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Preclinical development of EDIT-401, a durable *in vivo* CRISPR gene-editing therapy that upregulates LDLR protein to lower LDL-C

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Disclaimer: Anshul Gupta is an employee and equity holder of Editas Medicine, Inc.

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Introduction and Methods

ASCVD is a serious disease with significant opportunity for a transformative therapy to reduce LDL-C

ASCVD is driven by **cholesterol-rich** plaque accumulation in the arteries

- ASCVD is the primary cause of morbidity and mortality globally[1], including in patients with heterozygous familial hypercholesterolemia (HeFH), a genetic disease primarily related to loss of function mutations in *LDLR* gene[2]
- The link between lower LDL-C and reduced ASCVD risk is well established[1]
- ~75% of patients with ASCVD do not meet LDL-C goals[3,4]
- Standard of care requires multiple therapies and lifelong administration[1]

Robust, lifelong reduction of LDL-C provides maximal benefit[5,6]

1. Arnett DK *et al*. *Circulation* 2019; 140 (11): e596–e646. **2**. Gidding SS *et al. J Am Heart Assoc* 2025;14:e038458. **3**. Gu J *et al*. *Am J Prev Cardiol* 2022; 10: 100336. **4.** Klimchak AC *et al. Am J Prev Cardiol* 2020; 1: 100010. **5.** Cohen JC *et al. N Engl J Med* 2006; 354 (12): 1264–1272. **6.** Gaba P *et al. Circulation.* 2023; 147 (16): 1192–1203.
ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

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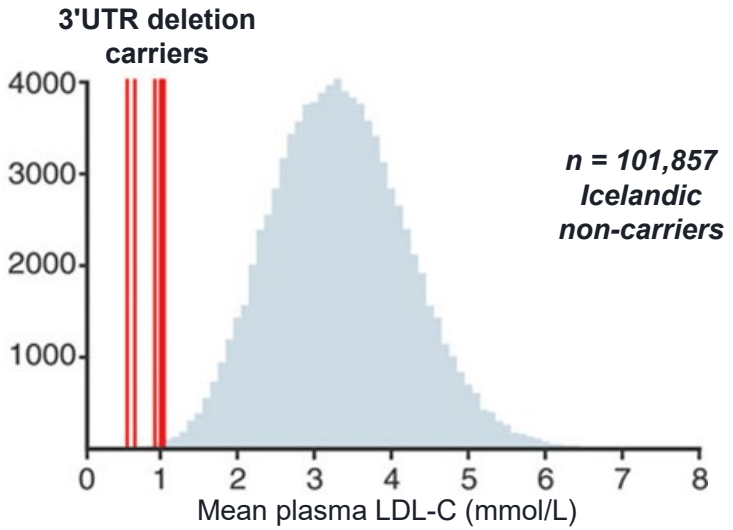
Editas' therapeutic strategy of LDLR upregulation for LDL-C reduction was informed by human genetics

Seven Icelandic family members identified as carriers of partial *LDLR* 3' UTR deletion[1]

Plasma LDL-C levels[1]



No adverse impacts on health[1]

LDL-C:

- **13–72 mg/dL** plasma levels (74% lower than population mean)

LDLR:

- **1.5–2.5-fold** higher surface LDLR*

Safety:

- No adverse events

1. Bjornsson E *et al*. *Circ Genom Precis Med* 2021; 14 (1): e003029.
*Noted value was for lymphocytes. Liver values are unknown. LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; UTR, untranslated region.

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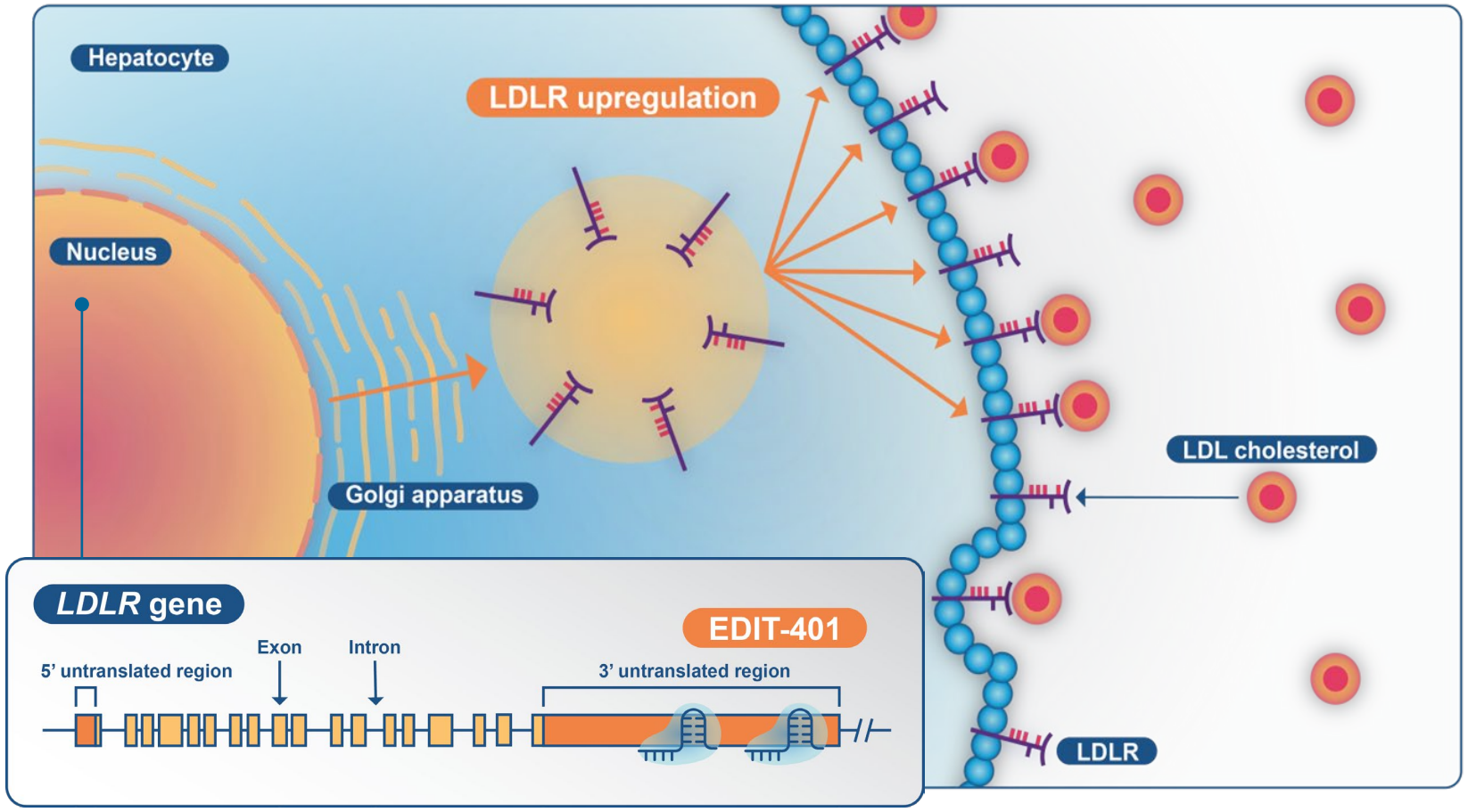
EDIT-401 uses a differentiated mechanism of action to reduce LDL-C

