



A Modular  
CRISPR/Cas9 Genome  
Editing Platform for Durable  
Therapeutic Knockout and  
Targeted Gene Insertion  
Applications

**Anthony L. Forget, Ph.D.**

September 29, 2020



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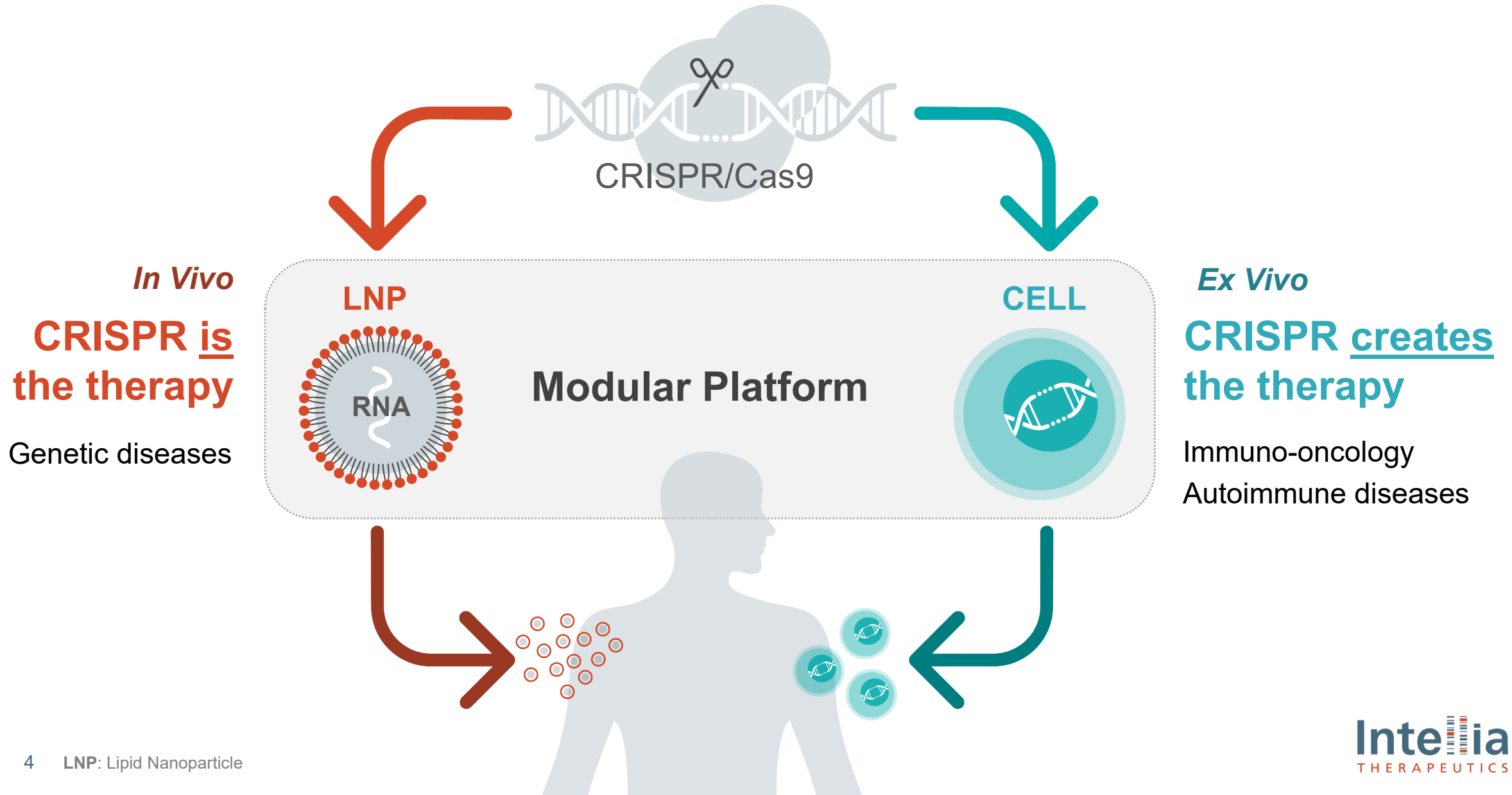
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# Today's Agenda

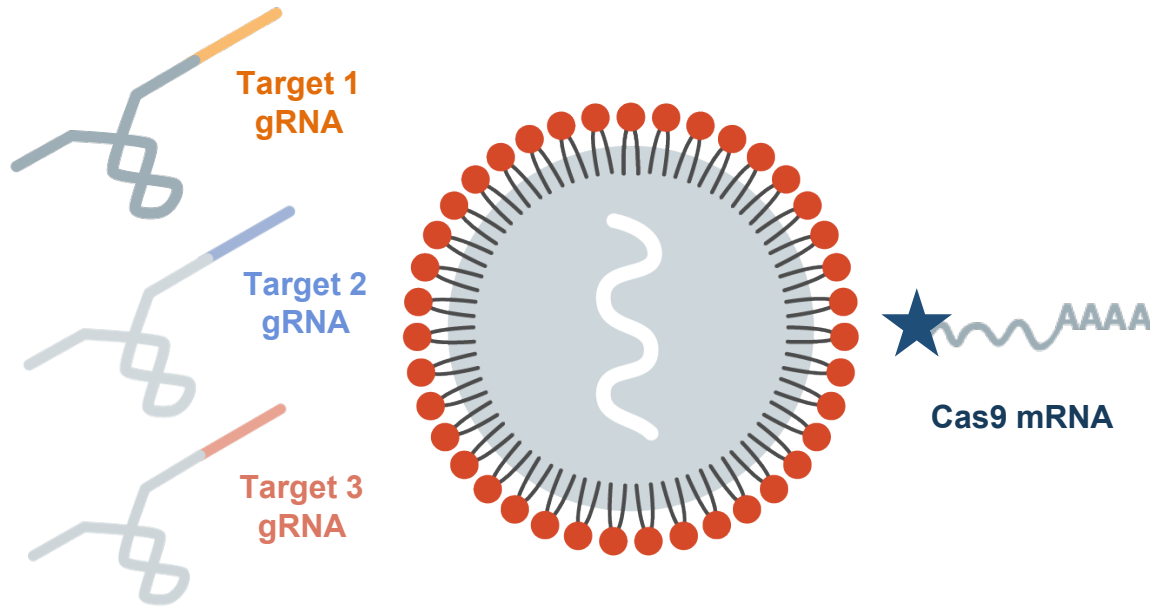
- 1 Intellia's Modular Platform
- 2 Durable Gene Knockout Applications
- 3 Targeted Gene Insertion Persistence

