OR069

A transformative LDL cholesterol-lowering *in vivo* CRISPR gene editing medicine that functionally upregulates LDLR in mice and non-human primates

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Speaker disclosures

- Linda Burkly, PhD
  - Financial disclosure and potential conflict of interest: Employee of Editas Medicine

EDIT-401: A potential best-in-class, *in vivo*, gene editing medicine to reduce LDL-C

Robust preclinical efficacy data with a **≥90% mean reduction of LDL-C**[1]

Potential **one-time treatment** designed for lifelong benefit

Compelling preclinical data supporting rapid progression to **human proof-of-concept**

LDL-C, low-density lipoprotein cholesterol.

1. Editas Medicine. Data on file.

Atherosclerotic cardiovascular disease 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]
- **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**[2,3]
- **Standard of care requires multiple therapies and lifelong administration**[1]

Intensive, lifelong reduction of LDL-C provides maximal benefit[4,5]

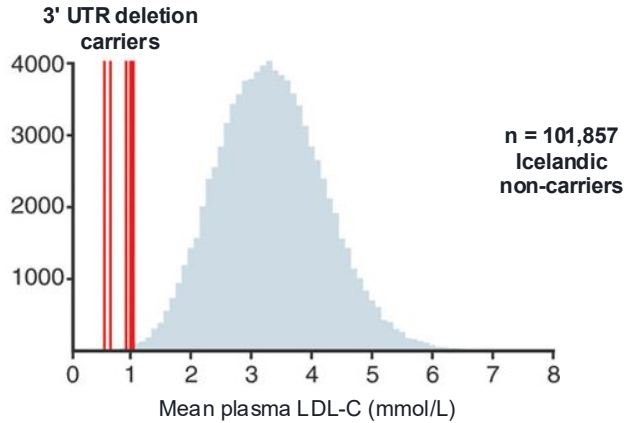
ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

1. Arnett DK *et al. Circulation* 2019; 140 (11): e596–e646. **2**. Gu J *et al. Am J Prev Cardiol* 2022; 10: 100336. **3.** Klimchak AC et al. Am J Prev Cardiol 2020;1:100010 4. Cohen et al. N Engl J Med 2006; 354:1264-72 **5.** Gaba *et al. Circulation.* 2023; 147(16):1192-1203.

Therapeutic strategy of LDLR upregulation for LDL-C reduction is informed by human genetics

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

Plasma LDL-C levels[1]



Impact on Carriers[1]

LDL-C:

- **0.35–1.87 mmol/L (13–72 mg/dL)** plasma levels
- **Mean 74% lower** in carriers compared to non-carriers

LDLR:

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

Safety:

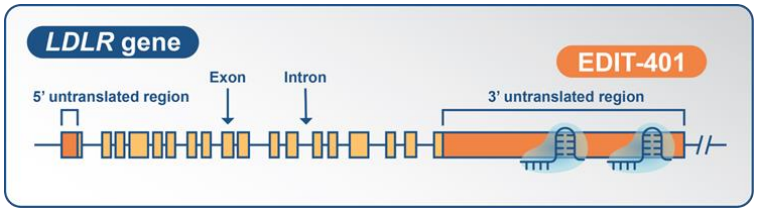
- No adverse events

LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; 3' UTR, three prime untranslated region.