EDIT-401 therapeutic strategy for LDLR upregulation



- CRISPR/Cas9 nuclease and dual gRNAs disrupt negative regulatory elements of the *LDLR* gene, increasing mRNA stability, enabling **≥6-fold increase in LDLR protein in NHP**[1]
- This amplification approach enables **≥90% mean reduction in serum LDL-C** in NHPs and mouse models with high baseline LDL-C and reduced LDLR function[1]

1. Editas Medicine. Data on file.

Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LDL, low-density lipoprotein; NHP, non-human primate.

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We conducted a series of studies to support the preclinical development of EDIT-401

- NHP data (presented here)
  - Pharmacology
  - Biodistribution
  - Safety and tolerability

- Mouse data (Poster #3423):

"Pharmacokinetics and pharmacodynamics of EDIT-401(mu), *in vivo* gene-editing therapy for lowering LDL-C in mice”

LDL-C, low-density lipoprotein cholesterol; NHP, non-human primates.

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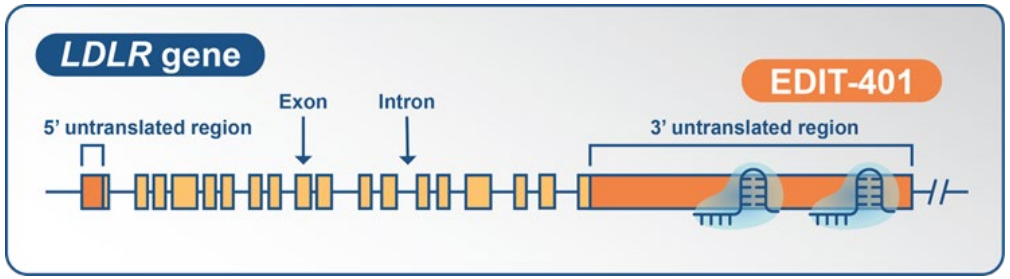
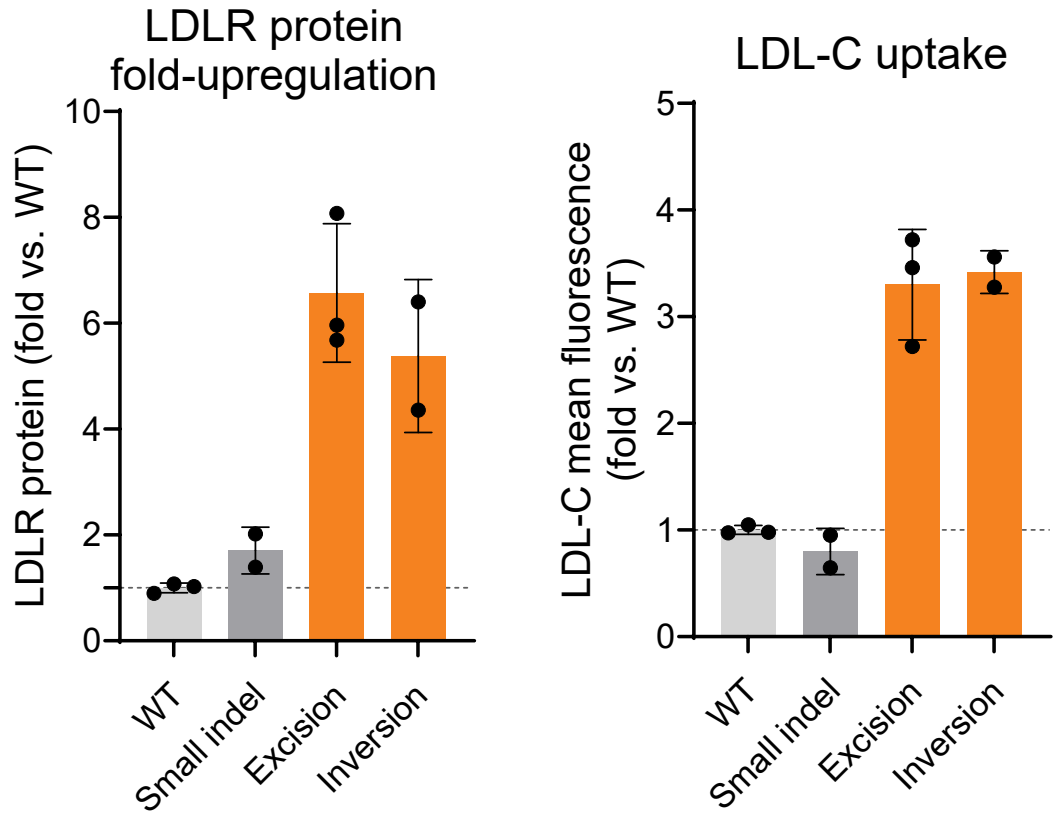
Pharmacology

