EDIT-401: Transformative *In Vivo* CRISPR Gene Editing Approach to Lower LDL Cholesterol

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Editas' differentiated *in vivo* gene editing upregulation strategy

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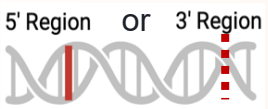
Functional Upregulation

***Differentiated use of CRISPR nuclease-based* technology**

Edit
Non-Coding, Regulatory
Regions



to *upregulate* a wild-type allele or functional homolog

- **Treats diseases by increasing the level of disease mitigating protein**
- **Does not alter sequence of naturally occurring protein**

Other Approaches

Edit
Coding
Regions

Knockdown of disease-causing protein

Gene correction of disease-causing protein

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, including in patients with heterozygous familial hypercholesterolemia (HeFH), a genetic disease primarily related to loss of function mutations in the *LDLR* gene[1,2]
- 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]

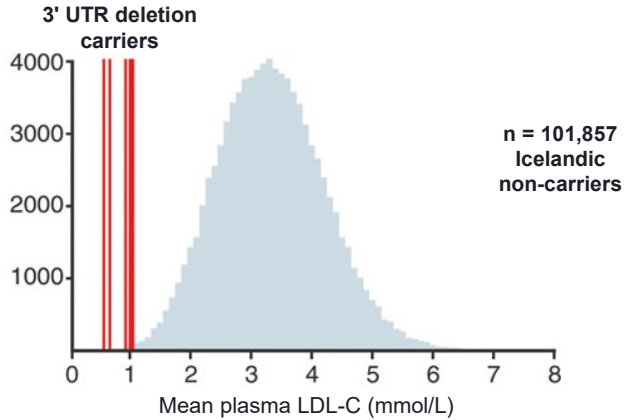
ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

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: 1264–1272. **6.** Gaba P *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 with non-carriers

LDLR:

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

Safety:

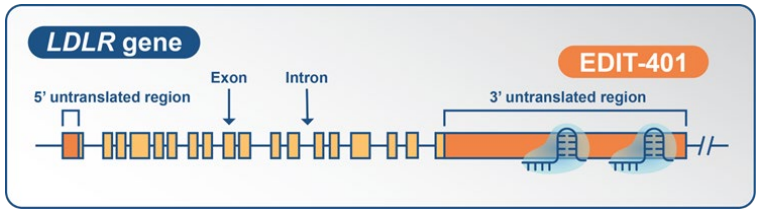
- No adverse events

*Noted value was for lymphocytes. Liver values are unknown.
3' UTR, three prime untranslated region; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor.

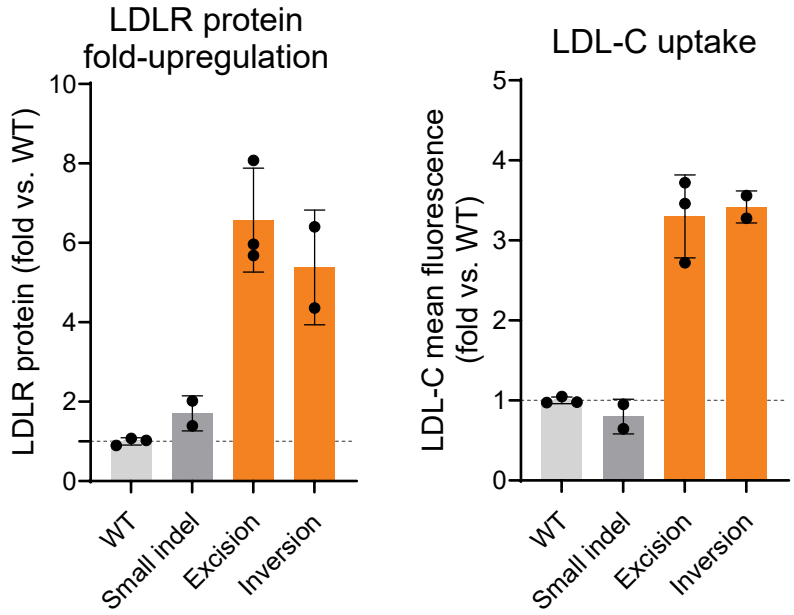
1. Bjornsson E *et al. Circ Genom Precis Med* 2021; 14 (1): e003029.