# Building a Full-Spectrum Genome Editing Company



# Intellia's *In Vivo* Liver Editing Modular Platform Employs Non-Viral Delivery

## Lipid Nanoparticles (LNPs)



gRNA target site specificity  
defined by 20mer at 5' end

Transient Cas9 expression  
from mRNA

## Key Advantages of LNP Delivery

- ✓ Clinically-proven delivery to liver
- ✓ Large cargo capacity
- ✓ Transient expression
- ✓ Biodegradable
- ✓ Low immunogenicity
- ✓ Well-tolerated
- ✓ Redosing capability
- ✓ Scalable synthetic manufacturing
- ✓ Tunable

# Modular Approach to Unlocking Treatment of Genetic Diseases

## PROPRIETARY LNP DELIVERY SYSTEM

Transient expression

Large cargo capacity

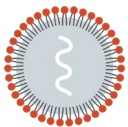
Redosing capability

## ENABLES MULTIPLE EDITING STRATEGIES

### Remove

#### KNOCKOUT

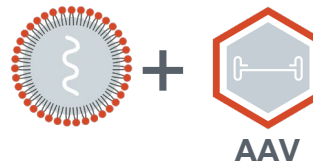
Knockout toxic or compensatory genes



### Restore

#### INSERT

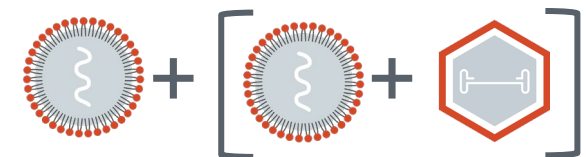
Introduce functional DNA sequence



### Remove / Restore

#### CONSECUTIVE EDITING

Any combination of knockout (KO) and insertion strategies



# Modular Approach to Unlocking Treatment of Genetic Diseases

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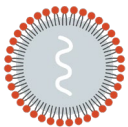
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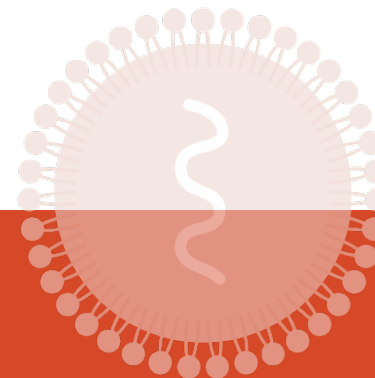


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## Durable Gene Knockout Applications



# Transthyretin Amyloidosis (ATTR)



Caused by accumulation of misfolded transthyretin (TTR) protein, which affects **nerves, heart, kidneys and eyes**

**50,000**

hATTR patients worldwide<sup>1</sup>

**~200-500K**

wtATTR patients worldwide<sup>2</sup>

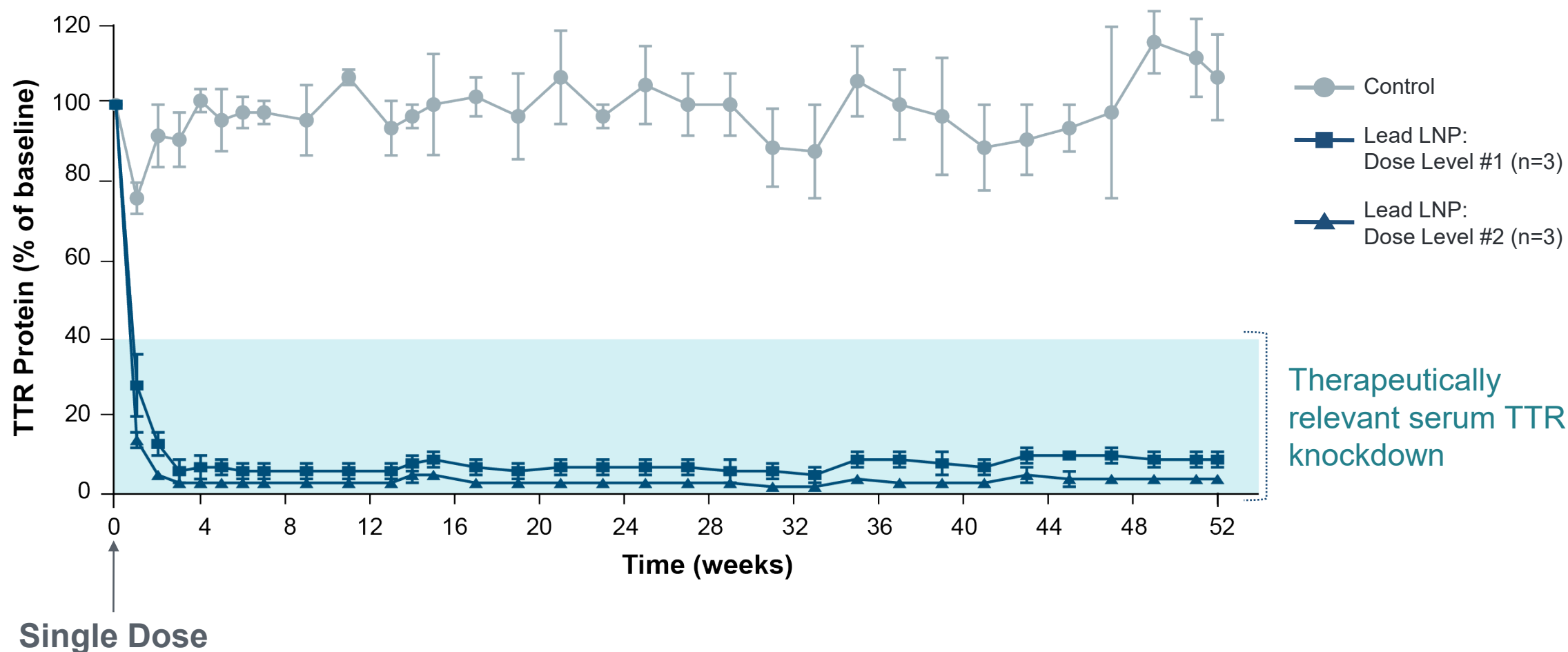
**2-15 years** typical life expectancy from onset of symptoms<sup>1</sup>

**Only chronic treatment options** currently available

## NTLA-2001 in development for ATTR

- Employs a KO edit to reduce circulating TTR protein levels
- Aims to address hATTR and wtATTR, both polyneuropathy and cardiomyopathy, with a single course of treatment