CRISPR/Cas9 and dual gRNA-based strategy with LNP delivery creates a potent approach to LDLR upregulation for LDL-C reduction

- CRISPR/Cas9 nuclease and dual gRNAs disrupt negative regulatory elements in the 3' UTR, increasing mRNA stability
- Functional editing events are the result of targeted excisions or inversions
- Non-functional editing events are small indels resulting from the action of one of the gRNAs



Functional edits increase LDLR protein expression and LDL-C uptake



3' UTR, three prime untranslated region; Cas, CRISPR-associated protein; CRISPR, clustered regularly interspaced short palindromic repeats; HepG2, hepatoma G2 cells; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; gRNA, guide RNA; mRNA, messenger RNA; WT, wild-type.

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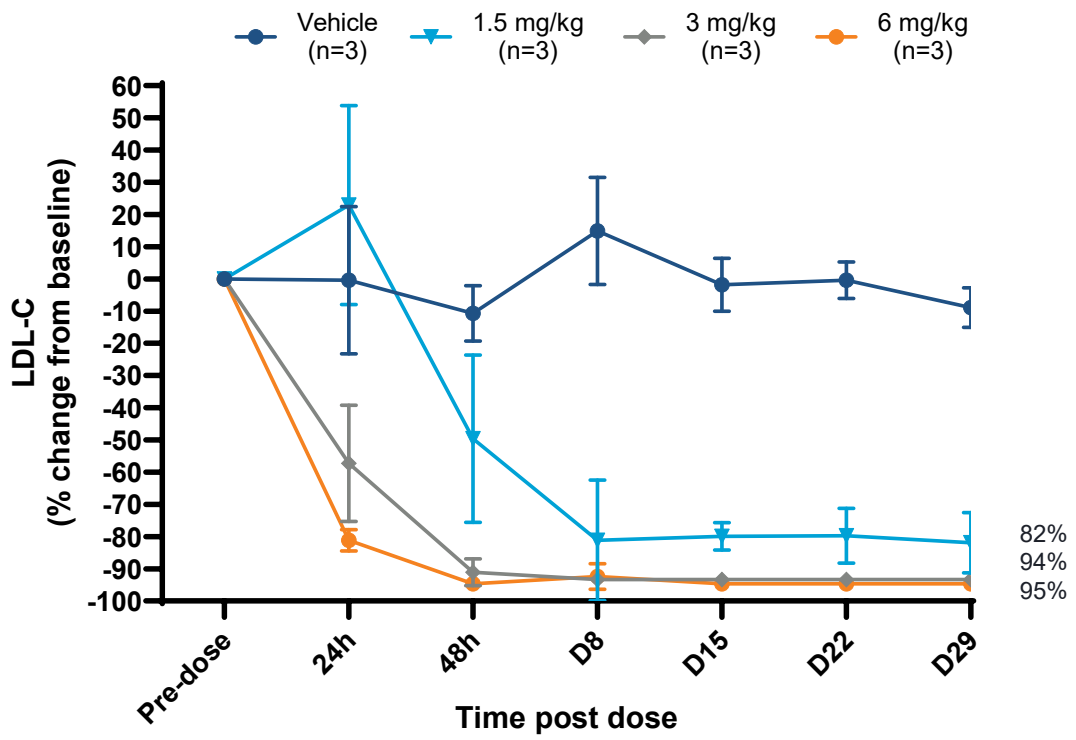
EDIT-401 achieved >90% mean LDL-C reduction by upregulating LDLR; Dose Range Finding (DRF) Study data shown

EDIT-401, CRISPR/Cas9 nuclease, and dual gRNAs for LDLR upregulation encapsulated in a GalNAc conjugated LNP administered to non-human primates

Single dose of EDIT-401



- >90% mean LDL-C reduction averaged across all dose groups
- Rapid LDL-C reduction observed
- Consistent data across 4 independent NHP studies

Pre-dose LDL-C was averaged across two timepoints to account for variability in measurements. Day 1 defined as day of dosing. Mean values are shown +/- SD, with mean values of 89% at 1.5 mg/kg, and 94% for all other dose groups at D29. Values below lower limit of quantitation assigned as LLoQ/2.

Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; D, day; GalNAc, N-acetylgalactosamine; gRNA, guide RNA; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LLoQ, lower limit of quantification; LNP, lipid nanoparticle; NHP, non-human primate, LNPs licensed from Genevant Sciences Corporation.

