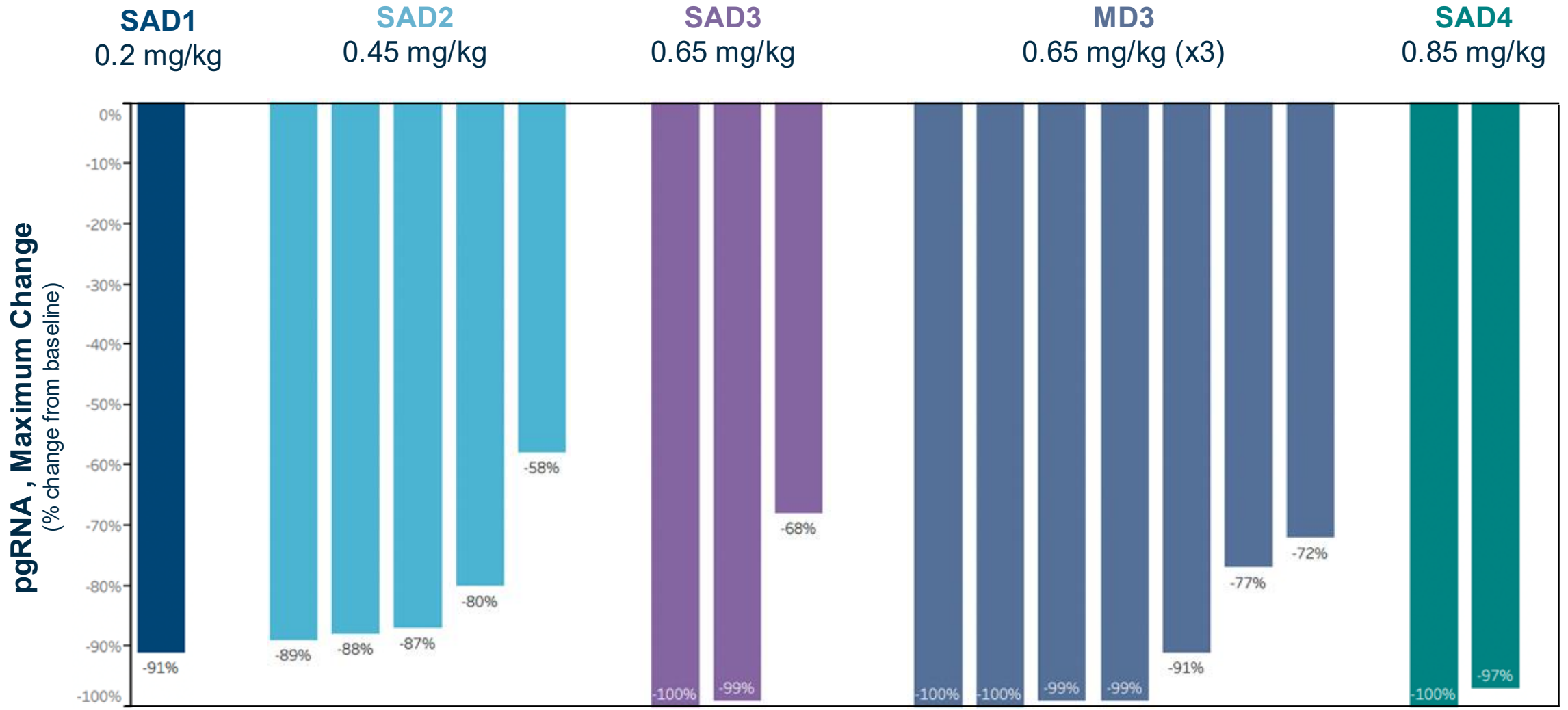
# HBsAg: Durable Change by Cohort