## ATTR: Sustained >95% Serum TTR Protein Reduction After a Single Dose in NHPs



Expect to dose first patient in Phase 1 study by year-end

# Hereditary Angioedema (HAE)



Genetic disease characterized by overproduction of bradykinin, which leads to **recurring, severe and unpredictable swelling** in various parts of the body

## 1 in 50,000

HAE patients<sup>1</sup>

Airway obstruction is particularly dangerous because it can cause death by asphyxiation

Attacks can occur every

## 7-14 days

on average for untreated patients<sup>1</sup>

**Only chronic treatment options** currently available

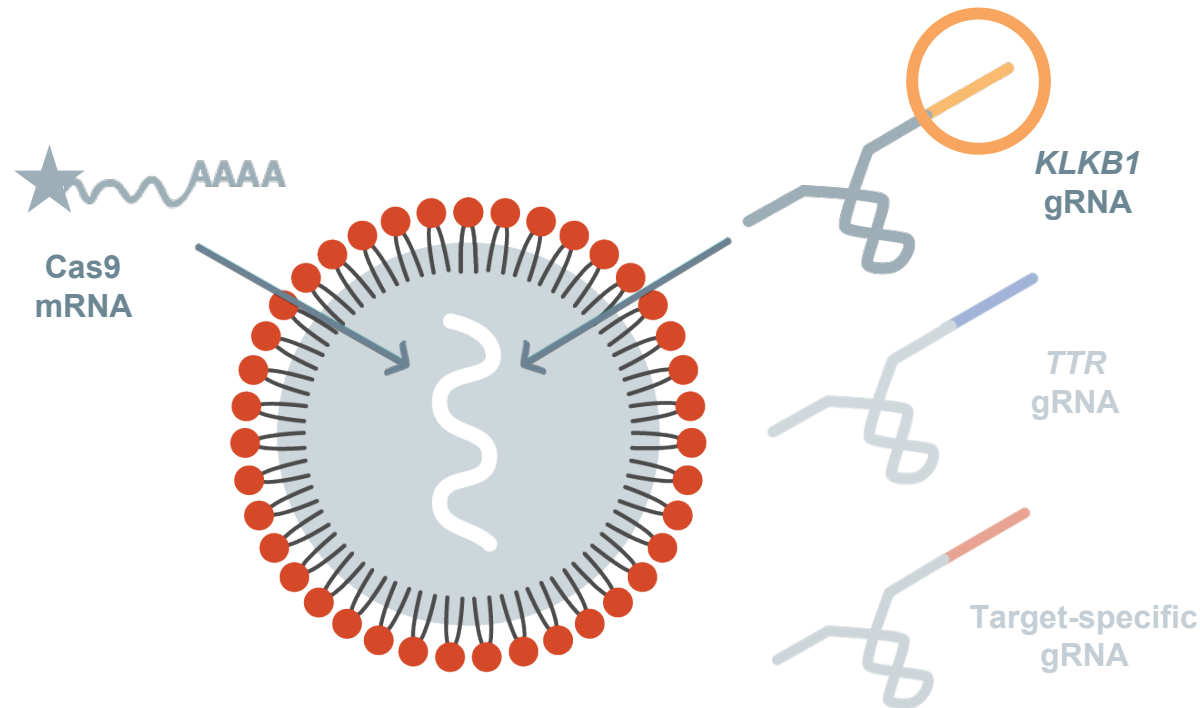
## NTLA-2002 in development for HAE:

- Employs a KO edit of *KLKB1* gene in hepatocytes
- Aims to reduce plasma kallikrein activity to prevent excess bradykinin production leading to HAE attacks after a single course of treatment

# HAE: Rapid Path to Clinic for Next KO Development Candidate, NTLA-2002

## LNP Delivery System

### *gRNA Reprograms Genetic Target*



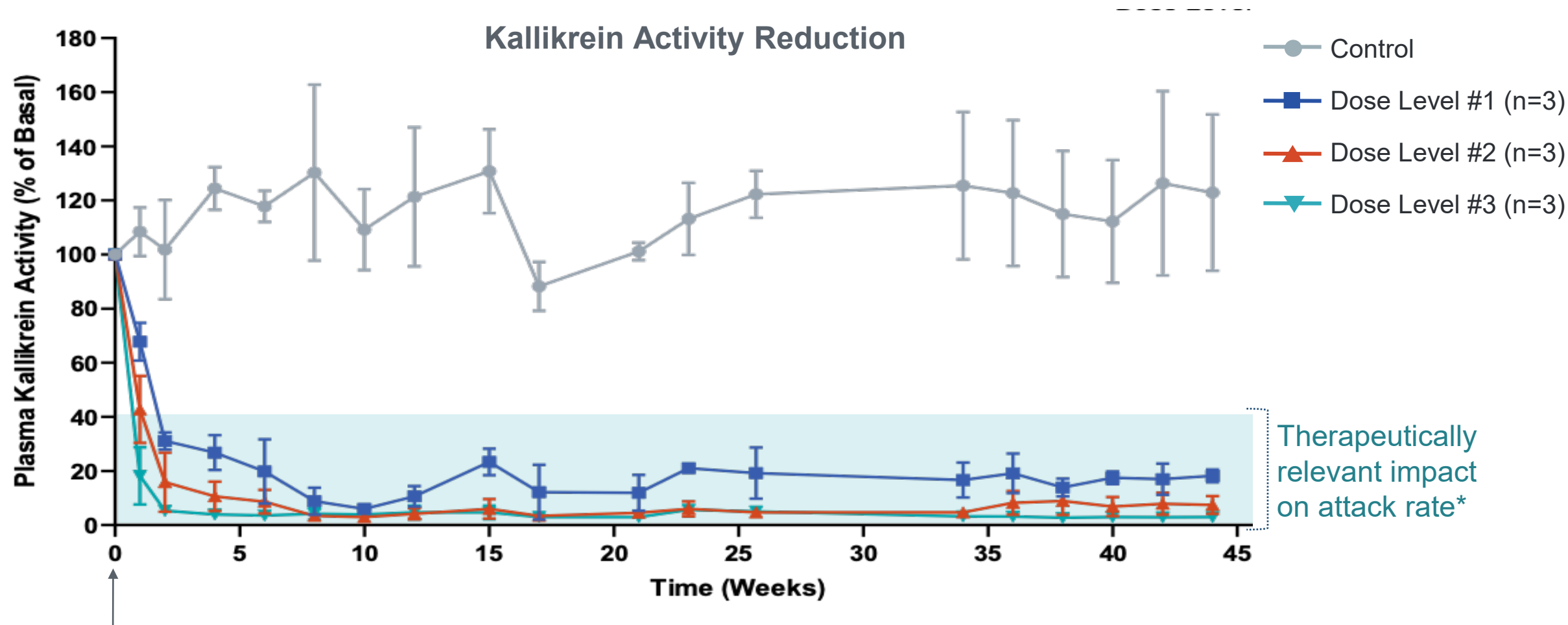
## HAE Program

Builds on ATTR program's infrastructure, including modular LNP delivery system

Applies insights gained from ATTR and other research programs to liver knockout target