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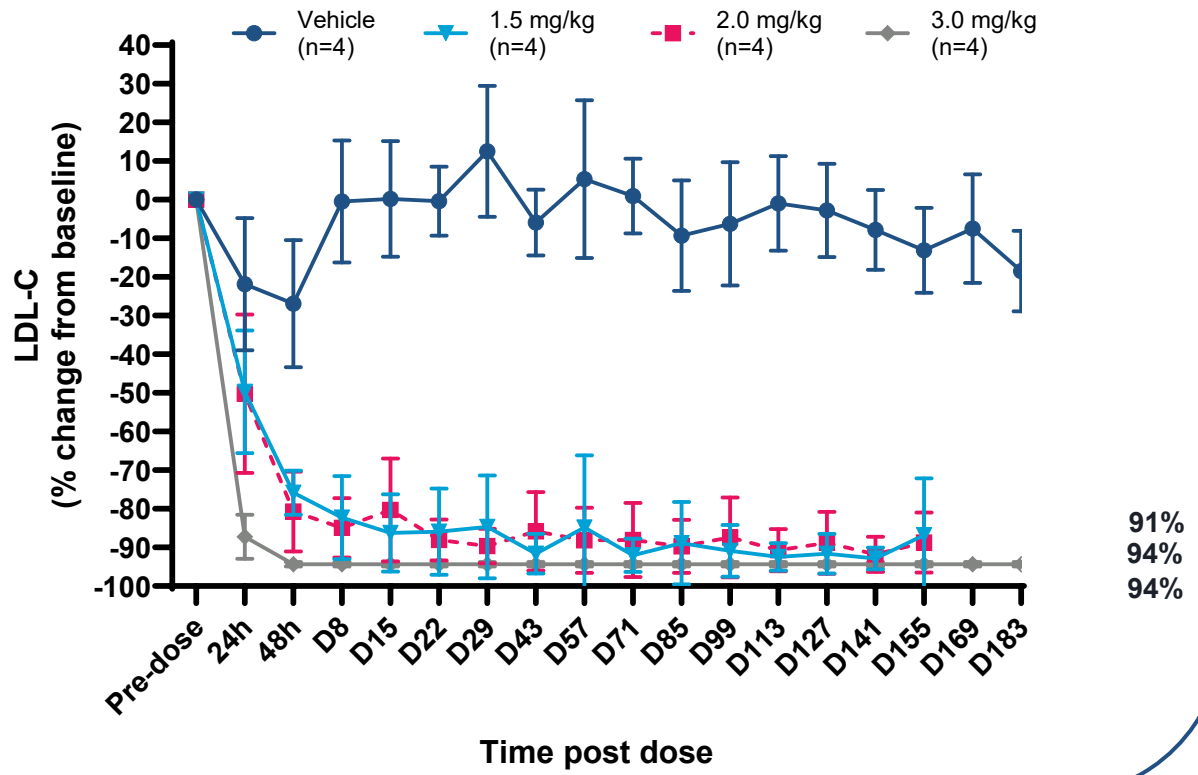
EDIT-401 displayed rapid, robust and durable LDL-C reduction

EDIT-401, CRISPR/Cas9 nuclease, and dual gRNAs for LDLR upregulation encapsulated in a GalNAc conjugated LNP administered to non-human primates

Single dose of EDIT-401



- Rapid LDL-C reduction
- Robust LDL-C reduction across a dose range
- Durability of LDL-C reduction at all doses through ~6 months

Pre-dose LDL-C was averaged across two timepoints to account for variability in measurements. Day 1 defined as day of dosing. Mean values are shown +/- SD, n=4/group.
Values below lower limit of quantitation assigned as LLoQ/2. ALT, alanine transaminase; AST, aspartate transaminase; Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; D, day; GalNAc, N-acetylgalactosamine; gRNA, guide RNA; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LLoQ, lower limit of quantification; LNP, lipid nanoparticle; NHP, non-human primate, LNPs licensed from Genevant Sciences Corporation.

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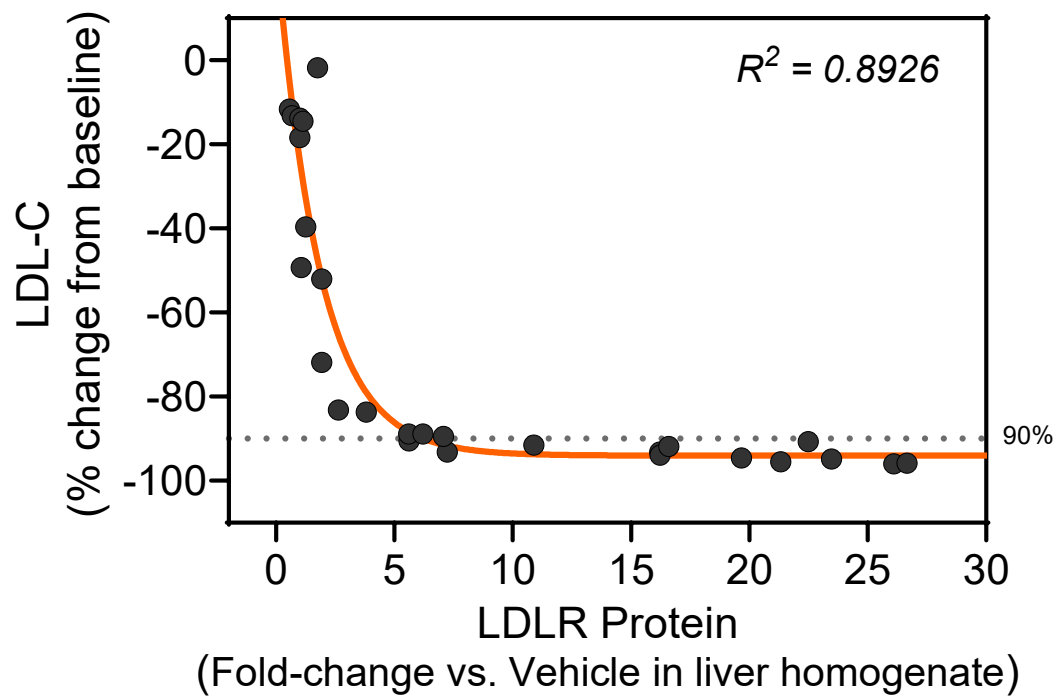
EDIT-401 enables increase in LDLR protein levels needed to achieve ≥90% LDL-C reduction in NHPs

