PRECISION BIOSCIENCES

PBGENE-HBV: ARCUS gene editing to eliminate the root cause of Hepatitis B

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VP Gene Therapy

HBV Forum 12
Session II: Gene Editing and Epigenetic Platforms for HBV Cure
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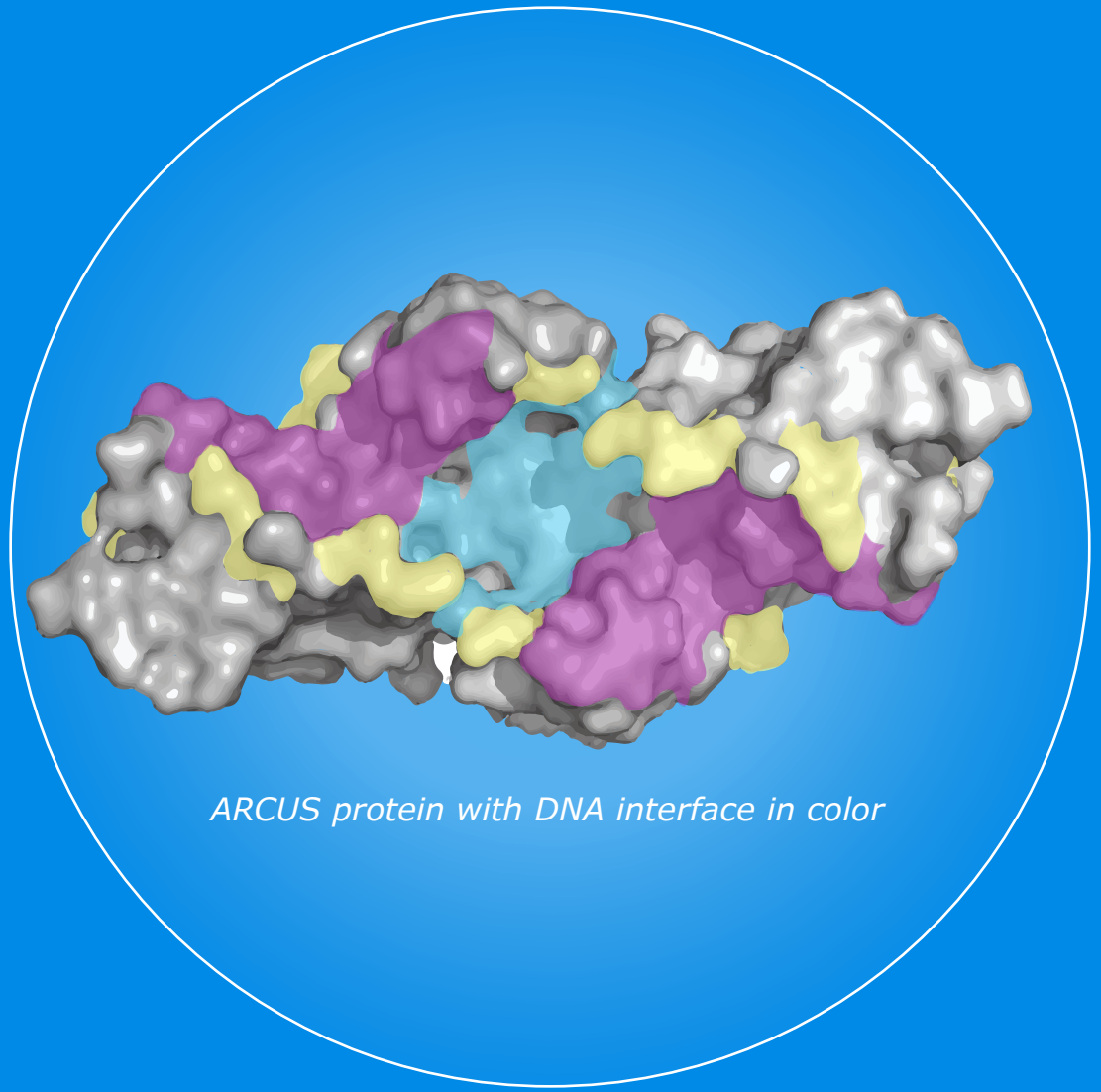
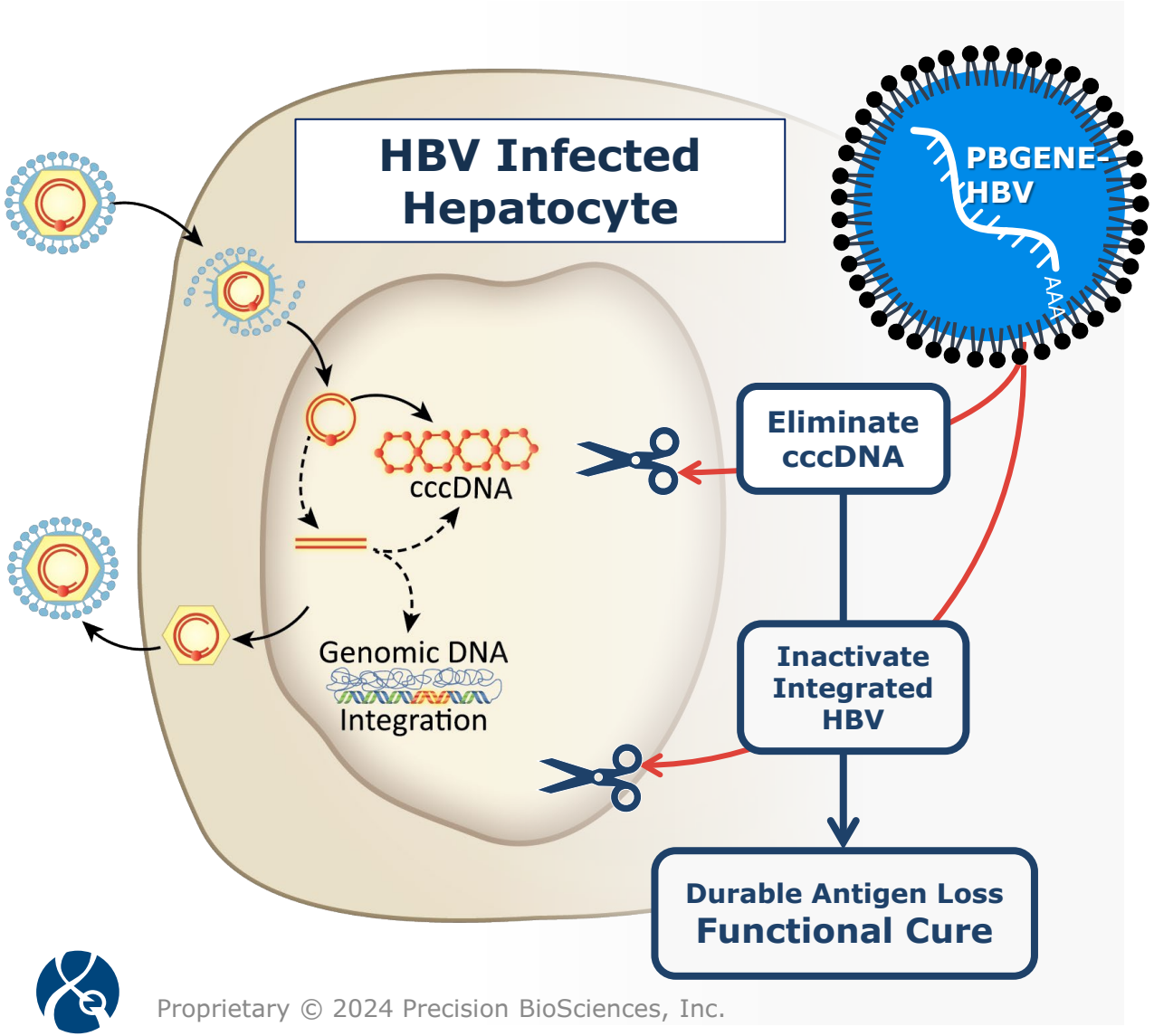
ARCUS: Engineering Nature's Gene Editing System



ARCUS protein with DNA interface in color

- Elimination of cccDNA requires a double strand break (DSB) by a nuclease.
- ARCUS is derived from **I-CreI**, a homing endonuclease from algae.
- Recognizes target through extensive **protein-DNA** interactions; Does not require guide RNA.
- Iterative protein engineering to optimize for safety.
- DNA recognition and cleavage activity are **fully integrated** into one protein for tight regulation unlike competing fusion proteins such as base and epigenetic editors.