Platform advances expedite progression to NHP proof-of-concept

## Achieved Sustained Therapeutically Relevant Kallikrein Activity Reduction After a Single Dose in NHPs

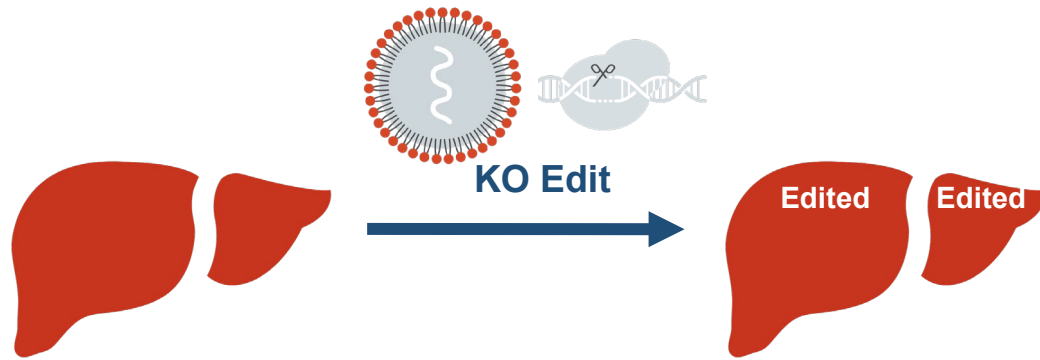


Single Dose

Expect to submit IND or IND-equivalent in 2H 2021

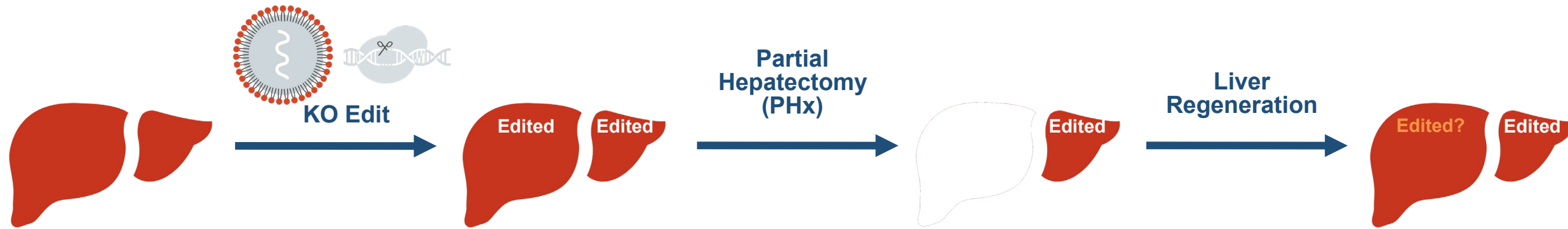


# Partial Hepatectomy Model for Investigating Persistence of KO Genome Editing



NHP studies demonstrate sustained KO editing and target TTR protein reduction carried through regular cell turnover for 12 months

# Partial Hepatectomy Model for Investigating Persistence of KO Genome Editing



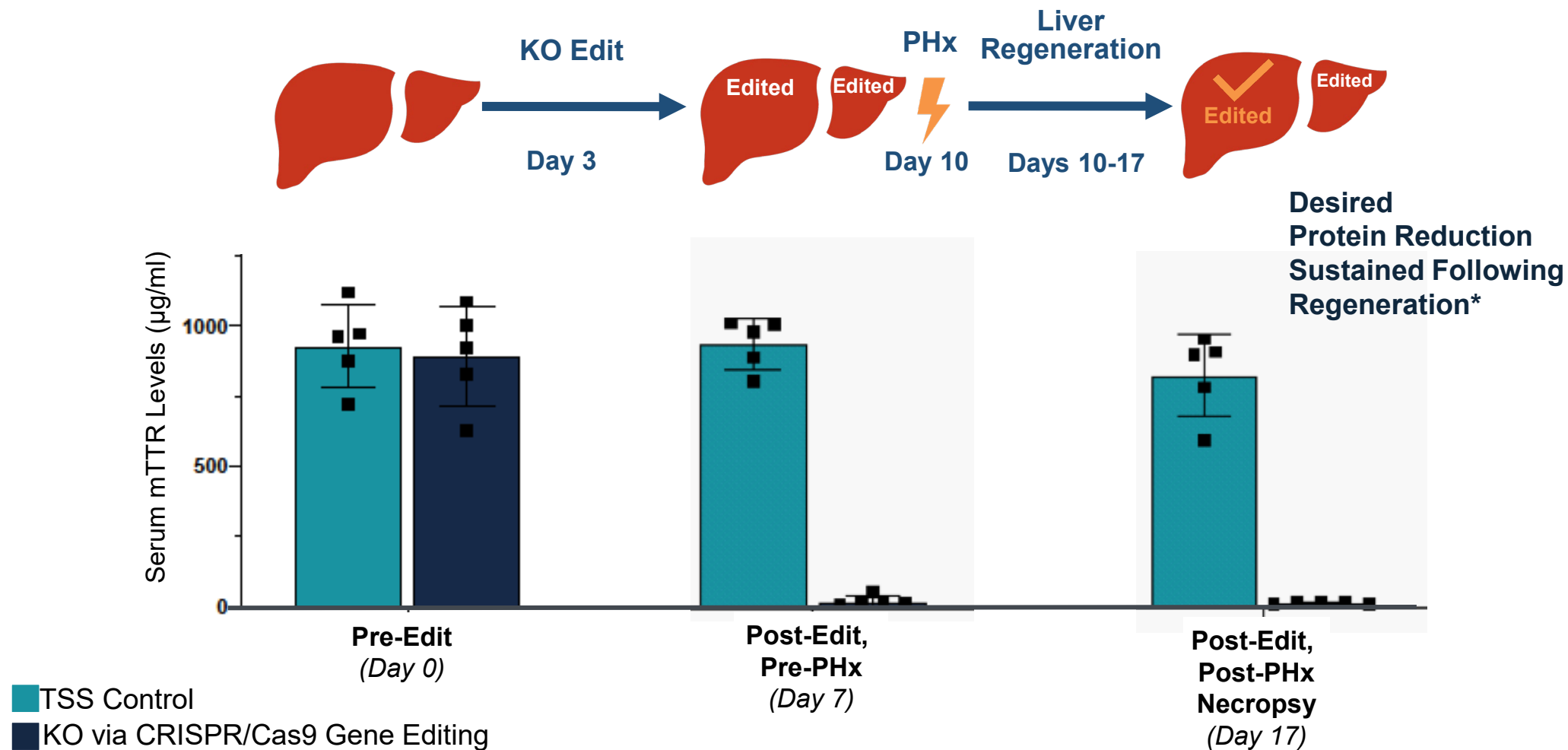
NHP studies demonstrate sustained KO editing and target TTR protein reduction carried through regular cell turnover for 12 months