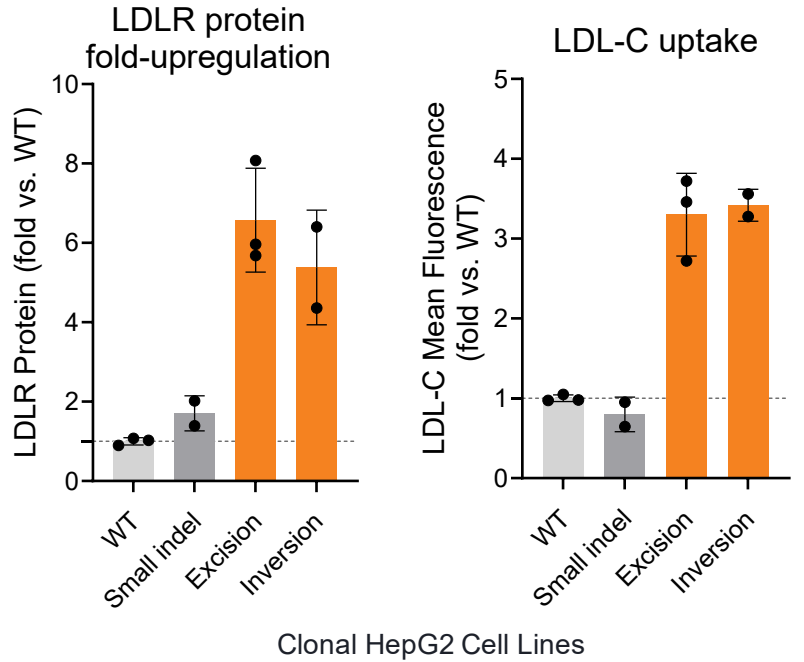
1. Bjornsson *et al. Circ Genom Precis Med* 2021; 14 (1): e003029.

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



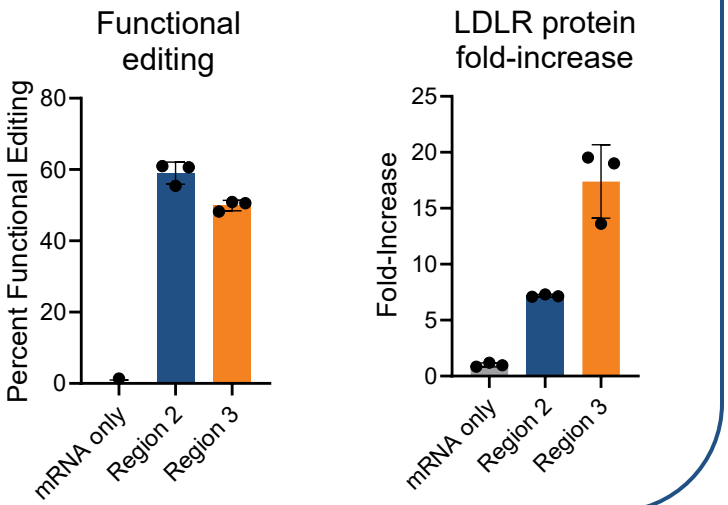
Functional edits increase LDLR protein expression and LDL-C uptake



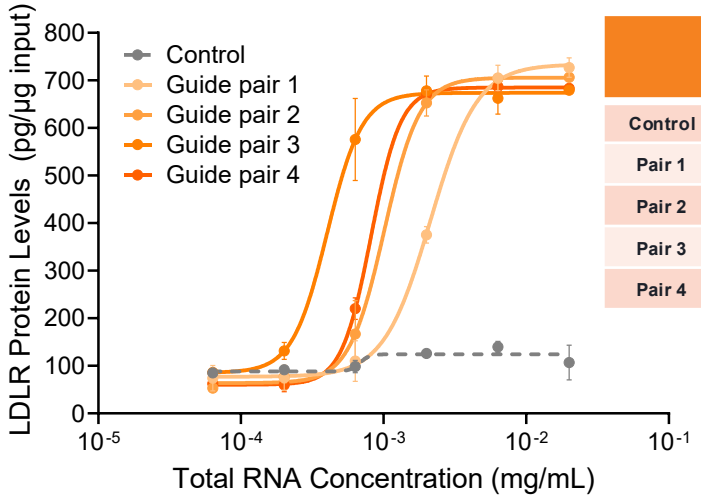
3' UTR, three prime untranslated region; Cas, CRISPR-associated protein; CRISPR, clustered regularly interspaced short palindromic repeats; HepG2, hepatoma G2 cells; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; WT, wild-type.