PBGENE-HBV:
ARCUS Gene Editing Designed to Eliminate cccDNA and Inactivate Integrated HBV to Drive Towards Durable Antigen Loss and Functional Cure



PBGENE-HBV *is an LNP-delivered ARCUS gene editing nuclease that recognizes a highly conserved sequence in CHB patients.*

Preclinical Development Must Demonstrate Efficacy and Safety for HBV Gene Editing

Efficacy

- Activity against both **cccDNA and integrated HBV DNA**
- Clinically-relevant **viral biomarkers** (HBsAg, HBV DNA, HBV RNA, etc)
- **Multiple, orthogonal models** to fully represent viral life cycle
- **Translatability of preclinical models** to humans

Safety

- Assessment of **potential genomic alterations**
- Demonstrate **pharmacokinetics and biodistribution** of the product
- Fully characterize the **potential toxicities** of the drug product

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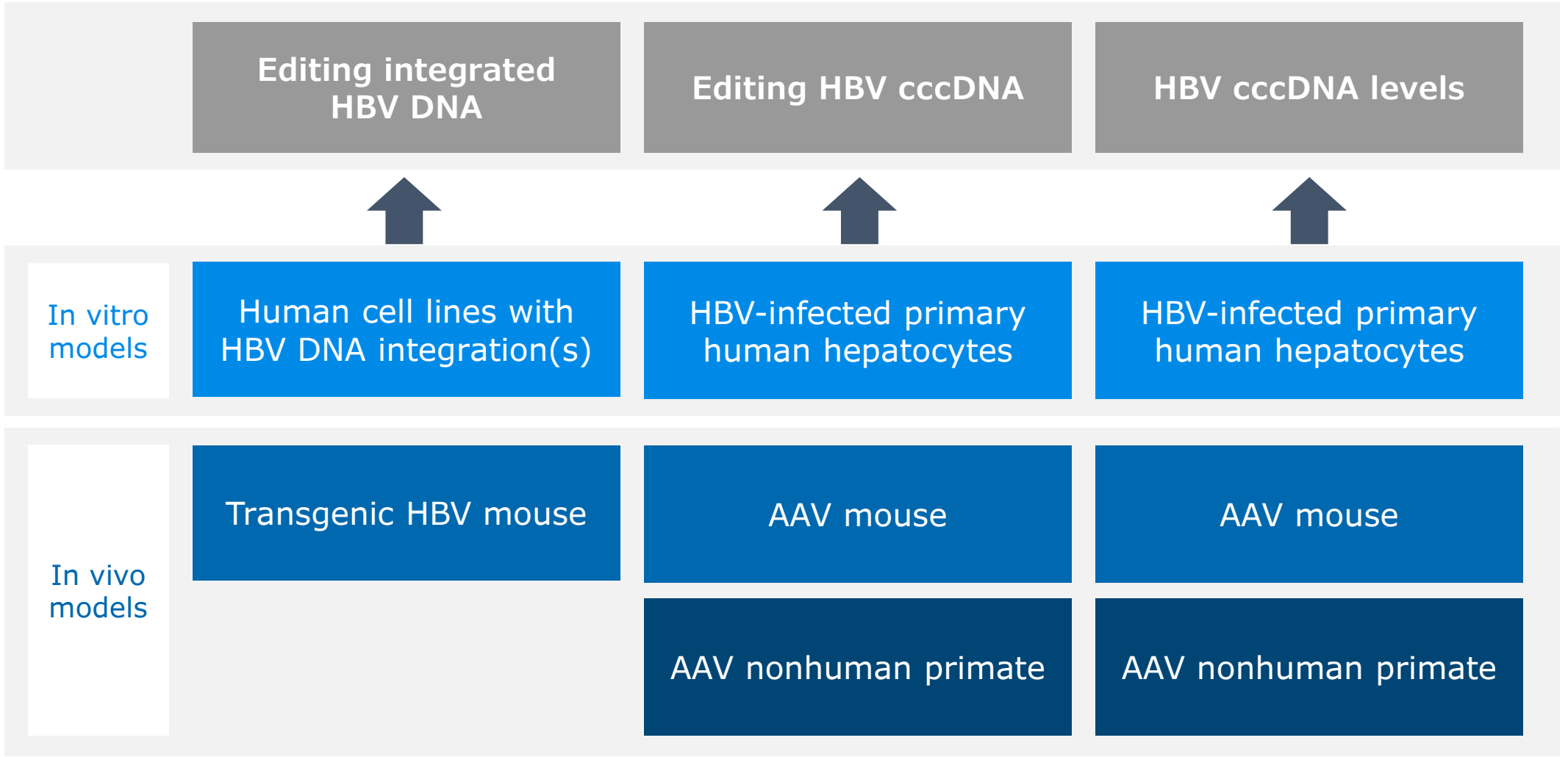
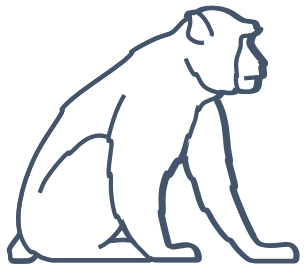
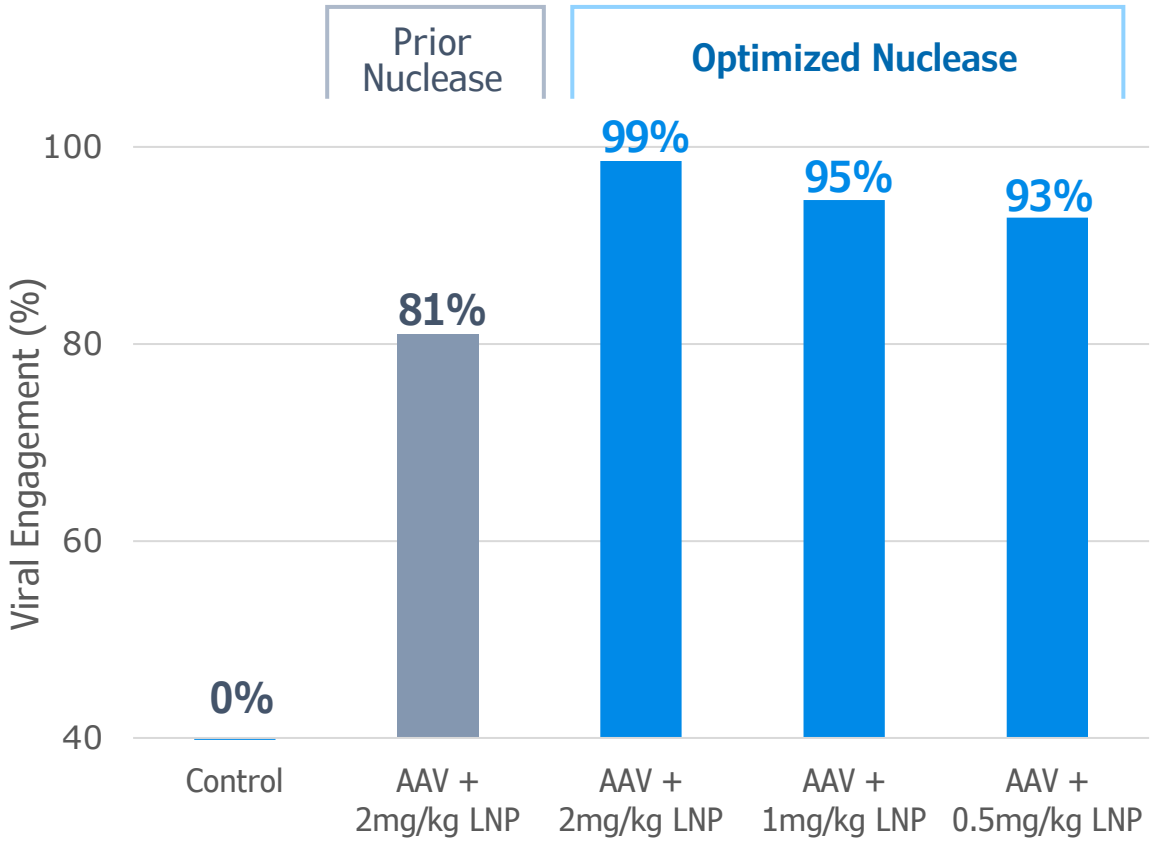
PBGENE-HBV: Preclinical Efficacy Strategy Utilizes Multiple Models and Viral Endpoints



