# CRMA-1001 an epigenetic editor for the treatment of chronic hepatitis B

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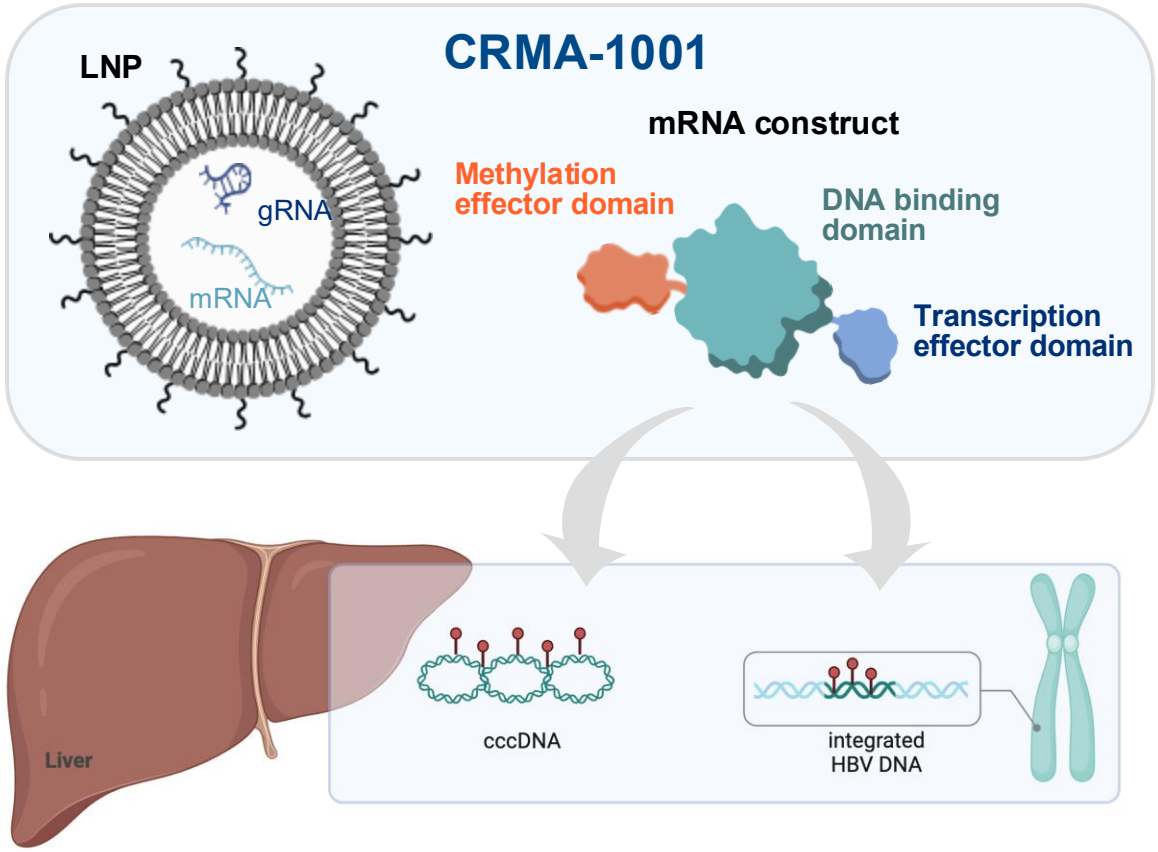
# Epigenetic editing is uniquely suited to address chronic HBV




***CRMA-1001 directly methylates and durably silences cccDNA and intDNA, halting viral replication and viral antigen production***