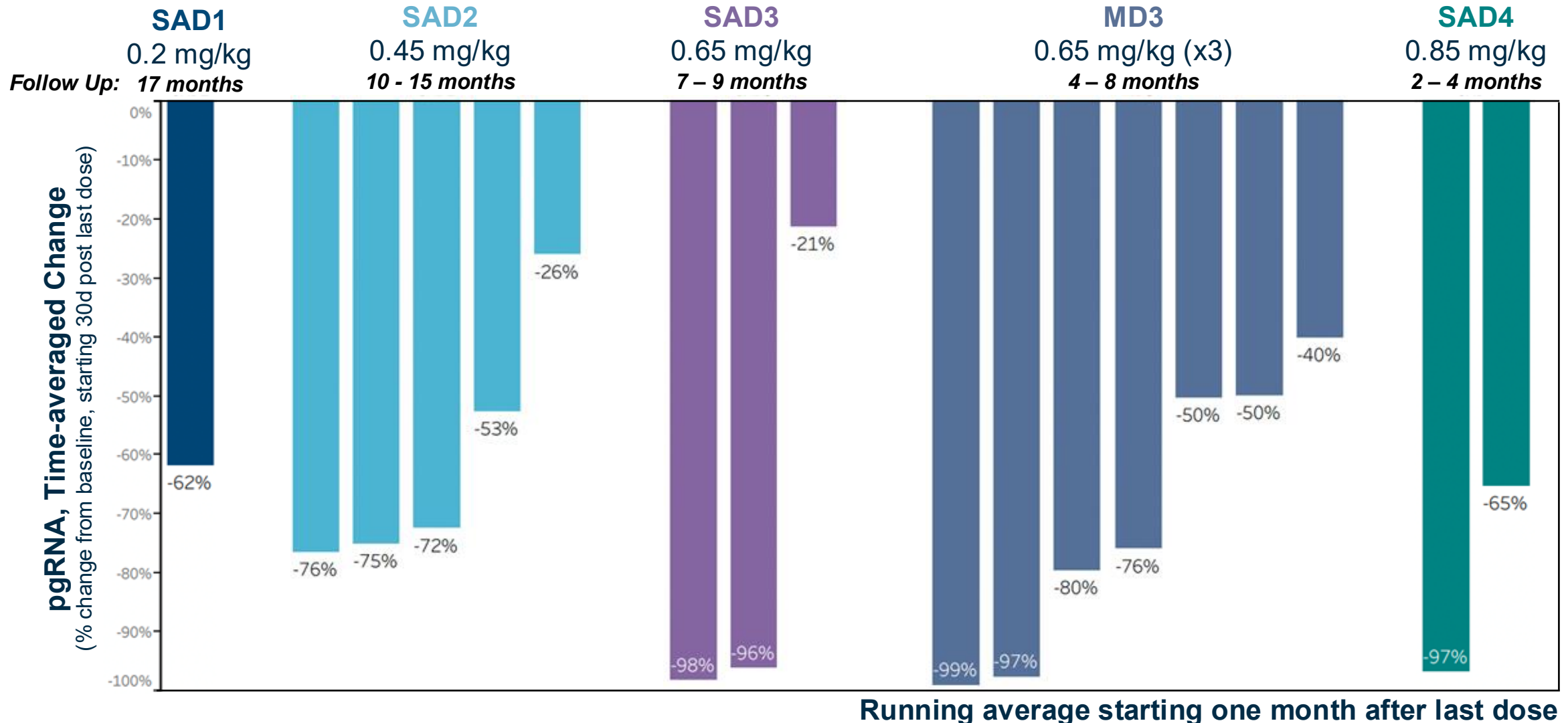
# HBsAg: Durable Change by Cohort (HBeAg-Positive)