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



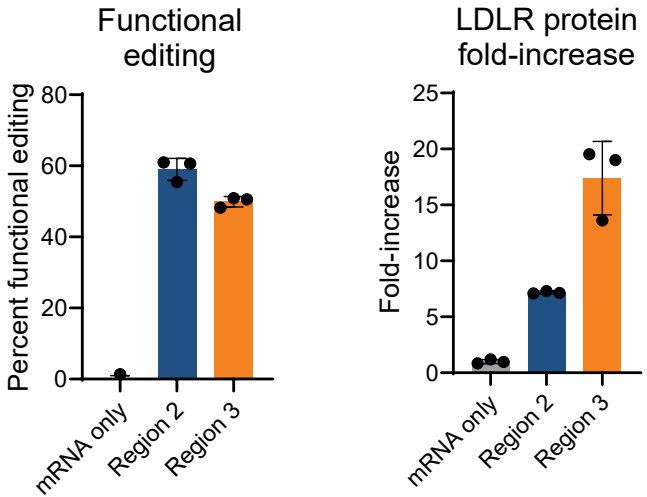
Functional edits increase LDLR protein expression and LDL-C uptake



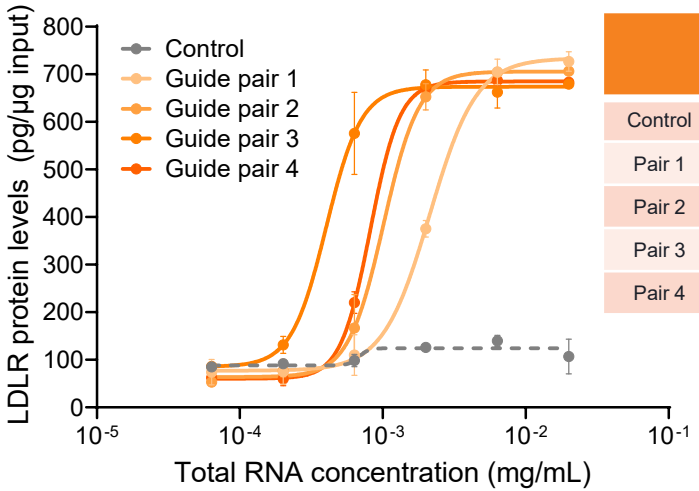
3' UTR, three prime untranslated region; Cas, CRISPR-associated protein; CRISPR, clustered regularly interspaced short palindromic repeats; HepG2, hepatoma G2 cells; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LNP, lipid nanoparticle; UTR, untranslated region;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



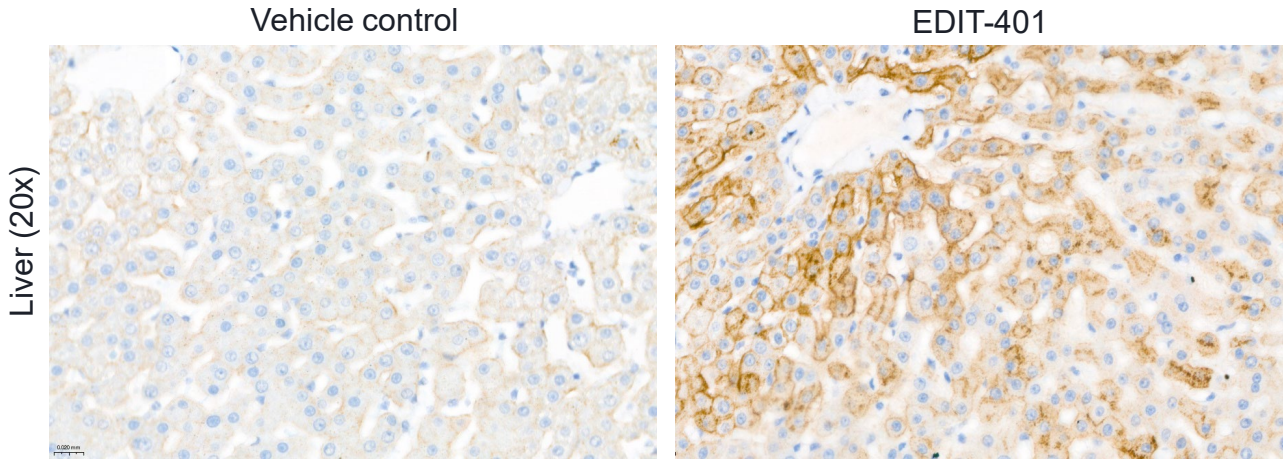
	Max protein upregulation (vs. control)	EC_{50}
Control	1	N/A
Pair 1	6.8	2.1×10^{-3}
Pair 2	6.6	1.0×10^{-3}
Pair 3	6.3	4.0×10^{-4}
Pair 4	6.4	8.2×10^{-4}