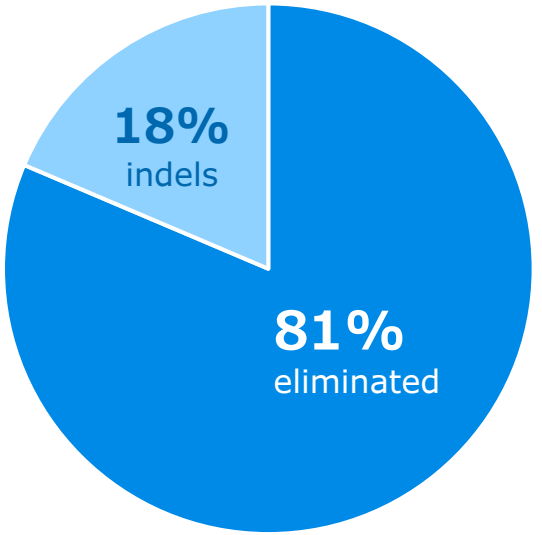
Efficacy: Non-Human Primate (NHP) Study Demonstrated Up to 99% Viral Engagement, Suggestive of Strong Potential Efficacy Profile of PBGENE-HBV



ARCUS LNP

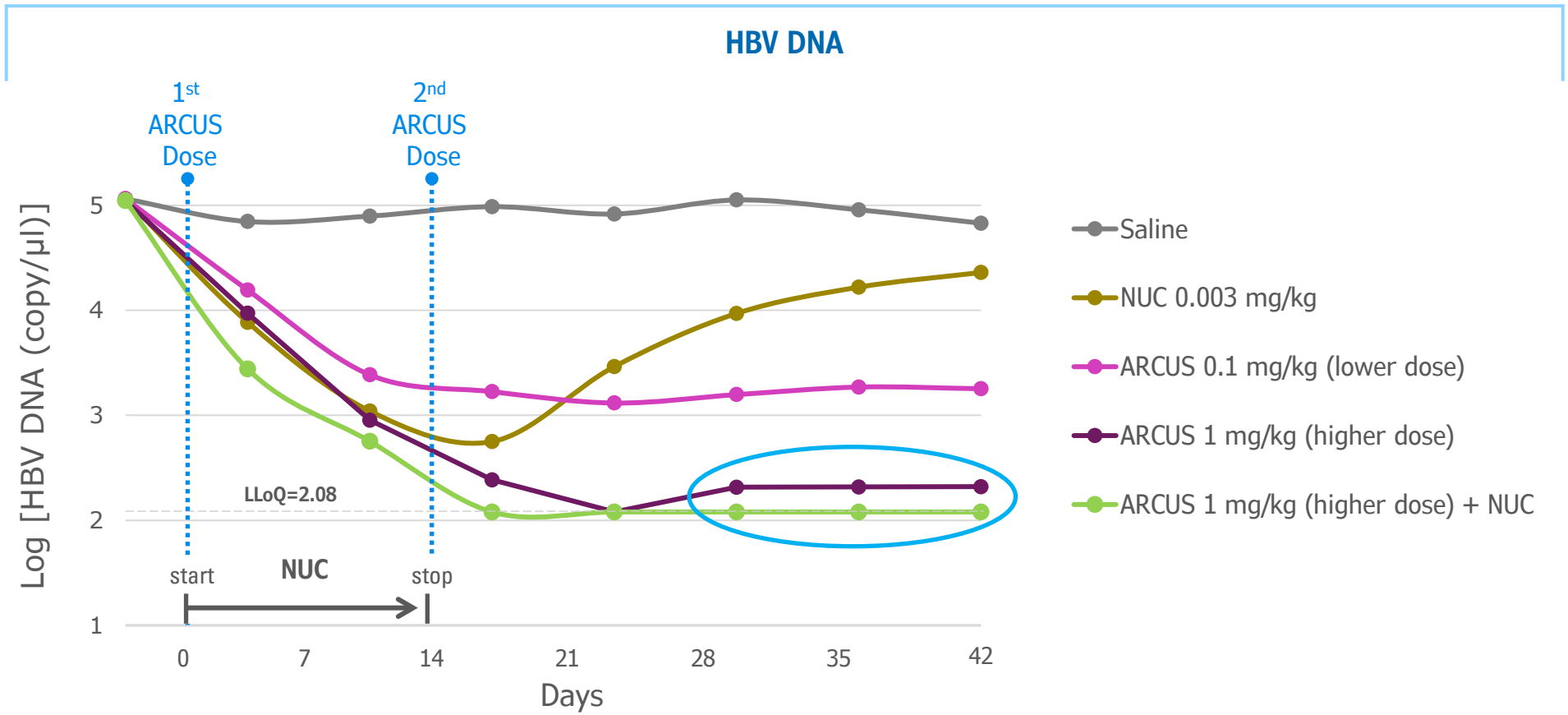


99% viral engagement
at highest dose in NHP study



Final clinical candidate designed to eliminate majority of cccDNA;
This unique mechanism of action is critical to drive durable functional cures

Efficacy: PBGENE-HBV Significantly and Sustainably Reduced HBV DNA as a Monotherapy in New Transgenic Mouse Model



Even after stopping NUC, PBGENE-HBV durably reduced HBV DNA as seen in combination cohort. Supports potential for stopping NUC and driving functional cures in future FIH study