# pgRNA: Maximum Change by Cohort



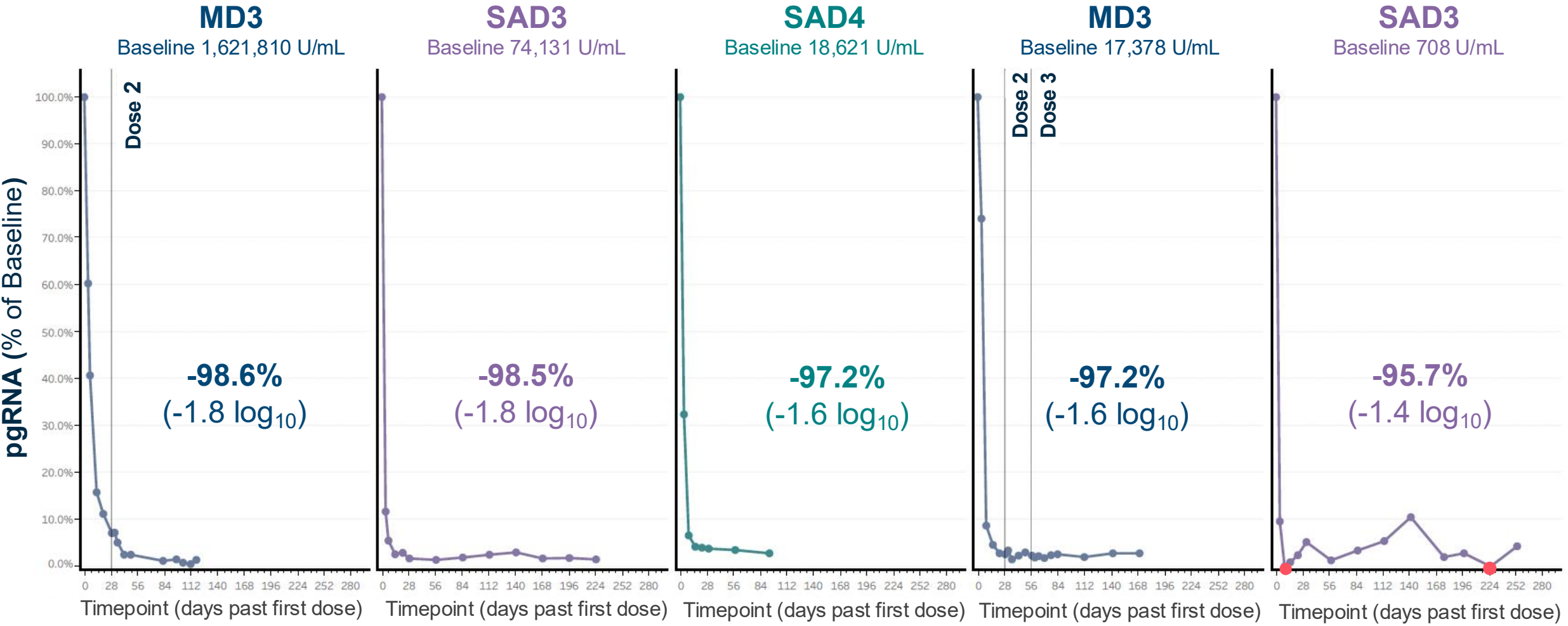
# pgRNA: Durable Change by Cohort



Running average starting one month after last dose



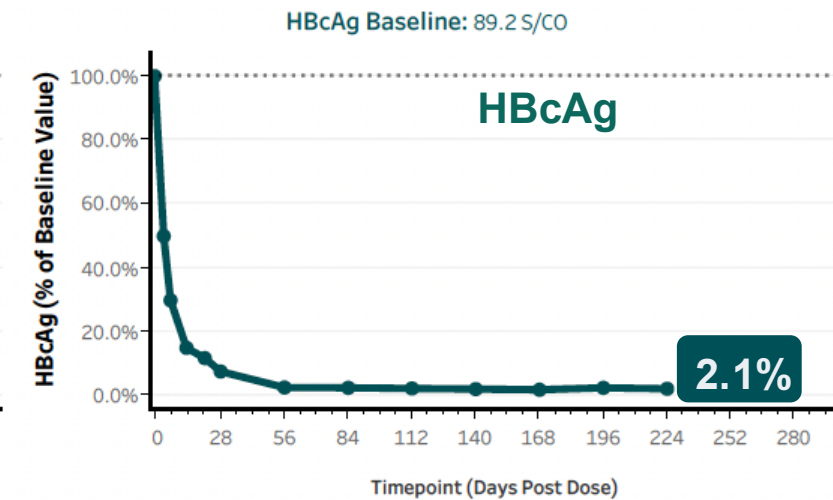
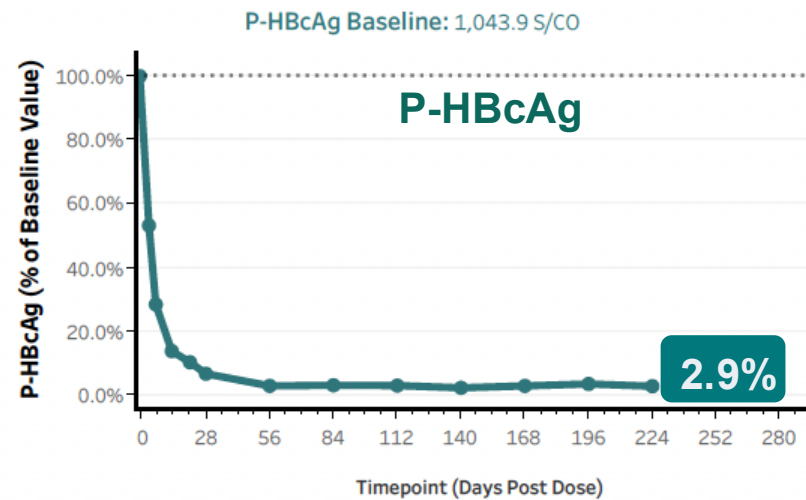