Comprehensive *in vitro* screening of LDLR regulatory regions and editing cargos identified optimal therapeutic strategy

Step 1: Identification of target region for optimal LDLR protein increase



Step 2: Identification of Region 3 lead guide pair for LDLR protein increase based on potency



	Max protein upregulation (vs. control)	EC_{50}
Control	1	N/A
Pair 1	6.8	2.1×10^{-3}
Pair 2	6.6	1.0×10^{-3}
Pair 3	6.3	4.0×10^{-4}
Pair 4	6.4	8.2×10^{-4}

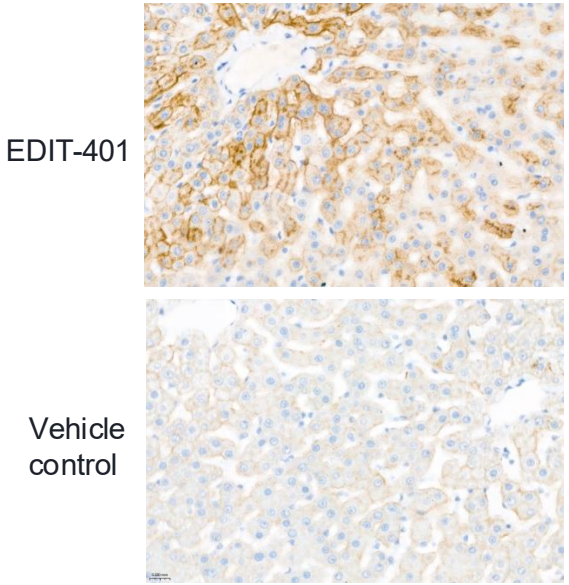
All optimization data are from primary human hepatocytes. Region 3 lead guide pair is Human-NHP cross-reactive. Step 1 delivery by RNA lipofection. Step 2 delivery by LNP.

EC_{50}, half maximal effective concentration; LDLR, low-density lipoprotein receptor; N/A, not available.

EDIT-401 achieved 98% mean LDL-C reduction by inducing LDLR upregulation in NHPs

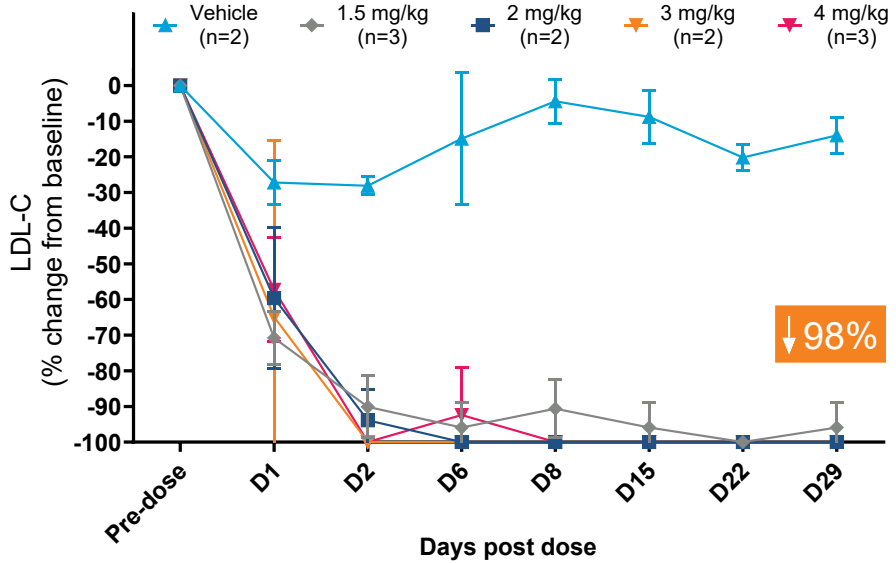
EDIT-401, CRISPR/Cas9 nuclease and dual gRNAs for LDLR upregulation encapsulated in a GalNAc LNP, administration to NHPs