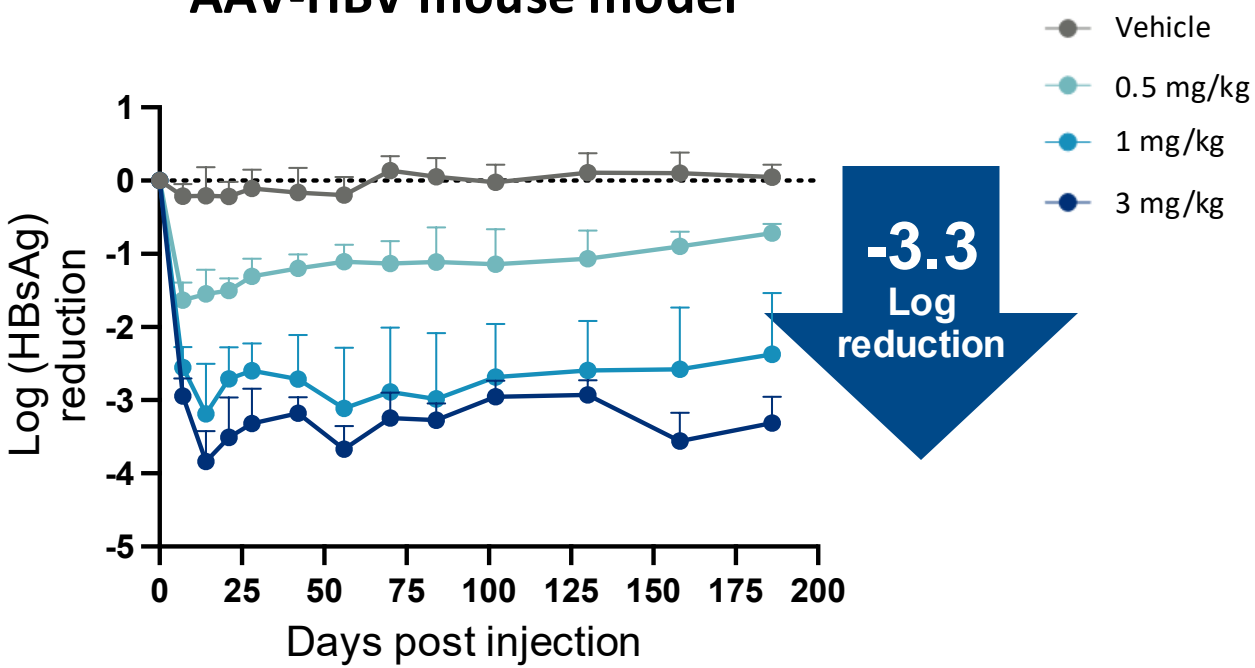
## Best-in-Class Therapy for Chronic HBV

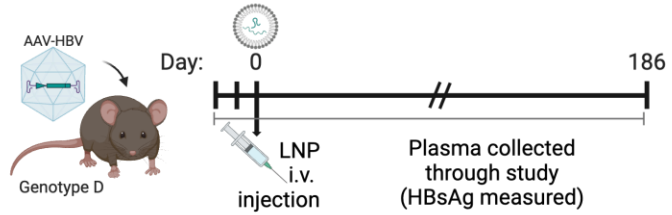
- ✓ **Permanently silences both forms of the genome,** cccDNA and integrated HBV DNA (intDNA), at the level of transcription
- ✓ **Conserved** target site across all HBV genotypes (>94% across genotypes A-H)
- ✓ **Potential for clinically meaningful rates of functional cure with a single course of treatment**
- ✓ **Avoids unintended genomic consequences** of cutting or nicking the DNA

Abbreviations: cccDNA (covalently closed circular DNA); integrated HBV DNA (intDNA)

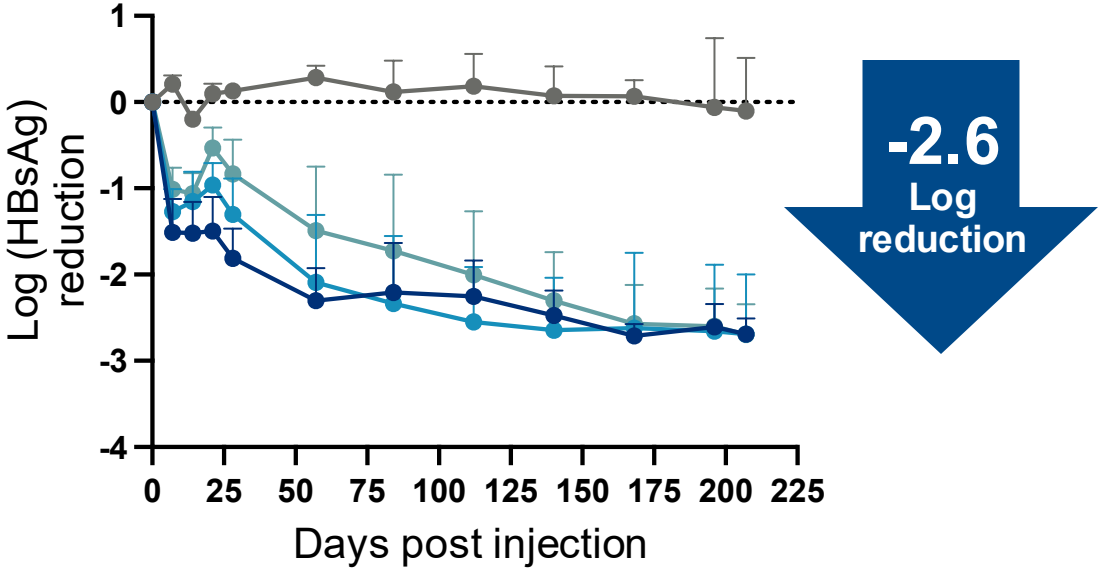
# HBV-EE prototype **deeply and durably** reduces HBsAg in both AAV-HBV and Tg-HBV mice for over 6 months