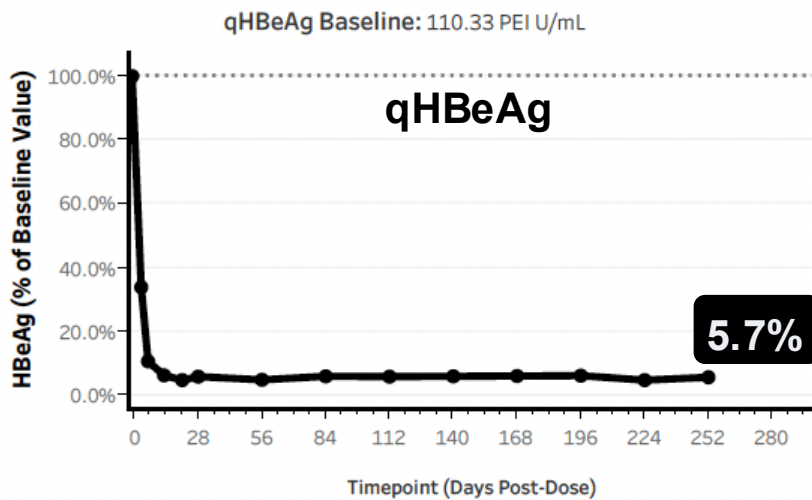
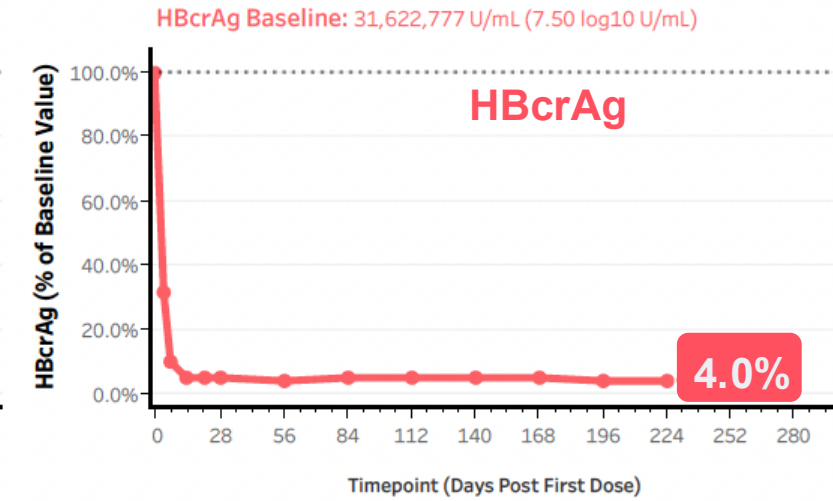
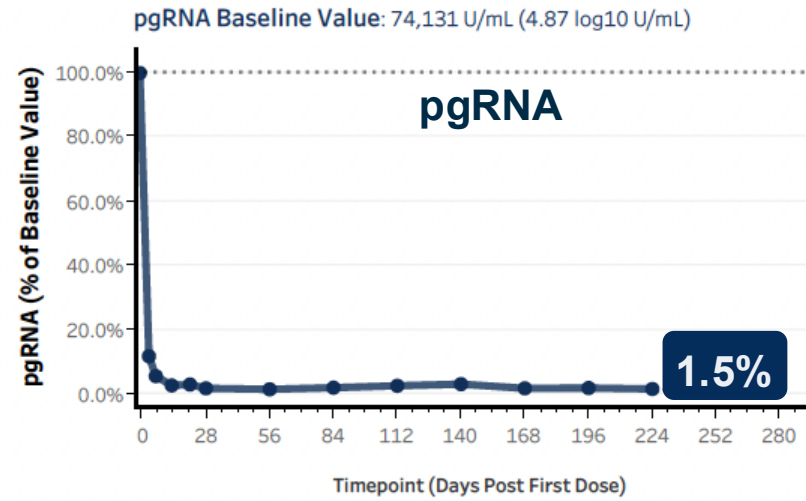
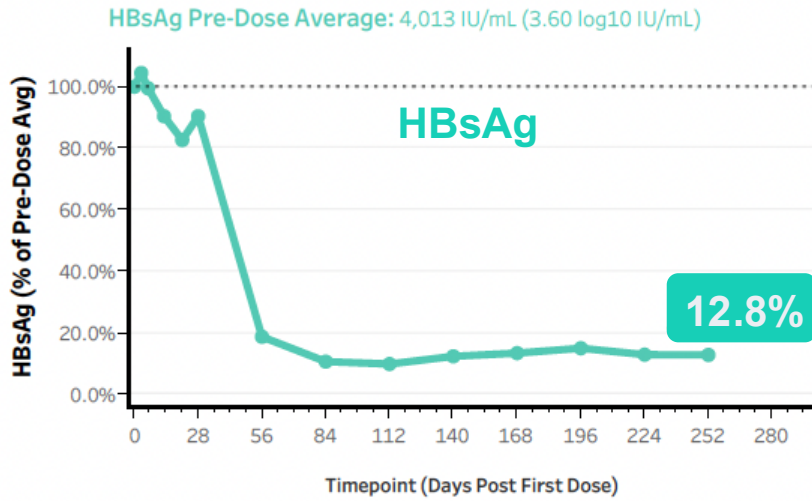
# pgRNA: Consistent Activity Across Highest pgRNA Baselines