PBGENE-HBV:
Robust Preclinical Efficacy Data Package Using Multiple Models

Eliminate cccDNA

- 99% viral DNA editing in **non-human primates**
- Eliminated cccDNA and inhibited viral markers in **primary human hepatocytes**
- ~95% Durable HBsAg reduction across multiple dose levels in **AAV mouse model**

Inactivate Integrated HBV

- Durable reductions in HBsAg and HBV DNA in **transgenic mice** after nucleoside withdrawal
- Dose-dependent editing and HBsAg reductions in **HBV cell lines** with stable integration

Preclinical Development Must Demonstrate Efficacy and Safety for HBV Gene Editing

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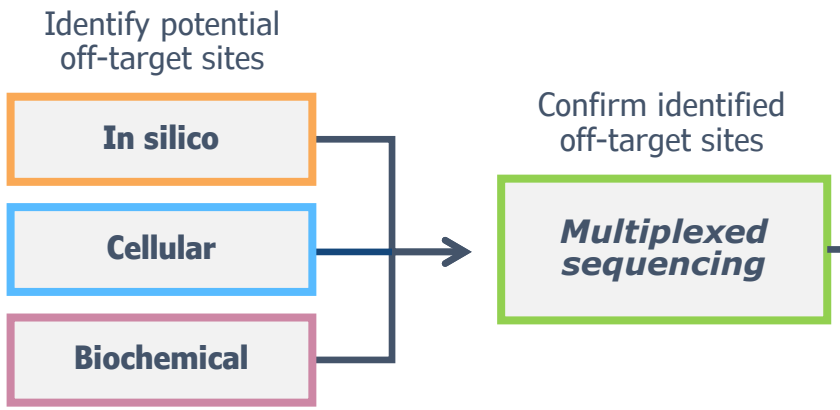
PBGENE-HBV: Preclinical Safety Strategy