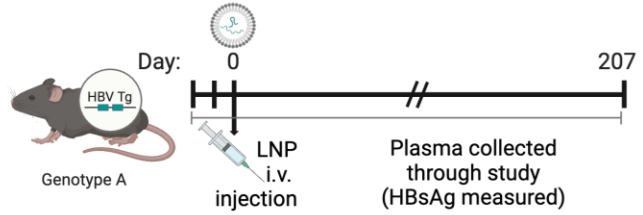
## AAV-HBV mouse model




## Tg-HBV mouse model

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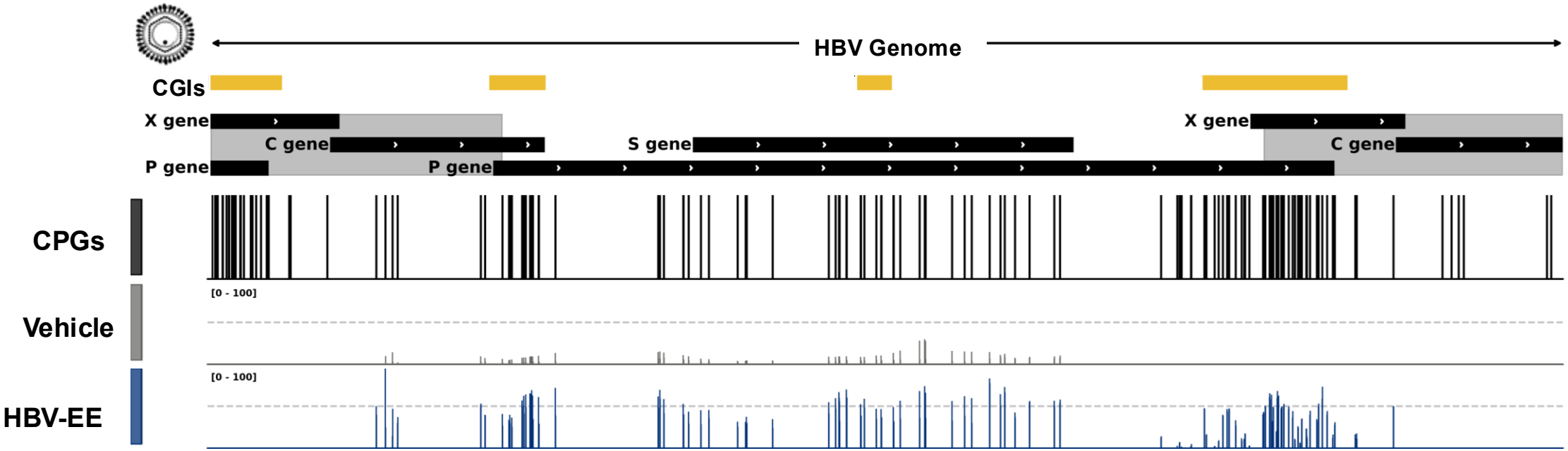
Abbreviations: EE (Epigenetic Editor); AAV (Adeno-associated virus); Tg (Transgenic); HBsAg (HBV surface antigen); LNP (Lipid nanoparticle); i.v. (intravenous)

# HBV-EE prototype drives in vivo robust, durable methylation of HBV DNA

**Methylation in Tg-HBV mouse liver at 6-months after treatment**




**Specific:** Confirmed DNA methylation at target site with no detectable off-target changes in expression or methylation to the host genome confirmed by specificity assessments.