LDL-C vs LDLR protein



- ✓ A >6-fold mean increase in LDLR protein in liver resulted in ≥90% LDL-C reduction in NHPs
- ✓ Approximately 10%–40% functional editing can lead to the LDLR protein increase resulting in ≥90% LDL-C reduction in NHPs

LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; NHP, non-human primate, LNPs licensed from Genevant Sciences Corporation.

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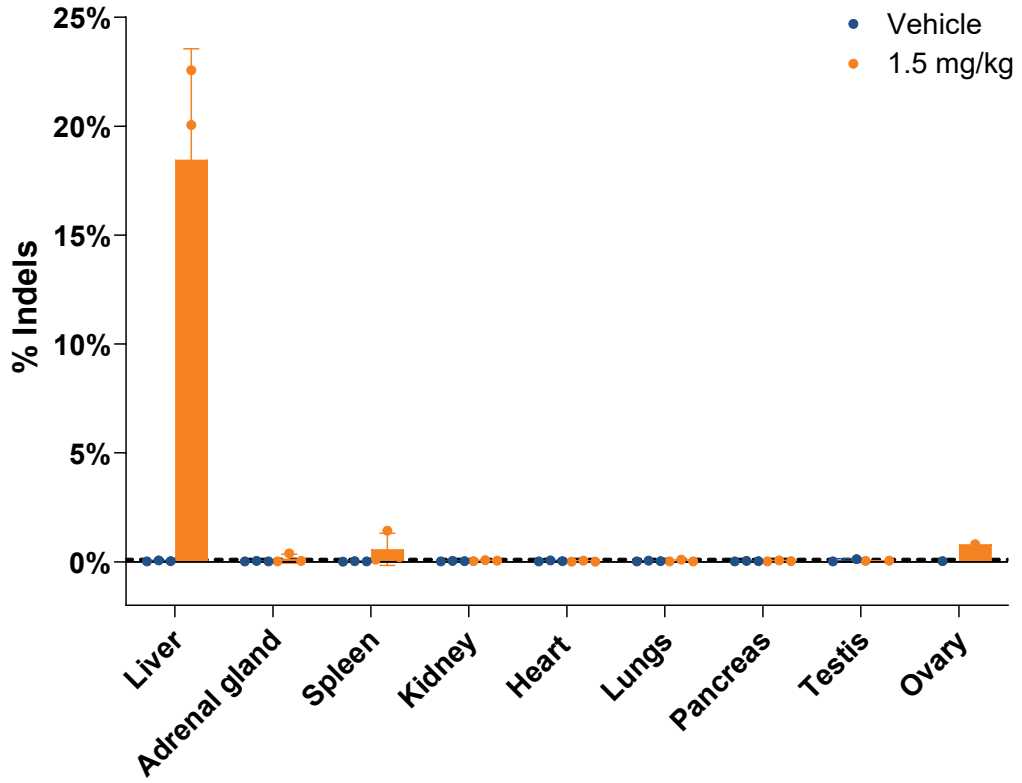
Biodistribution

Highest delivery of EDIT-401 observed in liver as compared to non-target tissues (assessed by editing levels)

Non-target tissue editing

- Low editing detected in adrenal gland, spleen and ovary of NHP
- No significant editing observed in any other of 31 total extrahepatic tissues tested (data from major organs shown)

Single dose of EDIT-401 at 1.5 mg/kg, D29



Graph show % indels in LDLR 3'UTR across liver and all non-target tissues. Representative data shown with one of the EDIT-401 gRNAs by targeted amplicon sequencing.

D, day; gRNA, guide RNA; LDLR, low-density lipoprotein receptor; NHP, non-human primate, LNPs licensed from Genevant Sciences Corporation.

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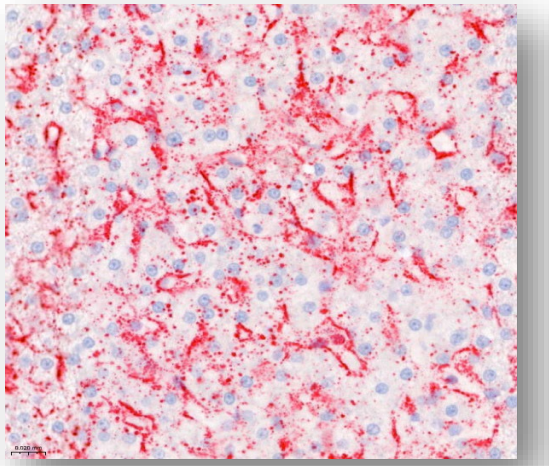
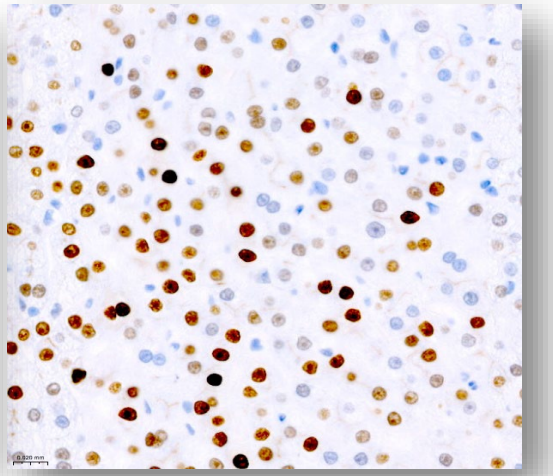
EDIT-401 demonstrates high delivery in hepatocytes and undetectable cargo in oocytes at therapeutically relevant dose of 1.5 mg/kg