Two timepoints <LOQ (<3 U/mL)

# SAD3 Participant: Durable Reduction in All Biomarkers

(0.65 mg/kg)

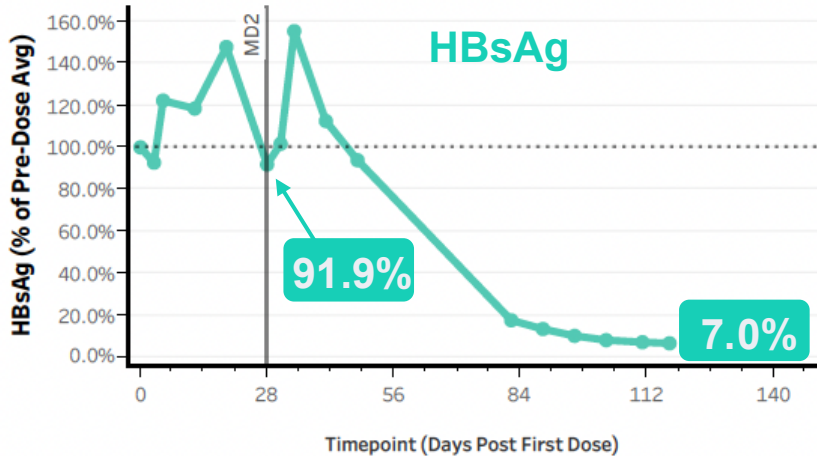


# Multi-Dose Participant: Potential Additive Antiviral Effects

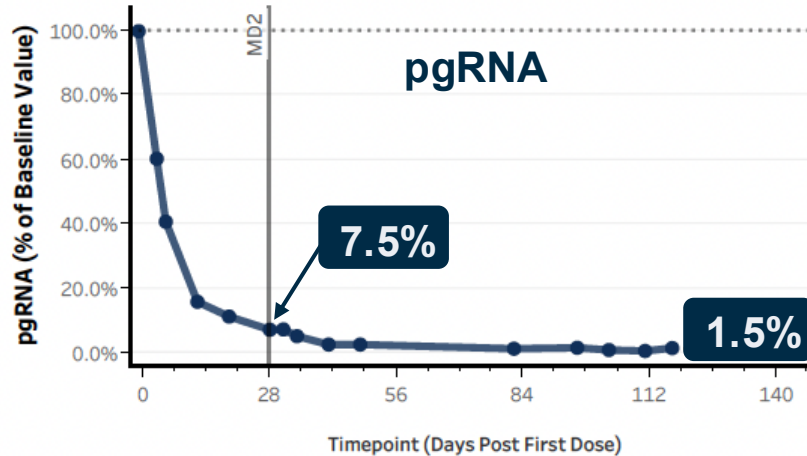
(0.65 mg/kg x 2 doses)



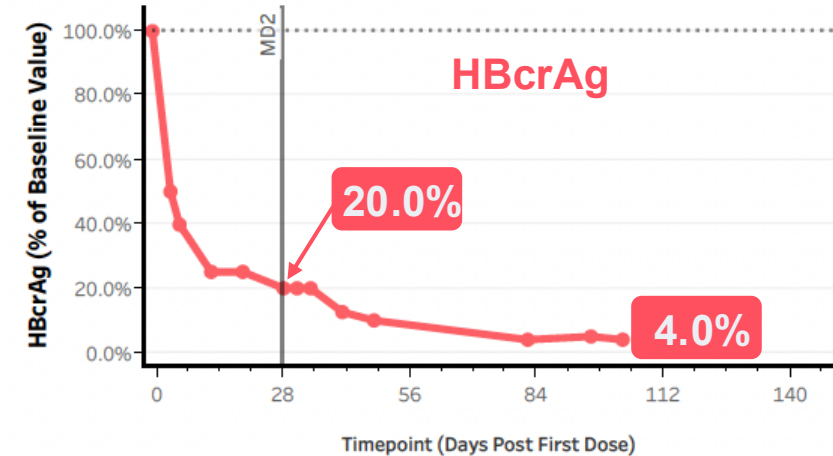
HBsAg Pre-Dose Average: 2,053 IU/mL (3.31 log<sub>10</sub> IU/mL)



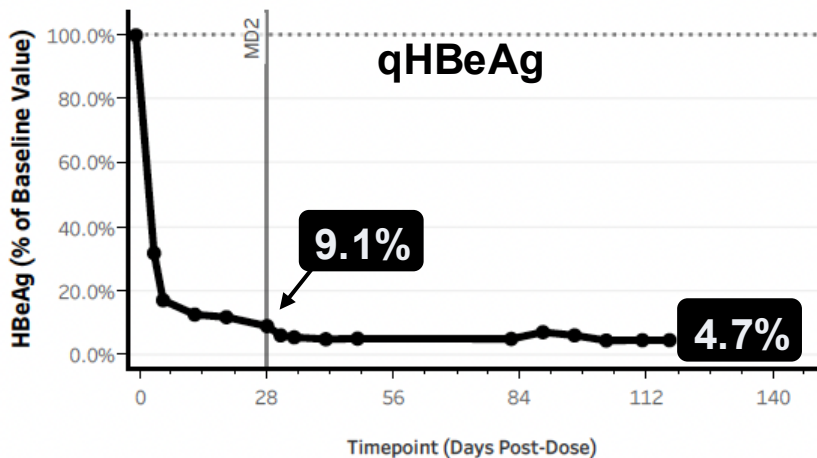
pgRNA Baseline Value: 1,621,810 U/mL (6.21 log<sub>10</sub> U/mL)