**Key Question:** Can editing be carried through tissue regeneration following partial hepatectomy and accelerated cell division?

# Protein Reduction Remains Unchanged Following Murine Liver Regeneration

*Correlating gene editing rate similarly remains unchanged post-PHx by NGS analysis<sup>1</sup>*





## Targeted Gene Insertion Persistence

# Modular Approach to Unlocking Treatment of Genetic Diseases

## PROPRIETARY LNP DELIVERY SYSTEM

Transient expression

Large cargo capacity

Redosing capability

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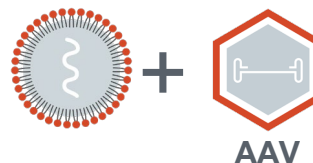
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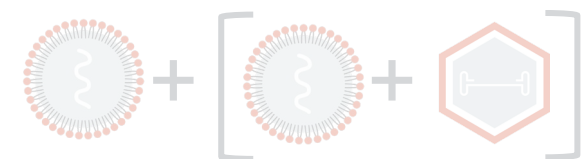
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# Hemophilia B (Hem B)



Rare genetic disorder caused by missing or defective **Factor IX (FIX)**, a blood-clotting protein encoded by the ***F9 gene***

## 1 in 30,000

Male births<sup>1</sup>

Primarily an X-linked disorder<sup>1</sup>

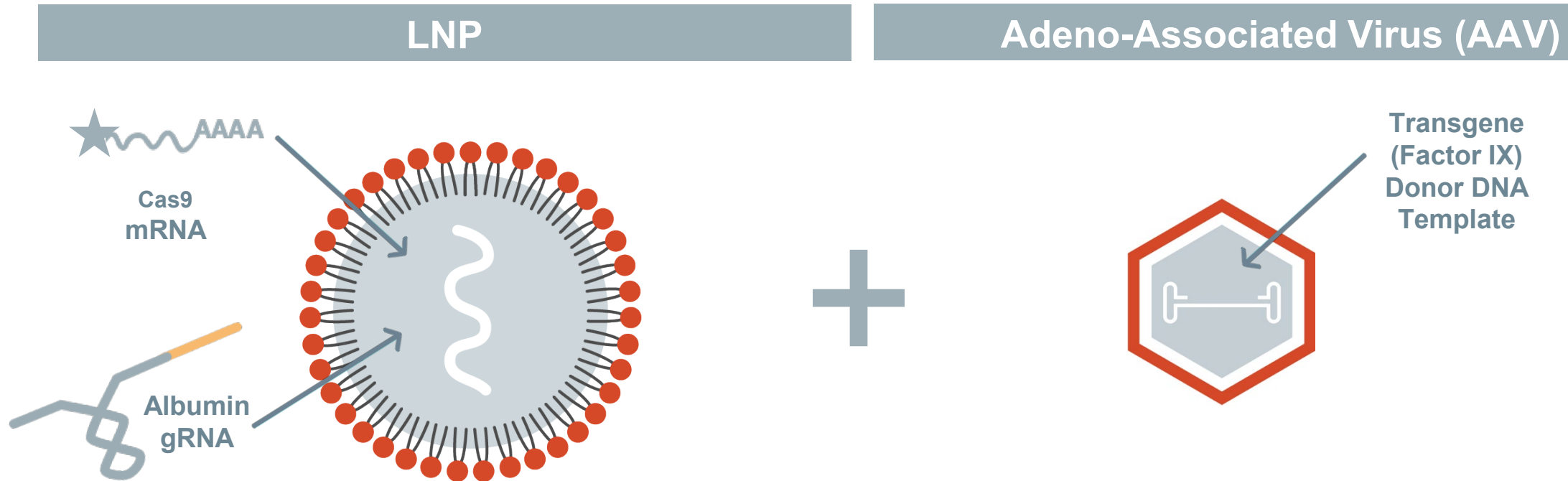
Severe cases often have **painful, spontaneous bleeding** into joints<sup>1</sup>

Patients treated chronically with replacement FIX protein

## Approach for Hem B:

- Targeted transgene insertion in albumin locus
- Aims to restore Factor IX protein
- First CRISPR-mediated transgene insertion in the liver of NHPs

# Effective Modular Approach for Targeted Gene Insertion in Liver

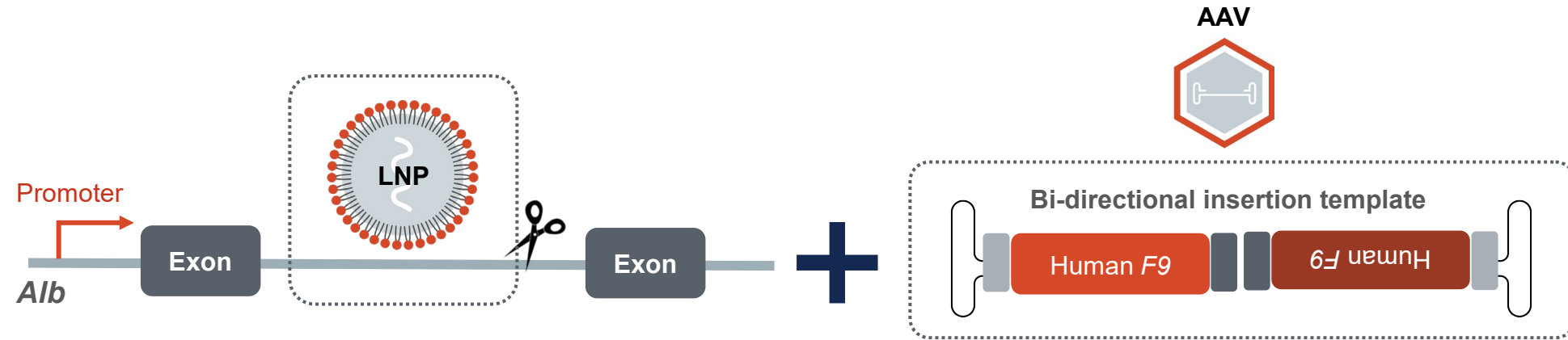


Precise integration under control of strong promoter, leads to strong, durable expression