24hr ISH

24hr IHC

Liver (20x)

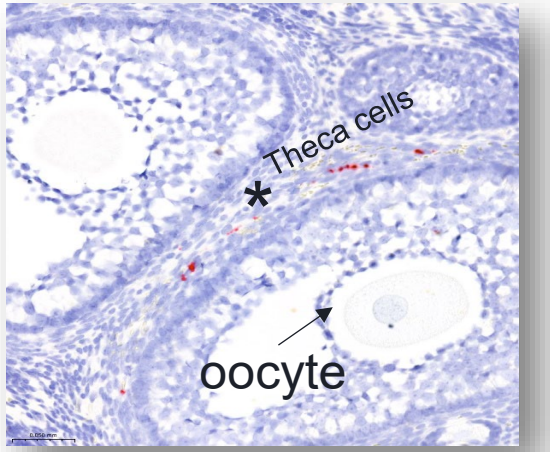


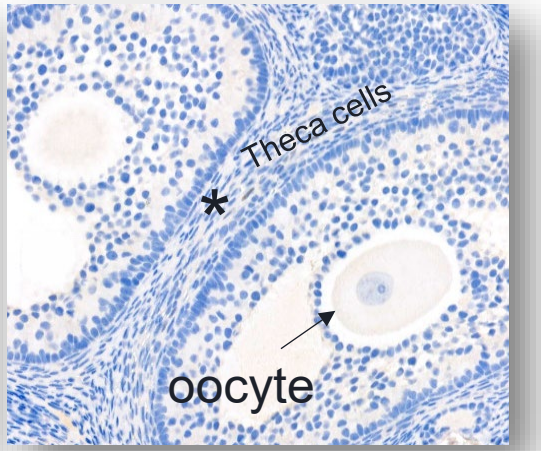


Cas9 mRNA Nuclei

Cas9 Protein Nuclei

Ovary (30x)

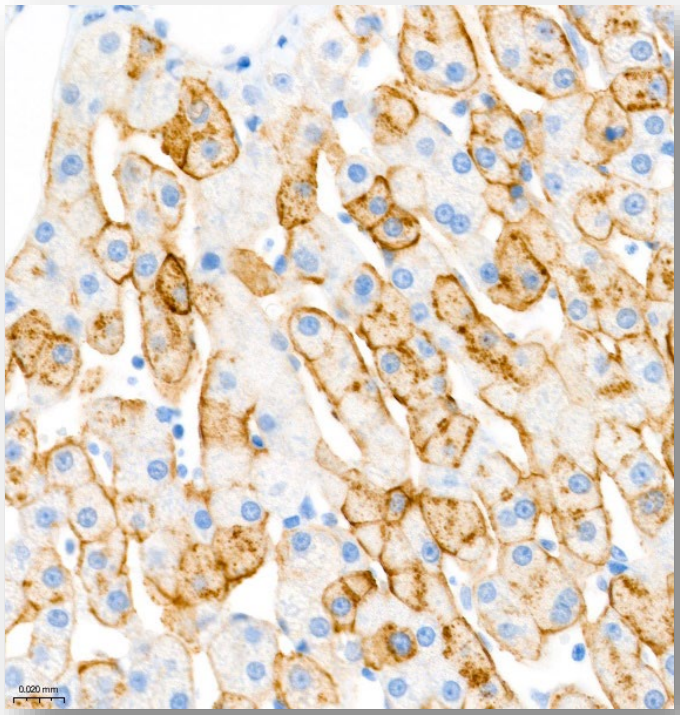




Positivity restricted to Theca cells

Day 29 IHC

Liver (20x)



LDLR Protein Nuclei

Consistent results observed with1.5 mg/kg dose and at 3 mg/kg of EDIT-401. Cas9 mRNA detected by *in-situ* hybridization. Cas9, CRISPR-associated protein 9; IHC, immunohistochemistry; ISH, *in-situ* hybridization; LDLR, low-density lipoprotein receptor, LNPs licensed from Genevant Sciences Corporation.