EDIT-401 induces upregulation of LDLR in hepatocytes in livers of NHPs



Immunohistochemistry for LDLR in liver sections

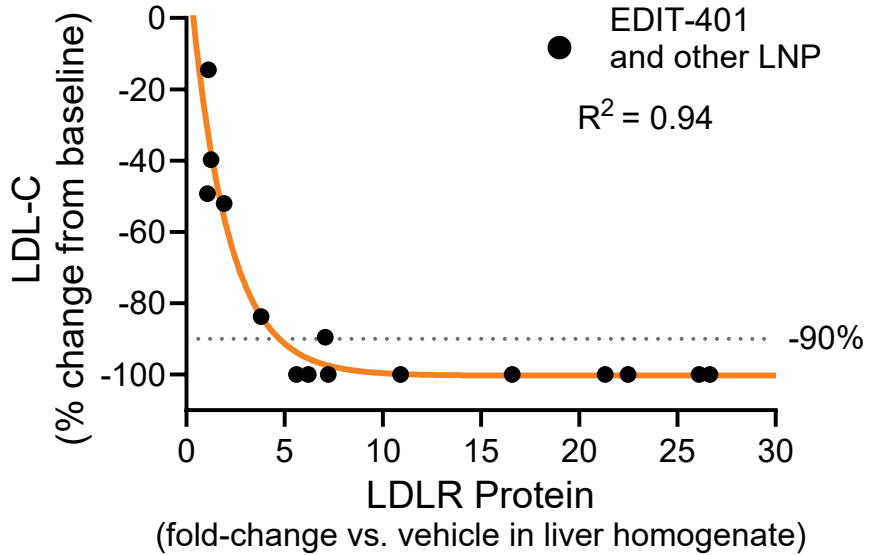
Single dose of EDIT-401



Pre-dose LDL-C was averaged across two timepoints to account for variability in measurements.
D, day; GalNAc, N-acetylgalactosamine; h, hour; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LNP, lipid nanoparticle; NHP, non-human primate.

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

LDL-C reduction correlated with total LDLR protein increase in the liver[1]



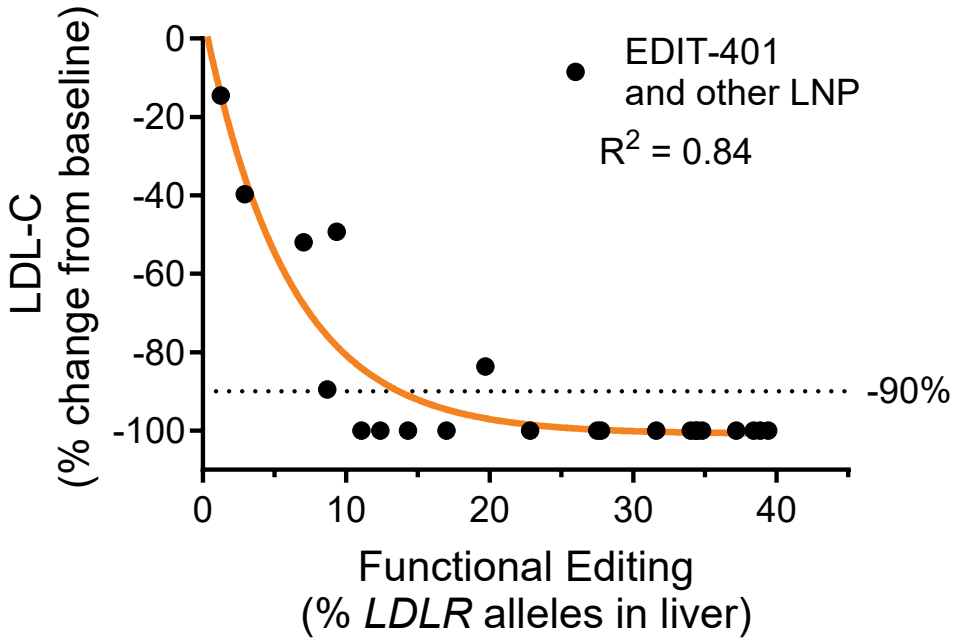
≥6-fold mean increase in LDLR protein resulted in ≥90% LDL-C reduction in NHPs with EDIT-401

LNP, lipid nanoparticle; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; NHP, non-human primate; PCSK9, proprotein convertase subtilisin/kexin type 9; SoC, standard of care.

1. Editas Medicine. Data on file. **2.** B-hPCSK9 mice. Available at: https://biocytogen.com/gene-humanized-models/b-hpcsk9-mice. Accessed September 2025. **3.** Rashid S *et al. Proc Natl Acad Sci U S A* 2005; 102 (15): 5374–5379. **4.** Thedrez A *et al. Arterioscler Throm Vasc Biol* 2018; 38 (3): 592–598.