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; LNP, lipid nanoparticle; N/A, not available; NHP, non-human primate.

EDIT-401 achieved LDL-C reduction by LDLR upregulation in livers of NHPs

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

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



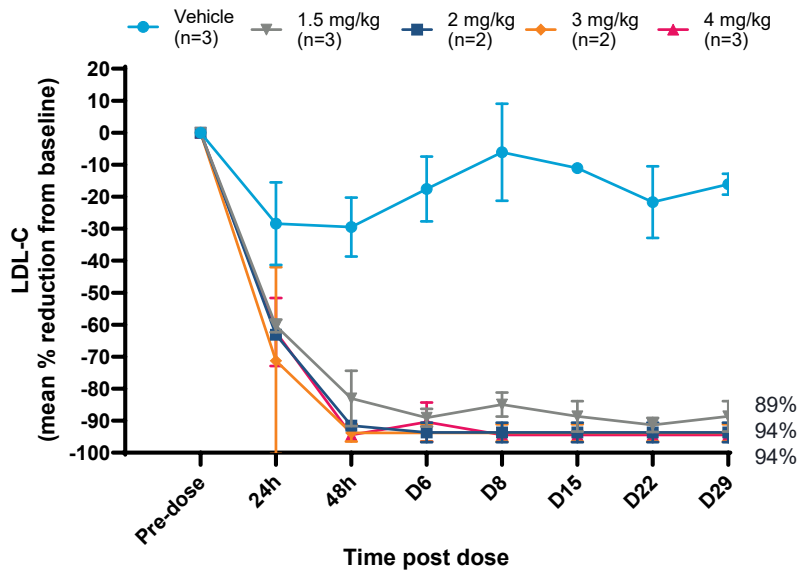
Immunohistochemistry for LDLR in liver sections

Cas, CRISPR-associated protein; CRISPR, clustered regularly interspaced short palindromic repeats; GalNAc, N-acetylgalactosamine; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LNP, lipid nanoparticle; NHP, non-human primate; LNPs licensed from Genevant Sciences Corporation.

EDIT-401 achieved >90% mean LDL-C reduction by upregulating LDLR

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

Single dose of EDIT-401



- >90% mean LDL-C reduction across all groups
- Rapid LDL-C reduction
- EDIT-401 in-life observations:
  - Well-tolerated across all doses administered
  - No adverse clinical observations
  - Transient increases in AST and ALT that resolved within a week
  - No significant changes in hematology or coagulation parameters