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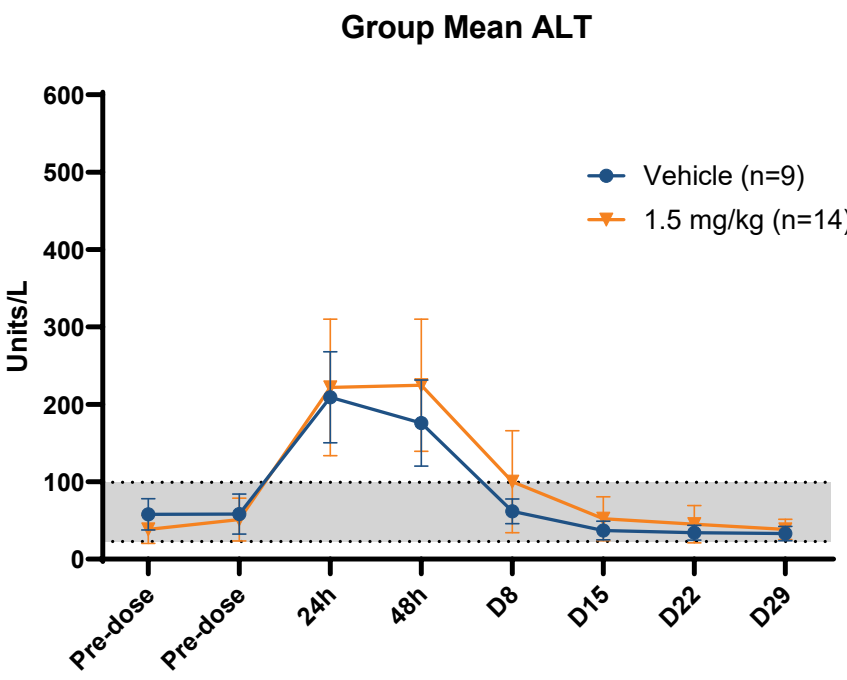
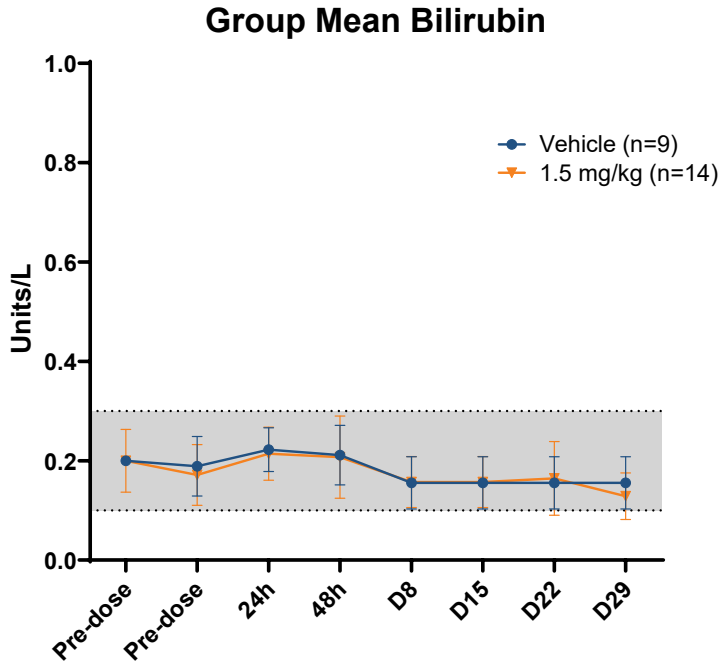
Safety and tolerability

No notable treatment-related liver enzyme elevations or liver histopathology findings at therapeutically relevant dose of 1.5 mg/kg





Data presented from 3 NHP studies
Shaded area represent normal range observed in NHPs
Vehicle dosed with saline following same pre-treatment regimen as EDIT-401

EDIT-401 safety observations at therapeutically relevant dose of 1.5 mg/kg:

- Well-tolerated with no adverse clinical observations
- Transient ALT elevations observed (similar to vehicle control) with resolution in ~1 week
- No liver histopathology findings

ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, day; NHP, non-human primate, LNPs licensed from Genevant Sciences Corporation.

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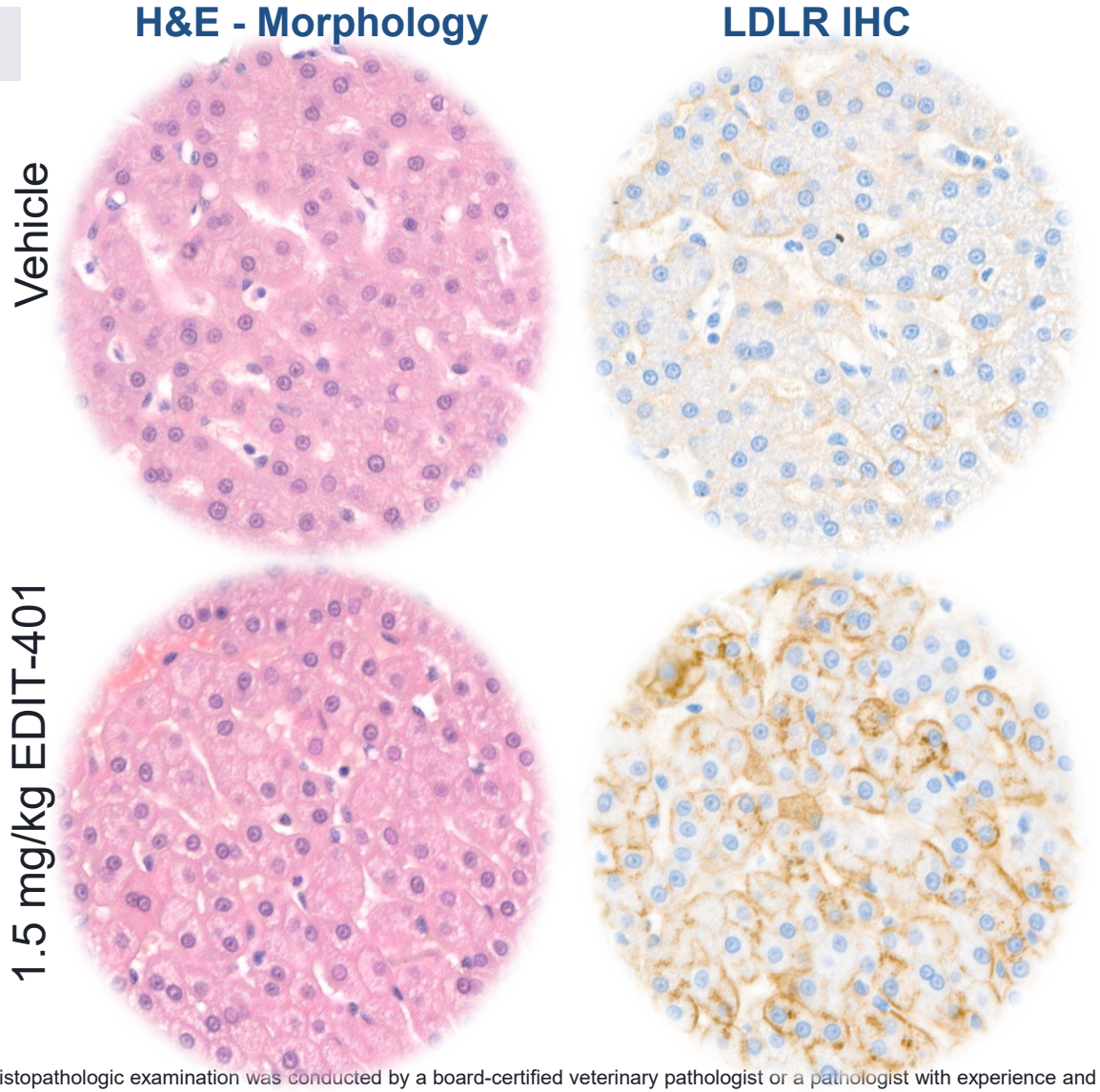
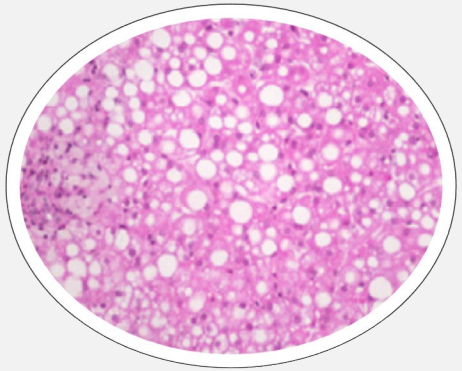
Histopathology shows no changes in EDIT-401 treated NHP livers compared to vehicle on D29