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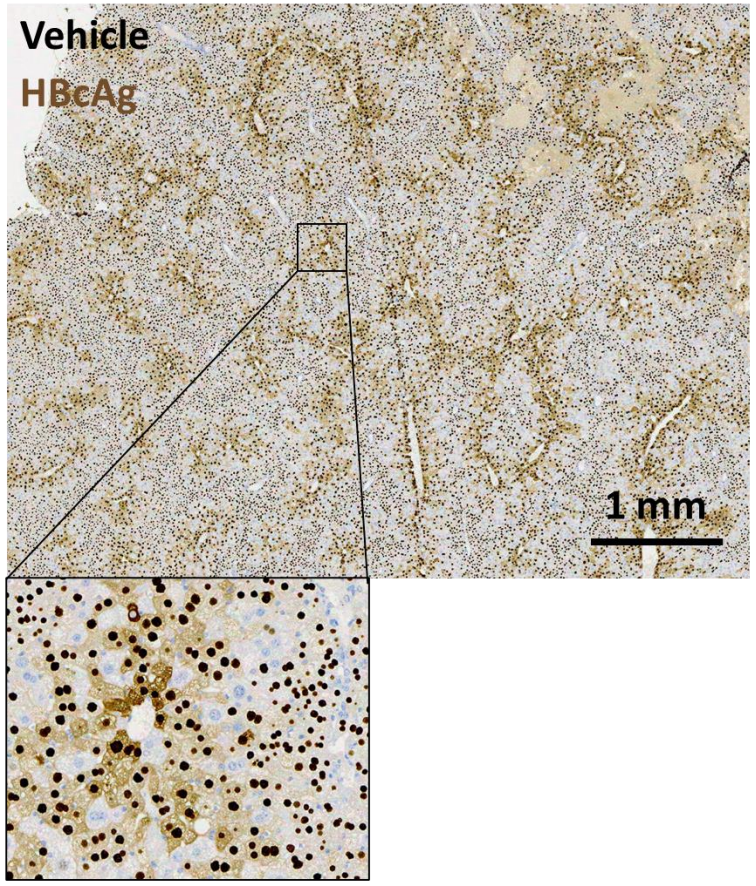
Gray regions represent duplicated regions in the 1.3x HBV genome
Abbreviations: EE (Epigenetic Editor); Tg (Transgenic)

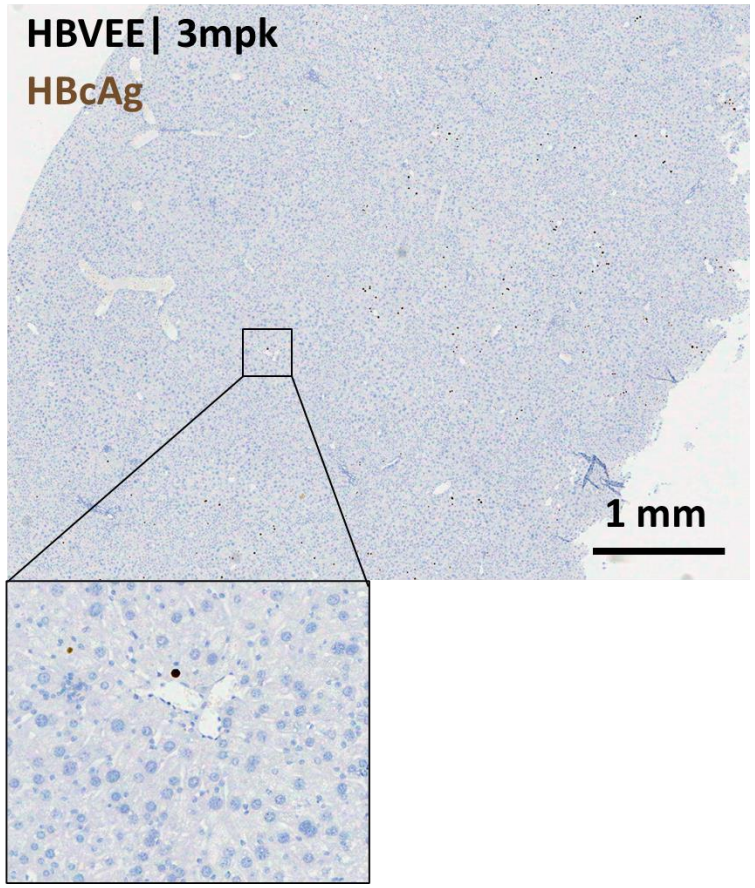
# Single dose of HBV-EE prototype eliminates HBV core antigen in nearly all hepatocytes