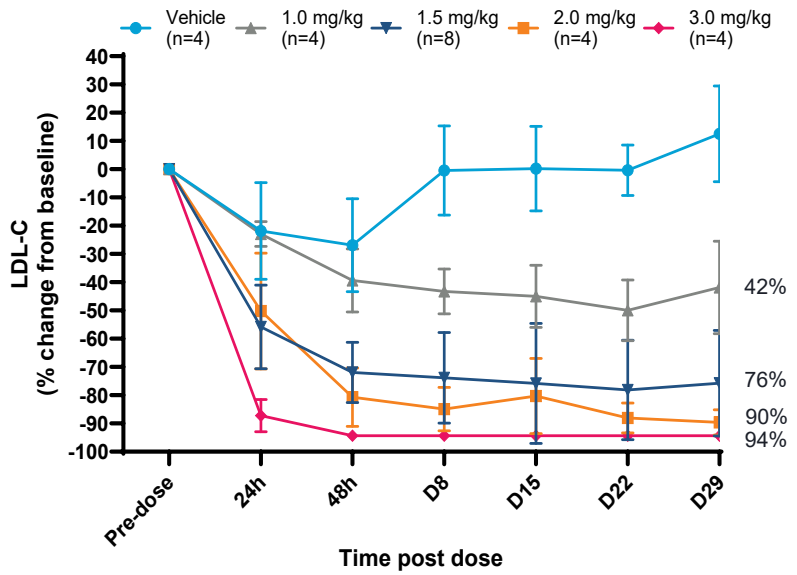
Pre-dose LDL-C was averaged across two timepoints to account for variability in measurements. Day 1 defined as day of dosing. Mean values are shown ± SD. Values below lower limit of quantitation assigned as LLOQ/2.

ALT, alanine transaminase; AST, aspartate transaminase; Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; D, day; GalNAc, N-acetylgalactosamine; h, hour; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LLOQ, lower limit of quantitation; LNP, lipid nanoparticle; NHP, non-human primate; LNPs licensed from Genevant Sciences Corporation.

EDIT-401 displayed dose-dependent and durable LDL-C reduction

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

Single dose of EDIT-401



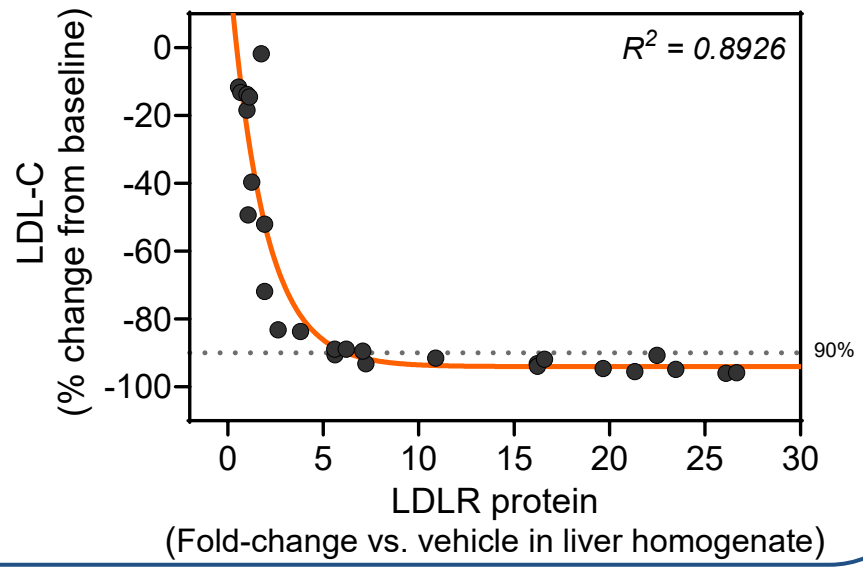
- Dose-dependent LDL-C reduction
- Rapid LDL-C reduction
- Durability of LDL-C reduction at all doses through D29

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.