Extensive Nuclease Specificity Pipeline to Derisk Potential Genomic Alterations

1 Orthogonal Assays to Identify and Confirm Any Potential Off-target Sites

- Genomic location and frequency of cutting
- Risk assessment, distance from genes



2 Account For Population Diversity

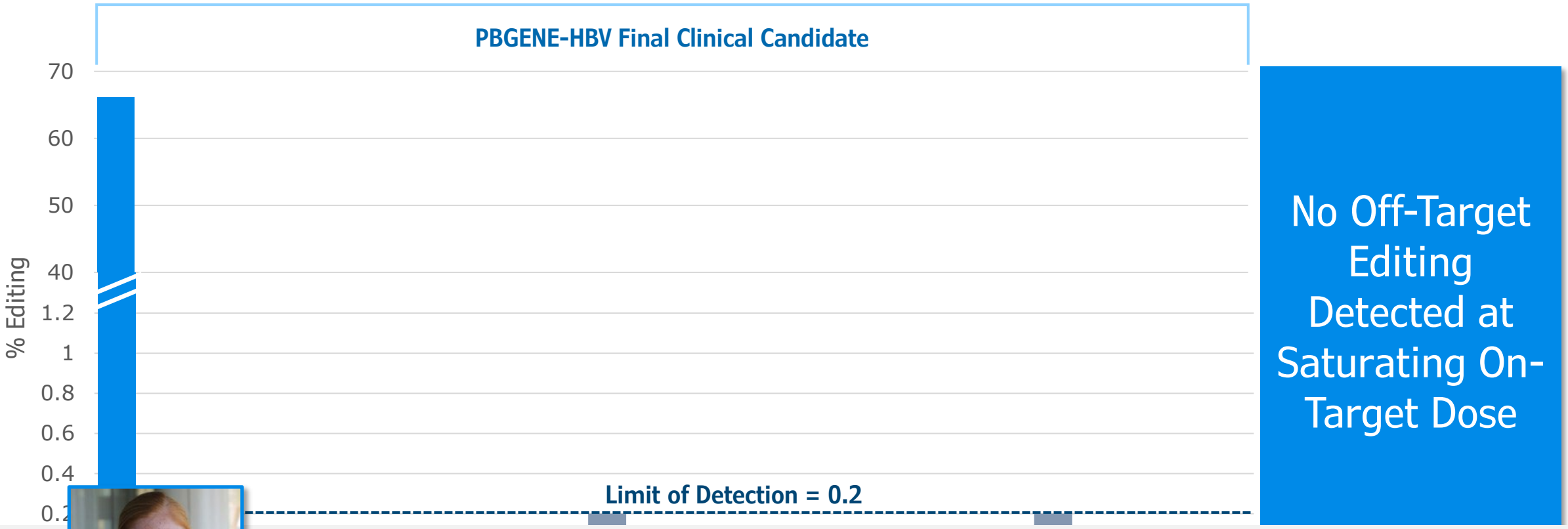
- Location and possible off-target sites created by genetic diversity (SNVs)
- Effects of common SNVs on in vitro cleavage

3 Assess Potential Genomic Rearrangements

- Between integrated viral genome and human genome
- Between multiple, integrated viral genome copies

SNV, single nucleotide variant.

Safety: PBGENE-HBV Final Clinical Candidate Shows Enhanced Specificity With No Detectable Off-Target Editing



PBGENE-HBV

More Comprehensive Specificity Analysis to be Shared at EASL — Late Breaker Poster 022 (LBP-022)

Safety: Nonclinical Toxicology Data

Important considerations for LNP Gene Editing Products

- **Demonstrate Pharmacokinetics and Biodistribution**: The LNP formulation drives PK and BD of the drug product
- **Fully Characterize Safety and Physiologic Parameters**: LNP-delivered mRNA can result in transient transaminase elevations that often resolve rapidly after dosing
  - The quality of the mRNA encapsulated within the LNP can contribute to the magnitude of the transaminase elevations

Preclinical safety data for PBGENE-HBV gene editing program supports advancement to clinical trials as a potentially curative treatment for chronic hepatitis B