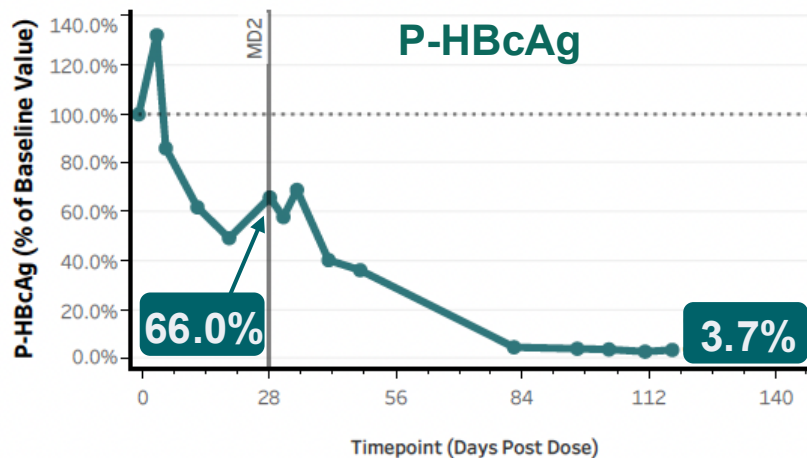
HBcrAg Baseline: 10,000,000 U/mL (7.00 log<sub>10</sub> U/mL)



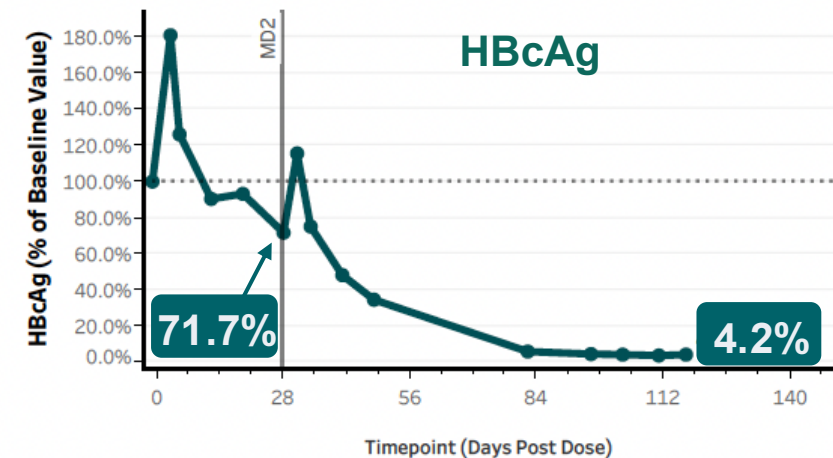
qHBeAg Baseline: 27.81 PEI U/mL



P-HBcAg Baseline: 539.1 S/CO



HBcAg Baseline: 35.3 S/CO

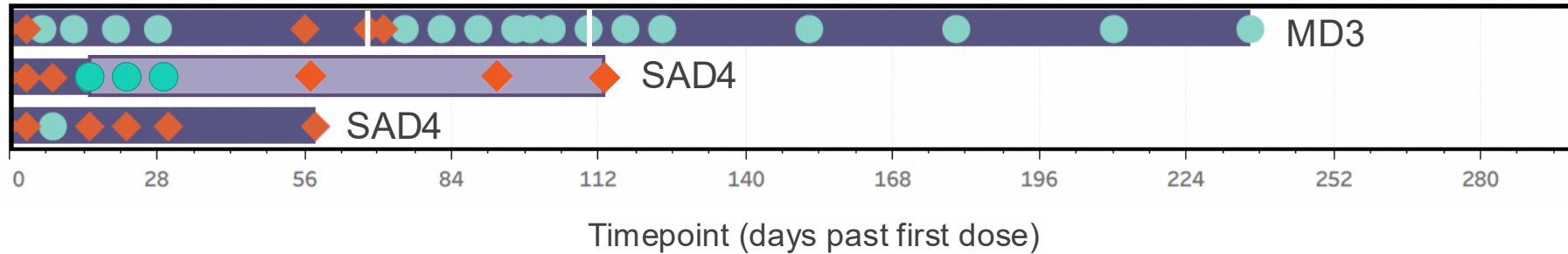


# Tune-401 Induces cccDNA Biomarker Loss at Dose Level 3/4



## A. HBeAg Loss in HBeAg(+)

● Biomarker Negative (below LOQ)    ◆ Biomarker Positive    ▭ HBe Seroconversion (anti-HBe+)



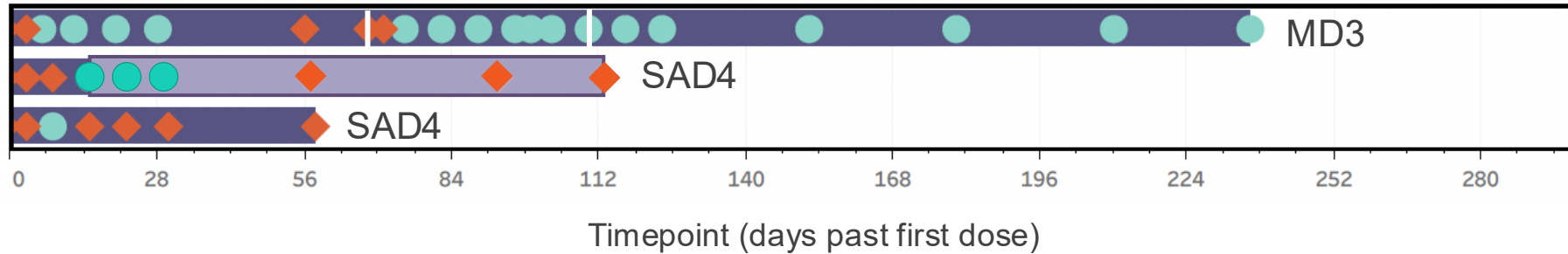
- **3 out of 5** HBeAg(+) participants achieved **HBeAg loss**