40X



EDIT-401 data at therapeutically relevant dose of 1.5 mg/kg:

- No evidence of steatosis or fatty liver was observed, even in areas of high LDLR IHC positivity
- Compare to reference image (below)



Qu P *et al*. *Cell Metabolism*, 2023; 35, 742-757.e10

Histopathologic examination was conducted by a board-certified veterinary pathologist or a pathologist with experience and training in toxicologic pathology. No abnormal findings reported in the liver sections examined from the study in all the animals dosed at 1.5 mg/kg. D, day; H&E, hematoxylin and eosin; IHC, immunohistochemistry; LDLR, low-density lipoprotein receptor; NHP, non-human primate, LNPs licensed from Genevant Sciences Corporation.

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Conclusions

- EDIT-401 combines Editas' drug development expertise and Genevant's LNP to deliver a differentiated therapeutic strategy of functional LDLR upregulation
- A single dose of EDIT-401 achieved ≥90% mean LDL-C reduction with ≥6-fold mean increase in LDLR protein in the NHP liver, requiring only a moderate level of functional editing of *LDLR* alleles
- EDIT-401 showed durability of LDL-C reduction across a range of doses through Day 183
- EDIT-401 demonstrated a promising preclinical safety profile in NHPs that was well tolerated at therapeutically relevant dose.
- Biodistribution data shows highest delivery in hepatocytes with undetectable cargo signal in oocytes at therapeutically relevant dose
- Encouraging preclinical data supports advancing EDIT-401 towards a first-in-human clinical trial

CRISPR, clustered regularly interspaced short palindromic repeats; LDLR, low-density lipoprotein receptor; Ldlr, murine low-density lipoprotein receptor; LDL-C, low-density lipoprotein cholesterol; LNP, lipid nanoparticle; NHP, non-human primate.

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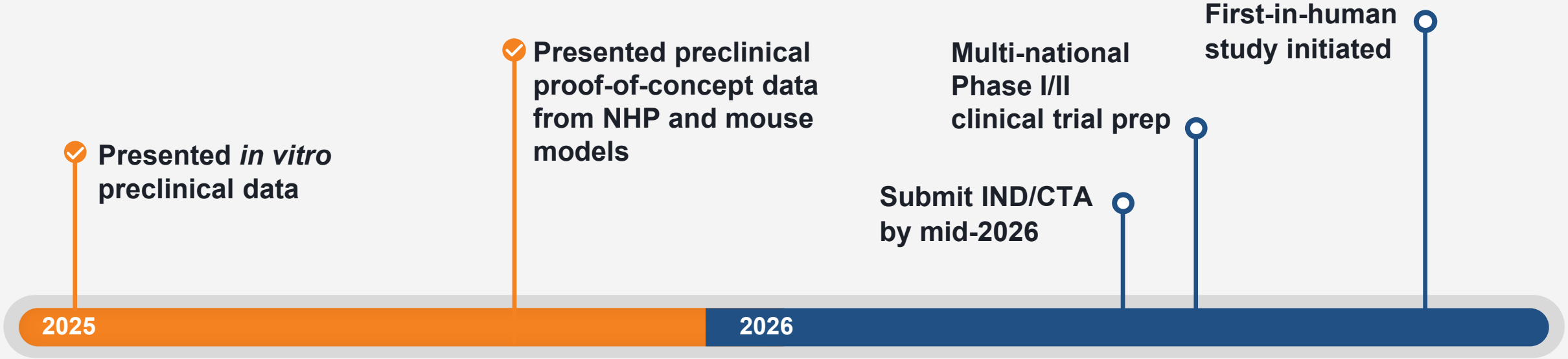
Next Steps & Timing



CTA, Clinical Trial Application; IND, Investigational New Drug Application; NHP, non-human primate.

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