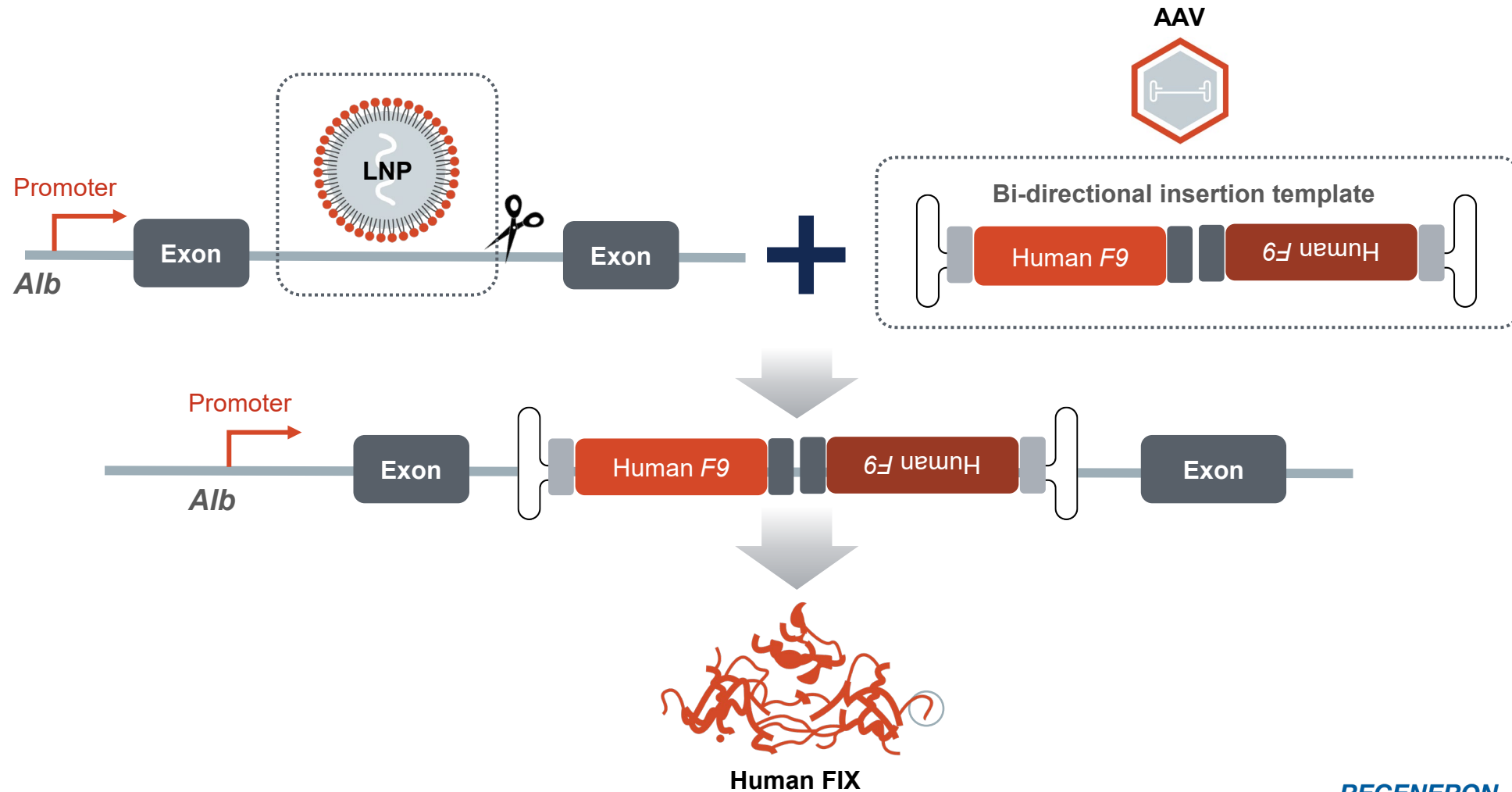
# *In Vivo* Insertion of *Factor 9* Gene at Albumin Intron Safe Harbor Site