# Tune-401 Induces cccDNA Biomarker Loss at Dose Level 3/4



## A. HBeAg Loss in HBeAg(+)

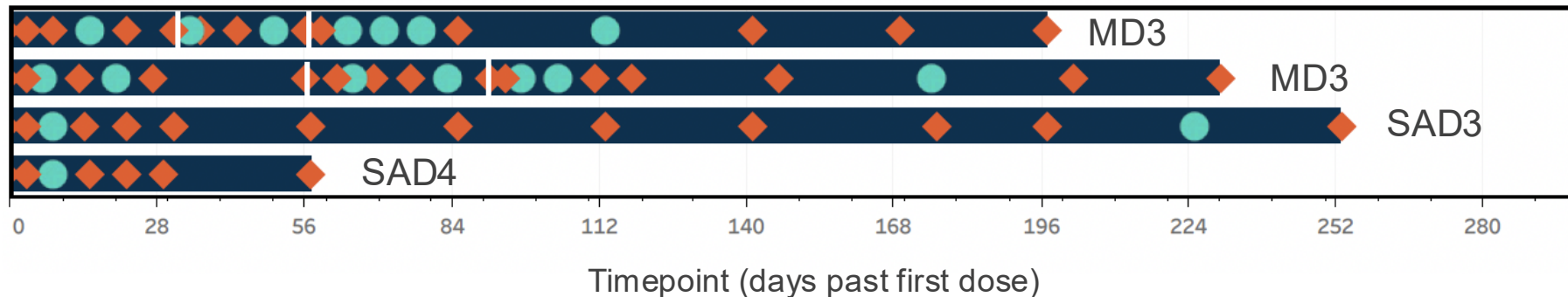
● Biomarker Negative (below LOQ)    ◆ Biomarker Positive    ▭ HBe Seroconversion (anti-HBe+)



- **3 out of 5** HBeAg(+) participants achieved **HBeAg loss**

## B. pgRNA loss in HBeAg(-)

● Biomarker Negative (below LOQ)    ◆ Biomarker Positive



- **4 out of 7** HBeAg(-) participants achieved **pgRNA loss**
- **3 out of 3** participants with HBcrAg >LOQ achieved **HBcrAg loss** alongside **pgRNA loss**

# Favorable Safety Profile Across Cohorts

	SAD1 0.2 mg/kg (N=2)	SAD2 0.45 mg/kg (N=6)	SAD3 0.65 mg/kg (N=3)	MD3 0.65 mg/kg			SAD4 0.85 mg/kg (N=8)
				Dose 1 (N=7)	Dose 2 (N=7)	Dose 3 (N=6)	
<b>Adverse Events</b>							
Any AE	10	17	9	9	15	16	18
Any AE related to Tune-401 <sup>+</sup>	4	14	5	6	8	11	14
Grade ≥ 3 AE	-	-	1	-	3	2	2
Any SAE	-	1*	1 <sup>◇</sup>	-	-	-	1**
Any SAE related to Tune-401 <sup>+</sup>	-	1*	1 <sup>◇</sup>	-	-	-	1**
Any AE leading to discontinuation	-	-	1 <sup>◇</sup>	-	-	-	1**
<b>AE of Special Interest</b>							
IRR	2	6	1	3	3	4	6
Grade 3 <sup>a</sup>	-	-	1	-	-	-	1

<sup>a</sup> Hypotension was most frequent symptom of Grade 3 IRR

\* SAE due to prolonged hospitalization for IRR observation (SAD2 participant), resolved within approximately 24 hours

<sup>◇</sup> SAE due to IRR (hypotension) (SAD3 participant), resolved within approximately 24 hours

\*\* SAE due to IRR (hypotension) (SAD4 participant), resolved within approximately 24 hours