EDIT-401 therapeutic strategy requires only a moderate level of functional editing to demonstrate ≥90% LDL-C reduction in NHPs

LDL-C reduction correlated with functional editing[1]



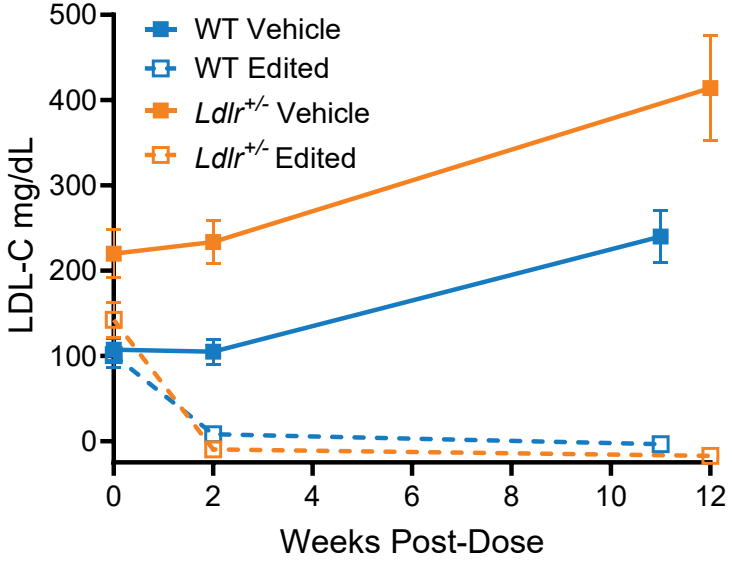
≥90% LDL-C reduction requires only ~10%–40% functional editing in liver

Functional editing: Percent of alleles containing targeted excisions or inversions from bulk liver. LDL-C, low-density lipoprotein cholesterol; LDL-C reduction from final D29 timepoint. LNP, lipid nanoparticle; NHP, non-human primate.

1. Editas Medicine. Data on file.

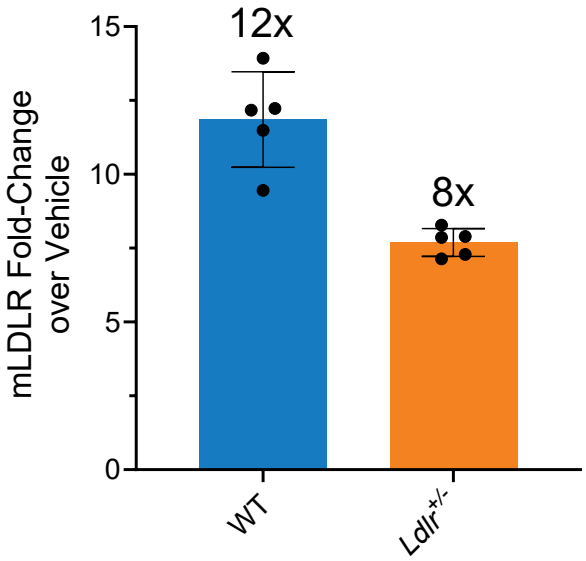
EDIT-401 murine surrogate achieved durable ≥90% mean LDL-C reduction in *LDLR* wildtype and heterozygous loss-of-function mice with high baseline LDL-C

WT and *Ldlr*$^{+/-}$ mice on high-fat diet administered a single dose of EDIT-401 murine surrogate



Mice on a high-fat diet had ≥3-fold elevated baseline LDL-C compared with mice on a regular-fat diet. N=5 for all WT and *Ldlr*$^{+/-}$ groups. *Ldlr*$^{+/-}$ Edited, 100% mean LDL-C reduction from baseline at 12 weeks; WT Edited, 99% mean LDL-C reduction from baseline at 11 weeks.