*Hybrid Delivery System Precisely Integrates Into the Genome*

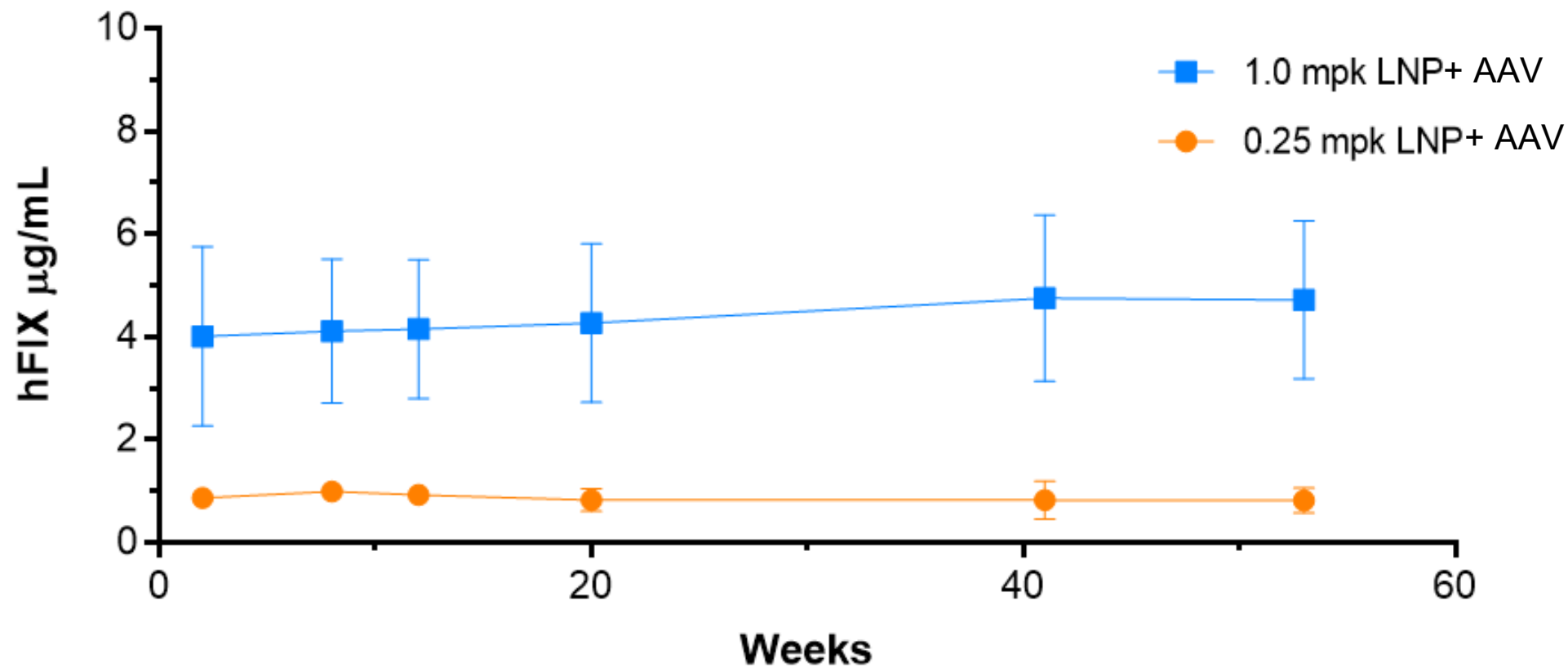


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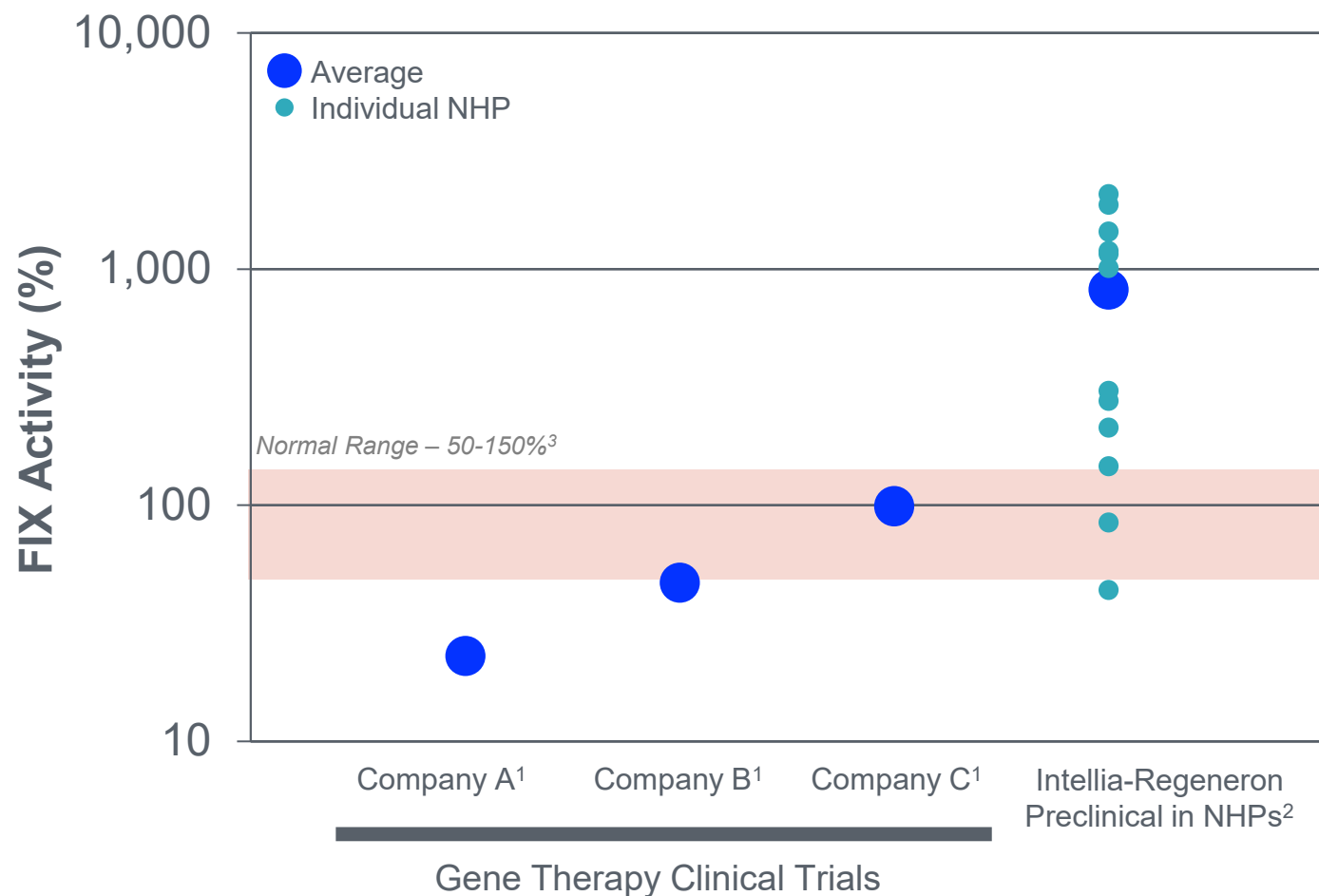


## FIX Levels in Adult Mice Are Stable Through the Completion of a 1-Year Durability Study





# Achieved Suprathreshold Levels of FIX Activity in NHPs



- Achieved an order of magnitude of greater activity than AAV gene therapy
- By varying multiple parameters we can achieve a range of circulating FIX levels and corresponding activity:

1. Guide RNA sequence to vary genomic insertion site
2. AAV dose that delivers inserted gene DNA sequence
3. LNP dose that delivers CRISPR tools