## Staining for HBcAg in AAV mouse model 6 months after administration of HBV-EE

**Untreated Control**




**HBV-EE**

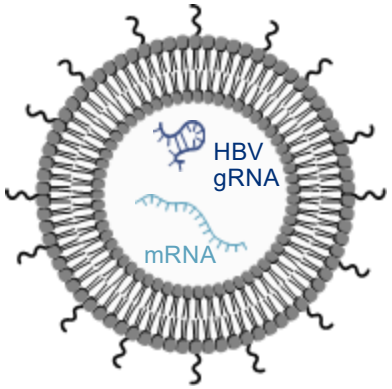


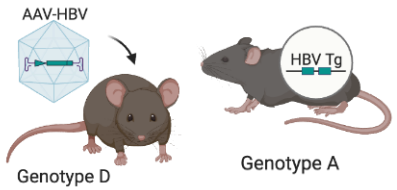



Abbreviations: EE (Epigenetic Editor); HBcAg (HBV core antigen); mpk (mg/kg)

# Epigenetic silencing of PCSK9 in NHPs informs efficiency, durability, and tolerability of silencing HBV

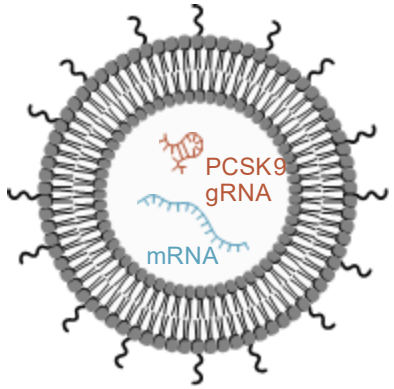
**CRMA-1001**

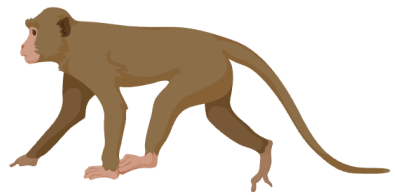



**No large animal models available for HBV**

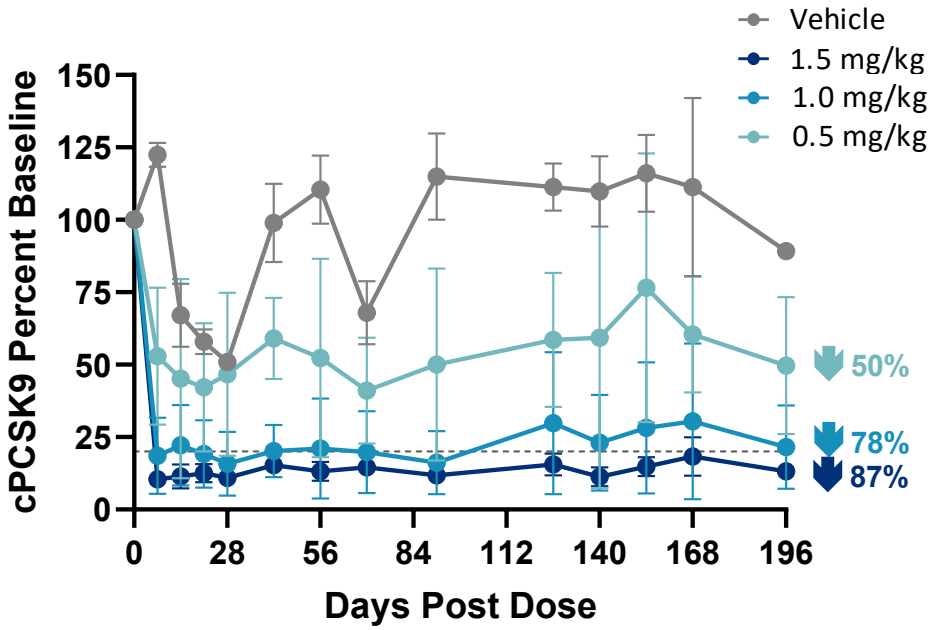