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

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

LDL-C reduction correlated with LDLR protein upregulation

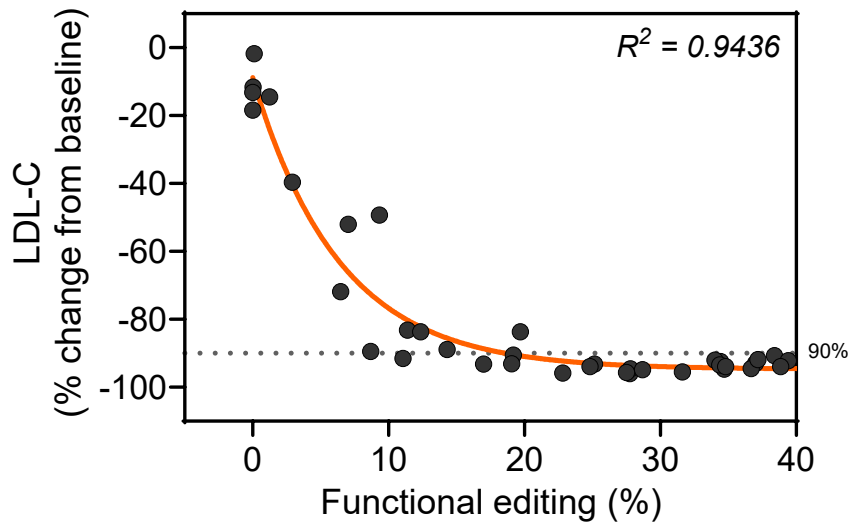


- A ≥6-fold mean increase in LDLR protein in liver resulted in ≥90% LDL-C reduction in NHPs

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

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



- Approximately 10%–40% functional editing can lead to the LDLR protein increase resulting in ≥90% LDL-C reduction in NHPs

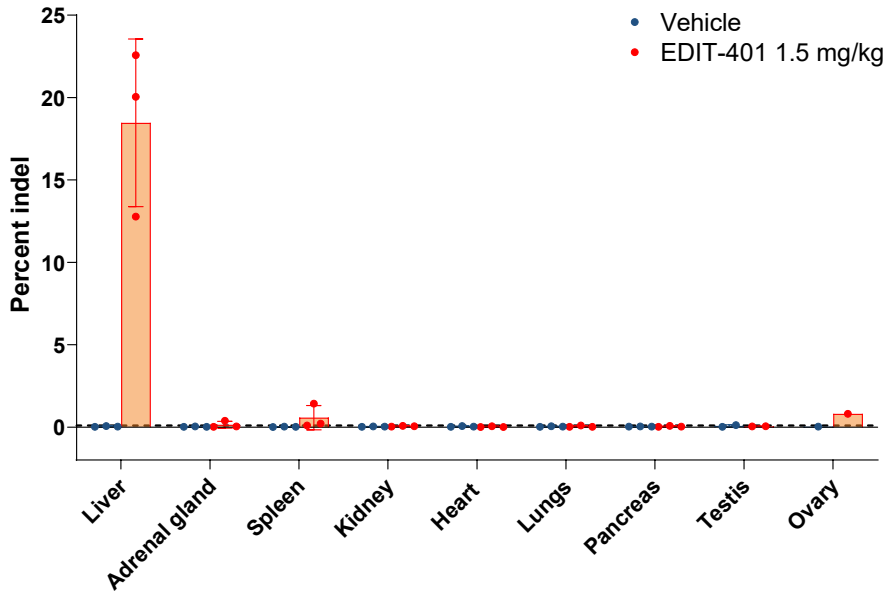
Functional editing: percent of alleles containing targeted excisions or inversions from bulk liver. LDL-C reduction from final D29 timepoint.
LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; NHP, non-human primate; LNPs licensed from Genevant Sciences Corporation.

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)