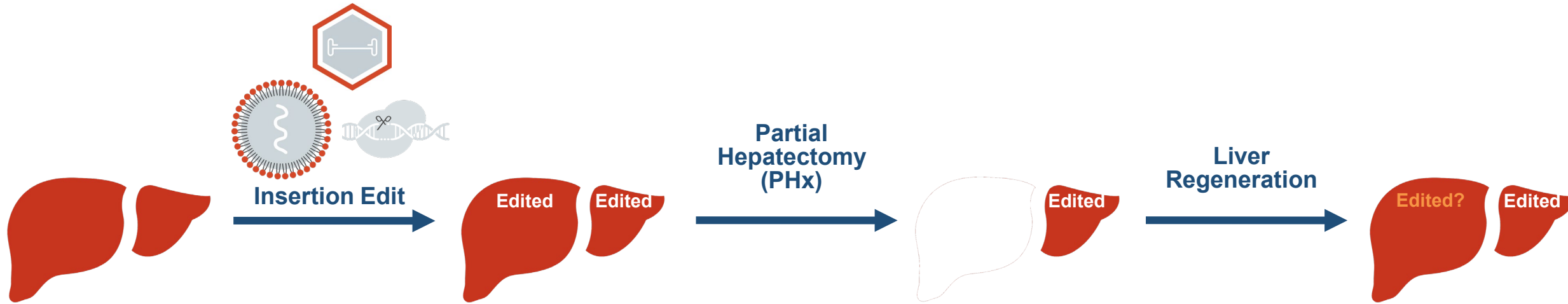
<sup>1</sup> Source: Representative presentations and press releases regarding clinical trials

<sup>2</sup> CRISPR-Cas9 targeted gene insertion technology day 42 post LNP/AAV dosing across multiple guides

<sup>3</sup> Source: National Hemophilia Foundation

All data generated with hyperfunctional FIX variant

# Partial Hepatectomy Model for Investigating Persistence of Insertion Genome Editing



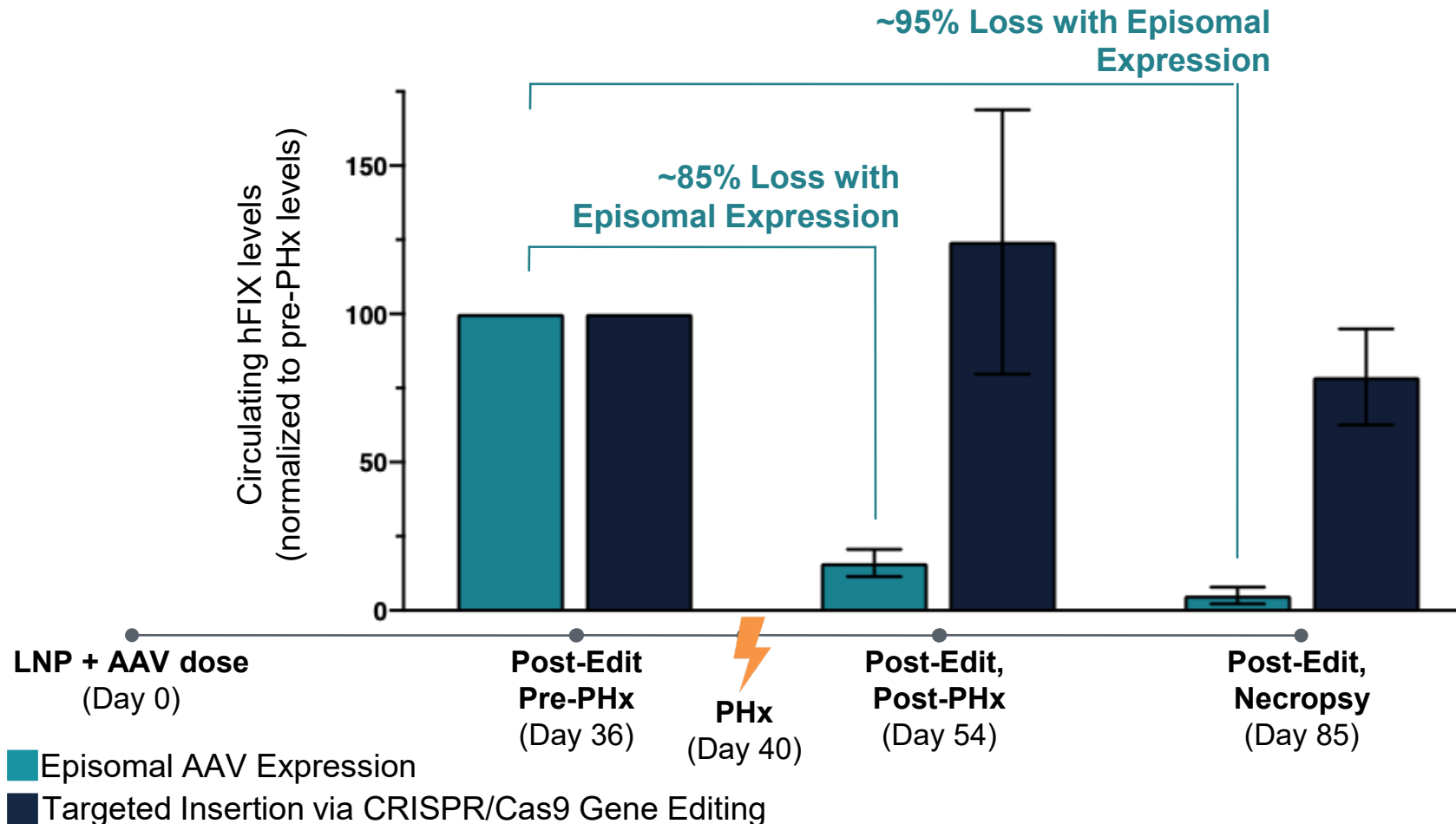
Rodent studies show sustained FIX insertion editing through 12 months, demonstrating that editing is carried through normal cell turnover



**Key Question:** Can insertion editing be carried through tissue regeneration following partial hepatectomy?

# Persistent Protein Levels Post-PHx from Targeted Gene Insertion in Murine Model, in Comparison to Significant Loss of Protein Expression with Gene Therapy

*Correlating editing rate similarly remains unchanged post-PHx by NGS analysis<sup>1</sup>*



# Key Takeaways

- Intellia's **non-viral LNP CRISPR/Cas9 modular platform** enables rapid pipeline development for liver targets
  - NTLA-2001 for ATTR: Expect to dose first patient by year-end
  - NTLA-2002 for HAE: Plan to submit a regulatory application in 2H 2021
- **Achieved supra-therapeutic levels of FIX activity in NHP** to advance targeted gene insertion for hemophilia B with partner Regeneron
- **Demonstrated persistence of gene KO and insertion** in a PHx model of accelerated hepatocyte turnover supporting potential for single-course curative therapies
- CRISPR gene insertion has **superior profile vs. AAV gene therapy**

# Intellia

THERAPEUTICS