+ Considered probably, possibly, or definitively related to Tune-401

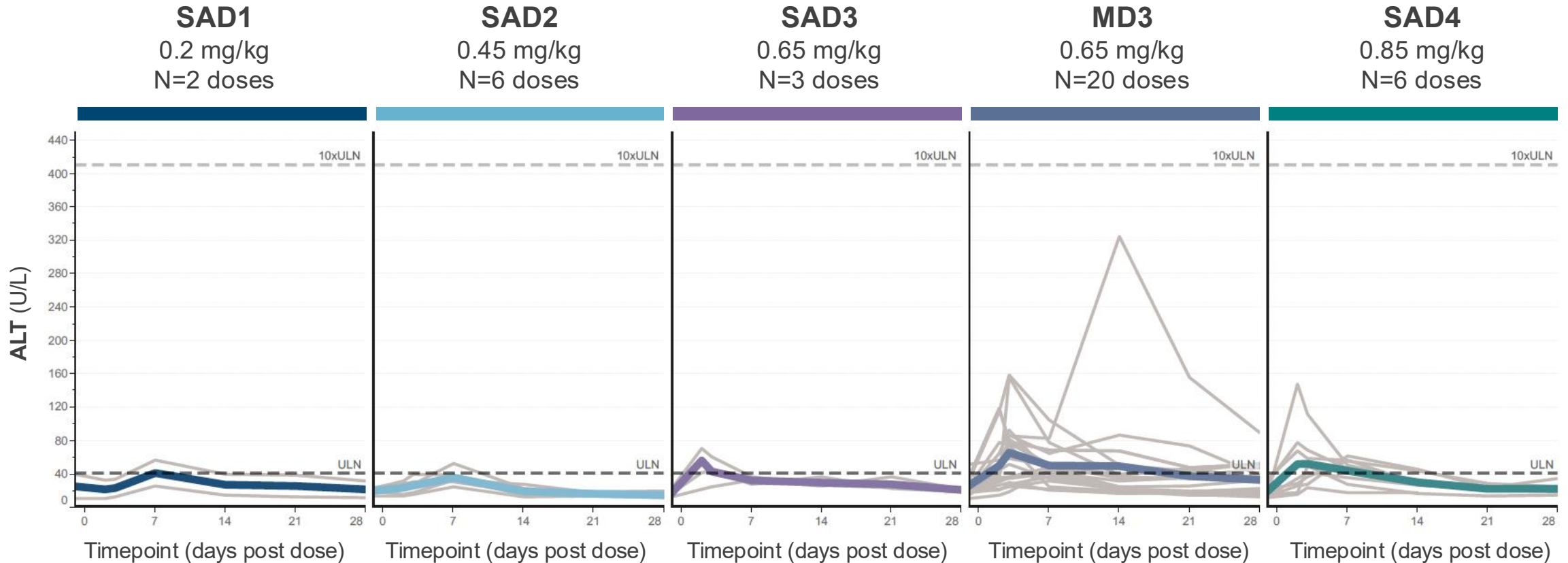
# Favorable Safety Profile Across Cohorts



	SAD1 0.2 mg/kg (N=2)	SAD2 0.45 mg/kg (N=6)	SAD3 0.65 mg/kg (N=3)	MD3 0.65 mg/kg			SAD4 0.85 mg/kg (N=8)
				Dose 1 (N=7)	Dose 2 (N=7)	Dose 3 (N=6)	

Laboratory Abnormalities							
ALT/AST Increase	-	-	1	1	4	2	3
Grade ≥ 3	-	-	-	-	3	-	1
Platelets Decrease	-	3	-	-	-	2	-
Grade ≥ 3	-	-	-	-	-	2	-

# Tune-401 Hepatic Safety Results To Date



## FOR BOTH SINGLE AND MULTIPLE DOSES:

- Transient asymptomatic transaminase elevations that rapidly return to normal
- No changes in bilirubin or other evidence of liver dysfunction

# Conclusions: First Clinical Proof of Epigenetic Silencing of HBV



## SAFETY

- Well-tolerated, with a favorable safety profile
- No additive toxicity from multiple doses

## ANTI-VIRAL ACTIVITY

- Biomarker repression observed in 100% of participants treated at Dose Levels 2-4
- Strong pgRNA, HBcrAg, HBeAg repression demonstrates direct cccDNA silencing
- HBsAg repression trends may reflect preferential silencing of cccDNA over intDNA

## BIOMARKER LOSS

- HBeAg loss in three of five HBeAg(+) participants at Dose Levels 3 and 4
- pgRNA loss in four of seven HBeAg(-) participants at Dose Levels 3 and 4

## DURABILITY

- Durable repression of multiple biomarkers following a single dose (out to 17 mo+)
- Durable pgRNA loss is expected to prevent viral replication

# Next Steps in the Tune-401-001 Study



## REGIMEN IDENTIFICATION FOR EXPANSION COHORT

- Continued dose escalation
- Initiation of new Multiple Dose cohorts

## OPTIONAL NUC DISCONTINUATION

- NUC discontinuation may be considered in participants who achieve durable cccDNA biomarker negativity (HBV DNA, HBeAg, pgRNA, HBcrAg) but have residual HBsAg antigen expression

## PH2 INITIATION

- A larger Ph2 trial will evaluate two maximally efficacious dose regimens of TUNE 401 as monotherapy, as well as in combination with other complimentary MOAs



We extend our thanks to all study participants and their families, site coordinators, and study investigators at the research centers in New Zealand, Hong Kong, and Moldova.

**New Zealand:** Edward Gane

**Hong Kong:** MF Yuen

**Moldova:** Alina Jucov

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The lipid nanoparticle for TUNE-401 is licensed from Acuitas Therapeutics Inc.