**PCSK9-EE**



**PCSK9 silencing can be evaluated in NHPs**

Saturating pharmacology at ≥ 1 mg/kg in NHPs through day 196




- CRMA-1001 and PCSK9-EE use the **same mRNA epigenetic editor** construct **and LNP delivery vehicle** to silence the target, only the gRNA is different

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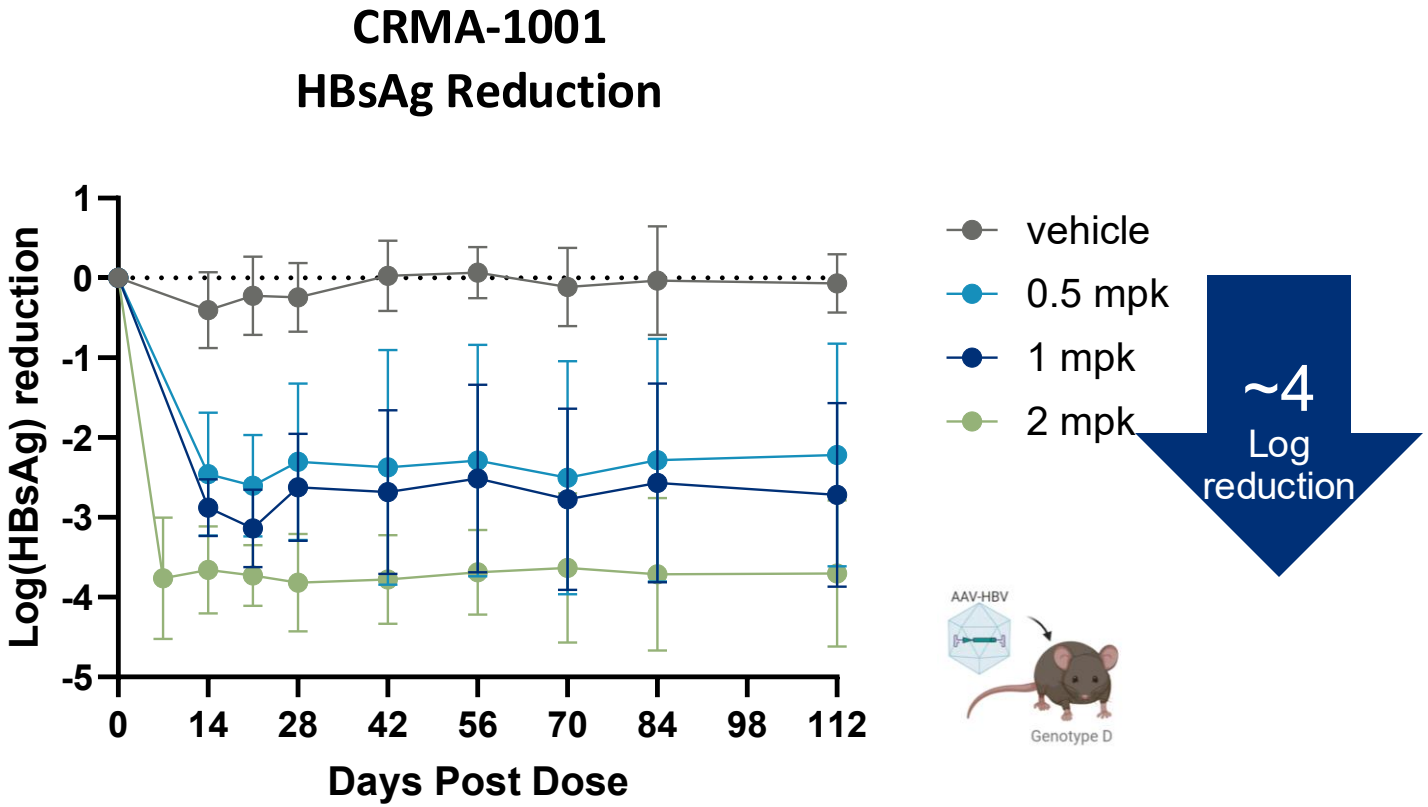
Abbreviations: PCSK9 (Proprotein convertase subtilisin/kexin type 9); NHP (Non-human primate) EE (Epigenetic Editor); HBcAg (HBV core antigen); LNP (Lipid nanoparticle); i.v. (intravenous)