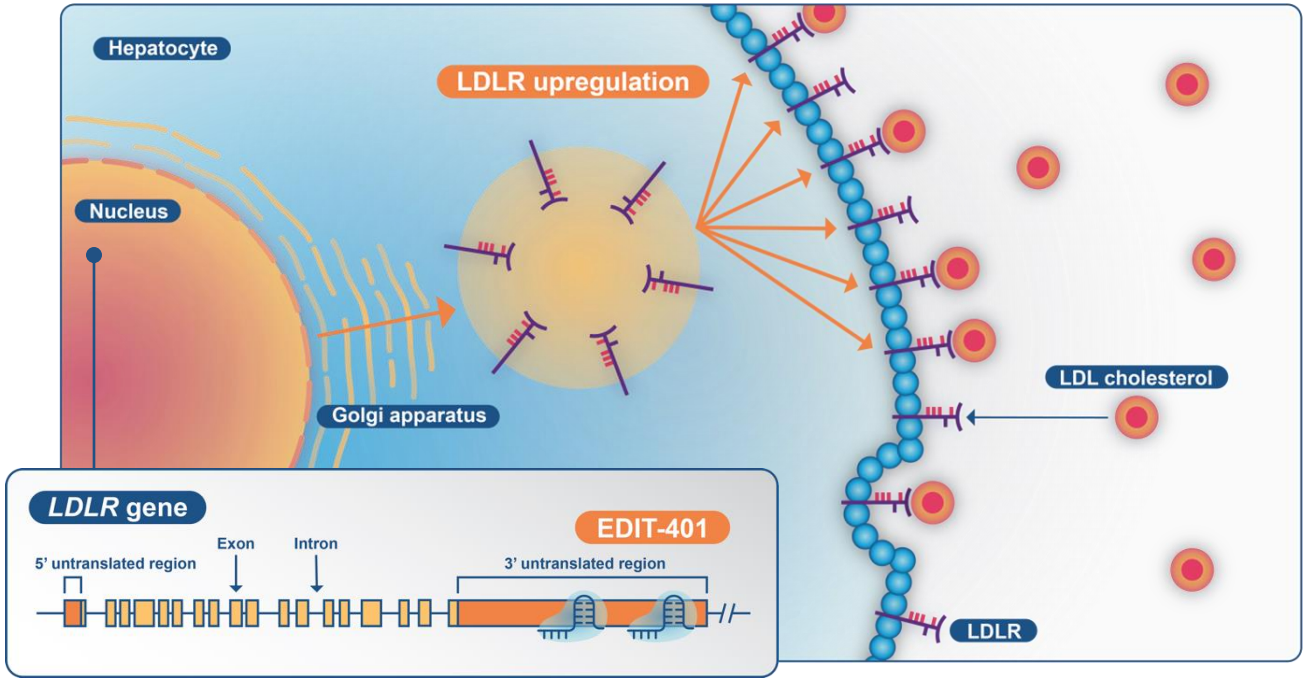
LDLR protein fold-upregulation in liver



LDL-C reduction calculated as mean % reduction from baseline; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; Ldlr, murine low-density lipoprotein receptor; WT, wild-type.

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

EDIT-401 therapeutic strategy for LDLR upregulation



- Disruption of negative regulatory elements of the LDLR gene increases the stability of the mRNA, enabling ≥6-fold increase in LDLR protein
- This amplification approach requires only a moderate level of functional editing of *LDLR* alleles in liver to achieve the ≥90% mean reduction in LDL-C

LDLR, low-density lipoprotein receptor; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

1. Editas Medicine. Data on file. **2.** B-hPCSK9 mice. Available at: https://biocytogen.com/gene-humanized-models/b-hpcsk9-mice. Accessed September 2025. **3.** Rashid S *et al. Proc Natl Acad Sci U S A* 2005; 102 (15): 5374–5379. **4.** Thedrez A *et al. Arterioscler Throm Vasc Biol* 2018; 38 (3): 592–598.

Conclusions

- EDIT-401 combines Editas' CRISPR and LNP expertise to deliver a differentiated therapeutic strategy of functional LDLR upregulation
- A single dose of EDIT-401 achieved ≥90% mean LDL-C reduction in NHPs and LDLR wildtype and heterozygous loss-of-function mice with high baseline LDL-C
- This differentiated therapeutic strategy 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 in the liver
- Durable LDL-C reduction was achieved with a single dose of EDIT-401 murine surrogate in wild-type and *Ldlr* heterozygous loss-of-function mice in a 3-month study

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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Thank you!