PBGENE-HBV

Nonhuman Primate Toxicology Data to be Shared at EASL — Late Breaker Poster 022 (LBP-022)

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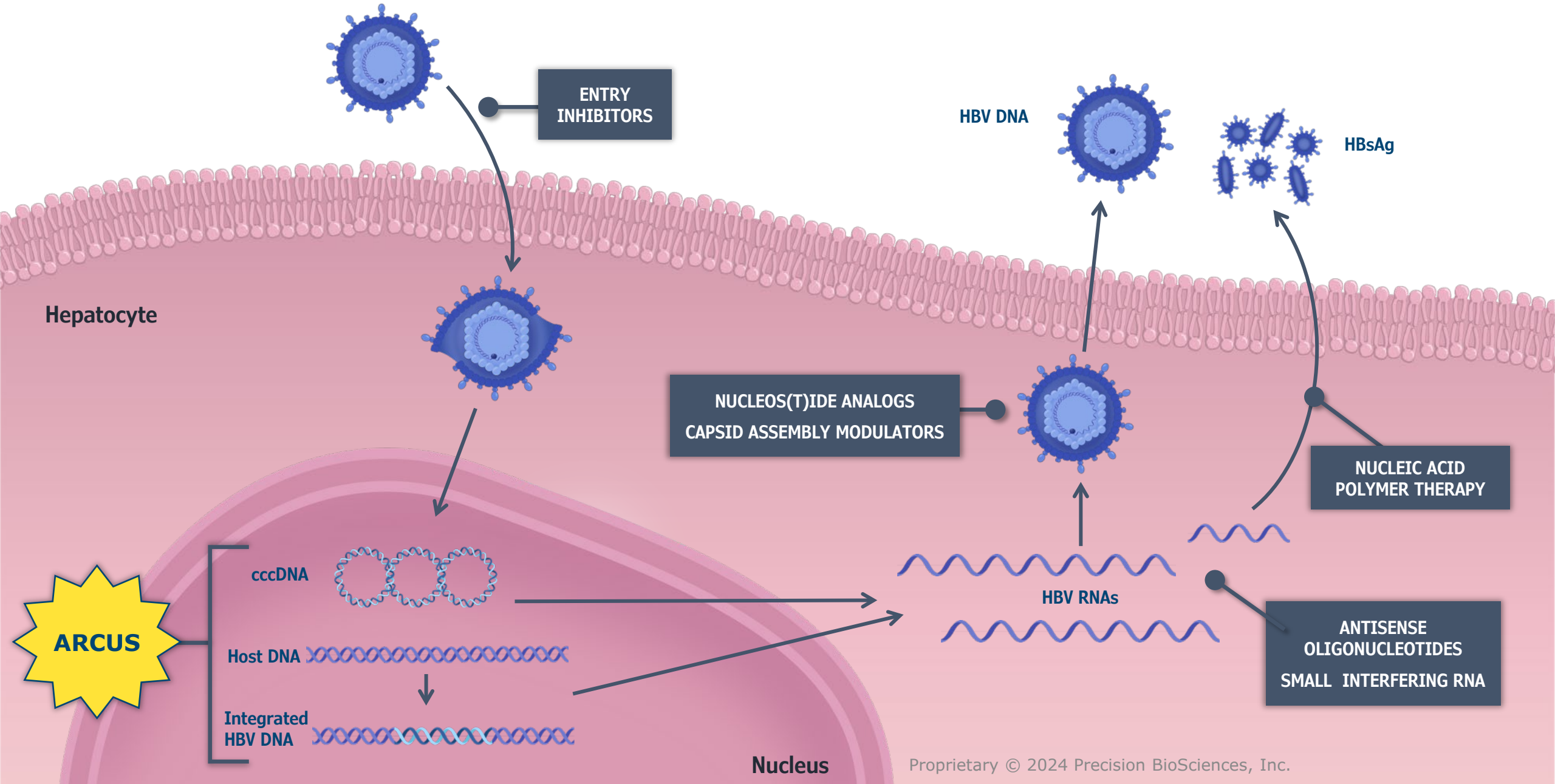

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Thank you for your attention.

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