# CRMA-1001 achieved >2 log reduction in HBsAg at 0.5 mg/kg, demonstrating increased potency

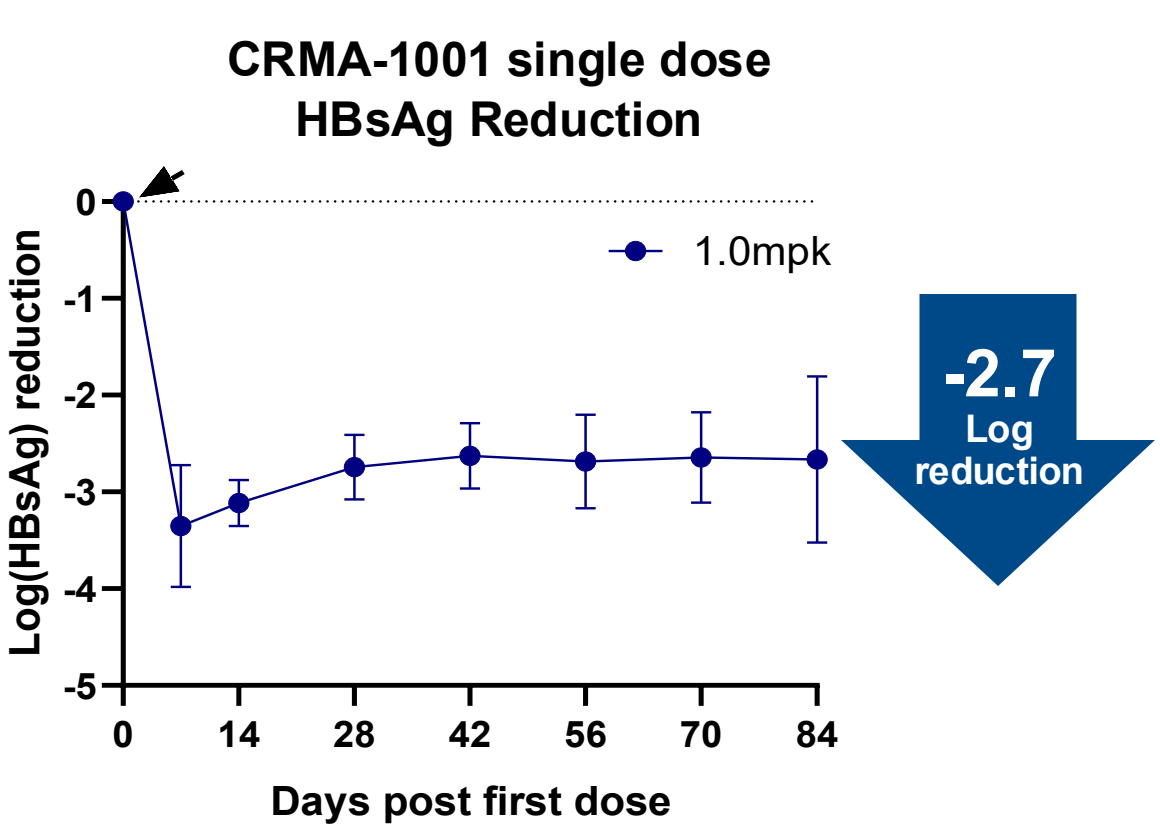


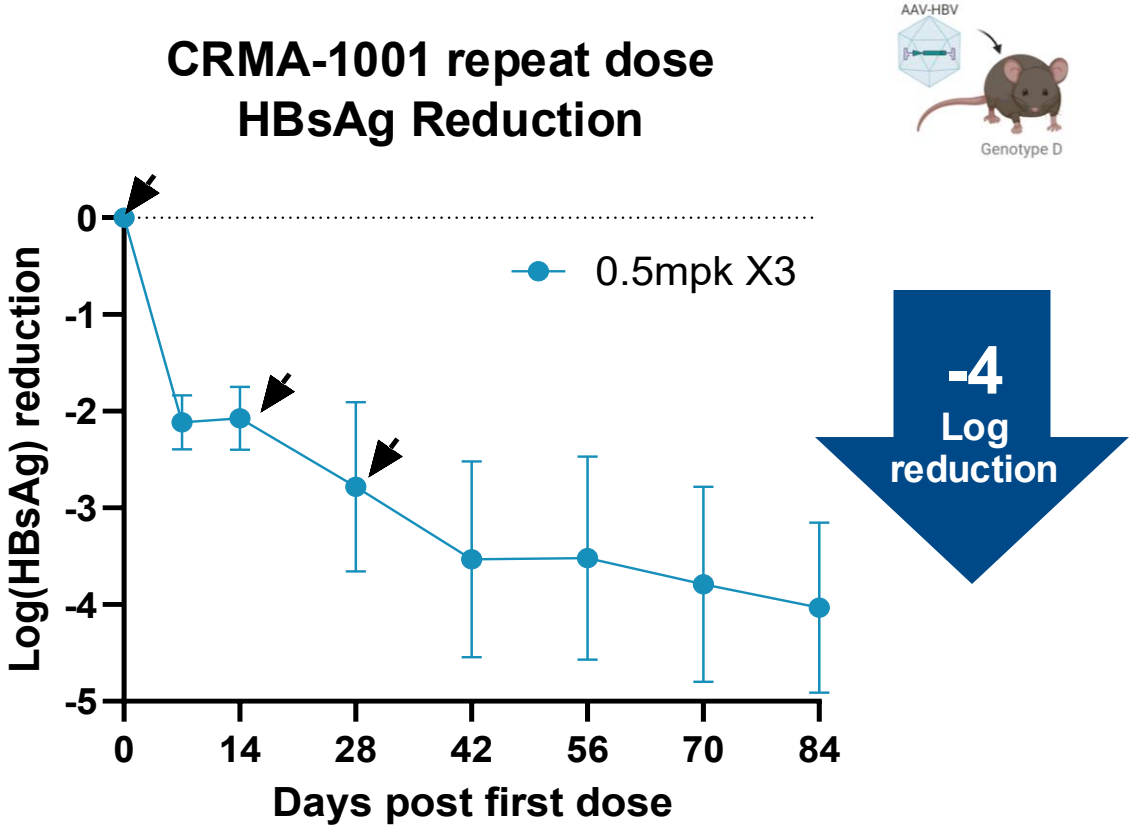

- CRMA-1001 at lower doses in AAV-HBV mice
- Development candidate CRMA-1001 achieved >2 log reduction of HBsAg at 0.5 mg/kg and nearly 4 log reduction at 2 mg/kg that is durably maintained
- **CRMA-1001 is highly potent,** showing robust HBsAg reduction at lower doses relative to HBV-EE prototype



Abbreviations: AAV (Adeno-associated virus); HBsAg (HBV surface antigen); LNP (Lipid nanoparticle); mpk (mg/kg)

# CRMA-1001 repeat dosing regimen drives additive pharmacology




***No animals reached undetectable HBsAg at 3 months***

***5/6 animals reached undetectable HBsAg at 3 months***



Abbreviations: AAV (Adeno-associated virus); HBsAg (HBV surface antigen); LNP (Lipid nanoparticle); mpk (mg/kg)

# CRMA-1001 is a highly potent and based on in vitro and in vivo activity specific epigenetic editor

- **Potent:** achieves ~4 log reduction of HBsAg at a single high dose in AAV-HBV mice or with multiple lower repeat doses
- **Durable:** Silenced all HBV viral markers examined for over 6 months
- **Specific:** Confirmed DNA methylation at target site with no detectable off-target changes in expression or methylation to the host genome
- **Translatable:** Achieved >80% PCSK9 silencing (saturating pharmacology) at ≥ 1 mpk in NHPs

**CRMA-1001 CTA/IND-enabling studies ongoing, regulatory filings planned in 2025**

# Thank you to the nChroma Bio team, collaborators, and partners!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ACUITAS THERAPEUTICS

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