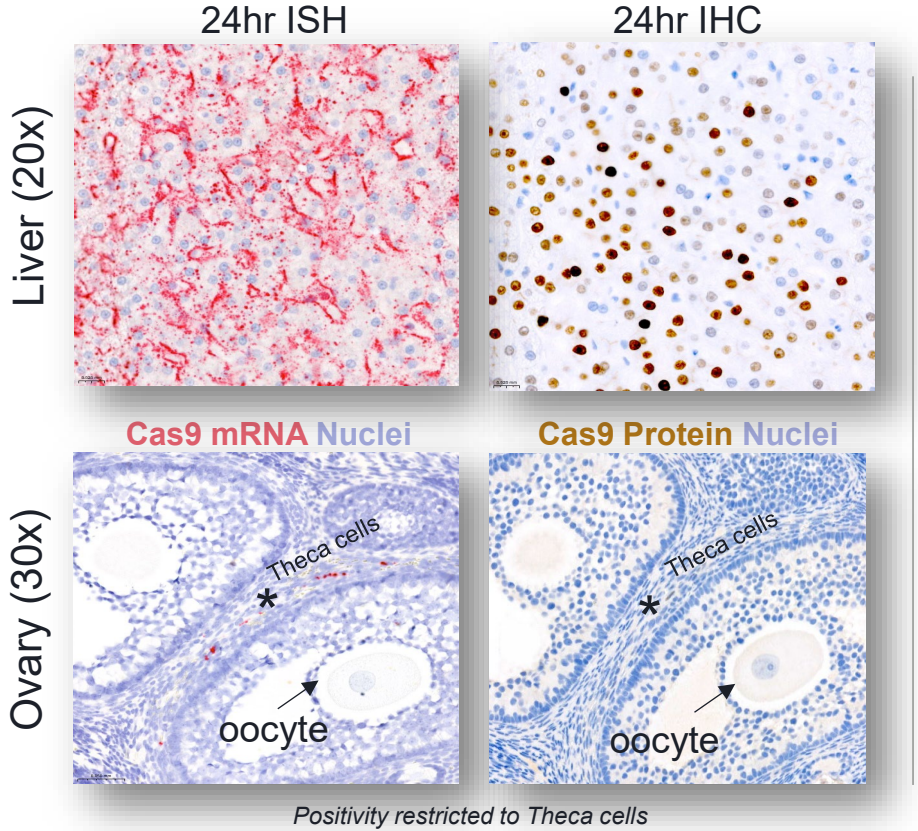
Single dose of EDIT-401 at 1.5 mg/kg, D29

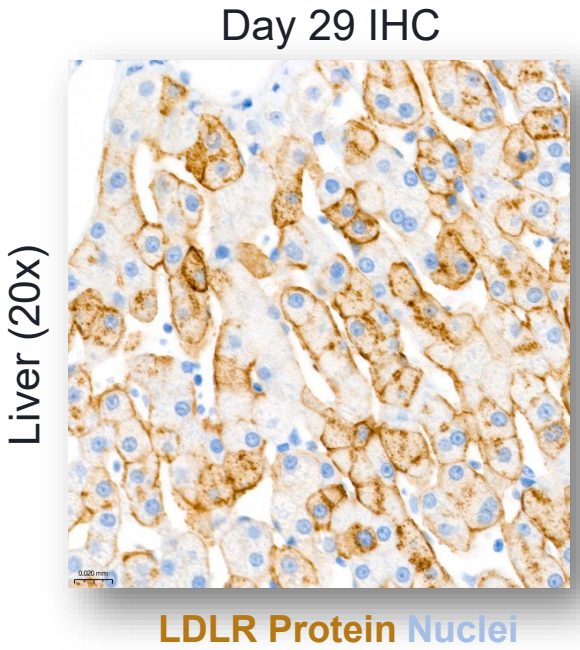


Graph show % indels in LDLR 3'UTR across liver and all non-target tissues. Representative data shown with one of the EDIT-401 gRNAs by targeted amplicon sequencing

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

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



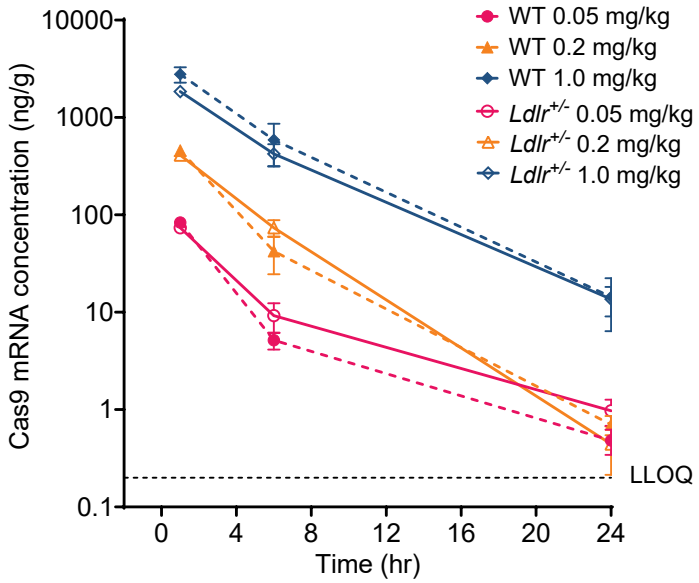


Consistent results observed with 1.5 mg/kg dose and at 3 mg/kg of EDIT-401. Cas9 mRNA detected by *in-situ* hybridization.

Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; h, hour; IHC, immunohistochemistry; ISH, *in-situ* hybridization; LDLR, low-density lipoprotein receptor; LNPs licensed from Genevant Sciences Corporation.

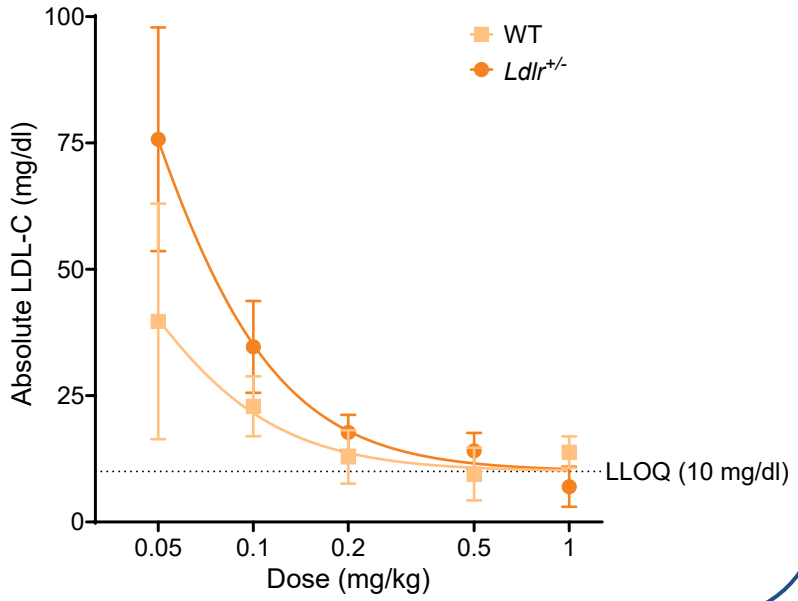
Wild-type and *Ldlr*$^{+/-}$ mice have similar liver exposure and biomarker reduction upon administration of EDIT-401(mu)

Similar Cas9 mRNA liver exposure in WT and *Ldlr*$^{+/-}$ mice



Representative graph from a full PK study with 5 doses: 1, 0.5, 0.2, 0.1, and 0.05 mg/kg.

Similar dose correlation with LDL-C reduction in WT and *Ldlr*$^{+/-}$ mice

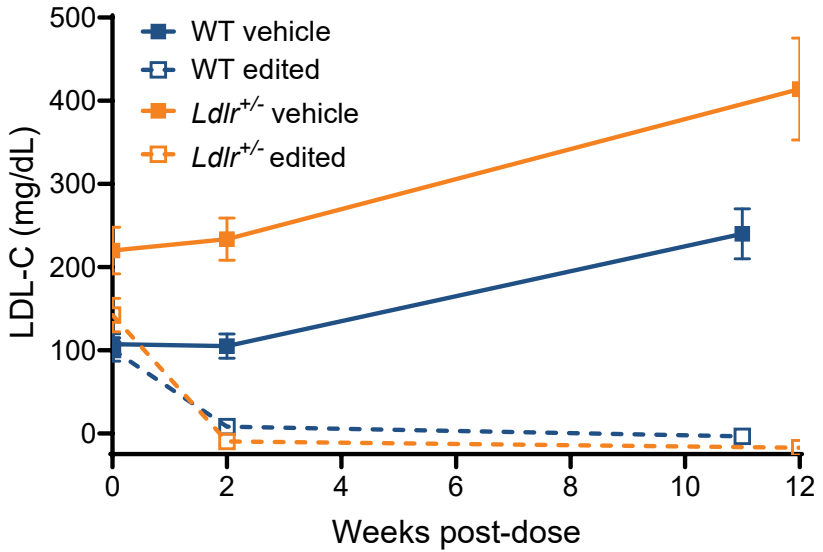


The slope of the dose-response curves were compared using an extra sum-of-squares F-test. No statistically significant difference in ED_{50} was observed (p=0.848).

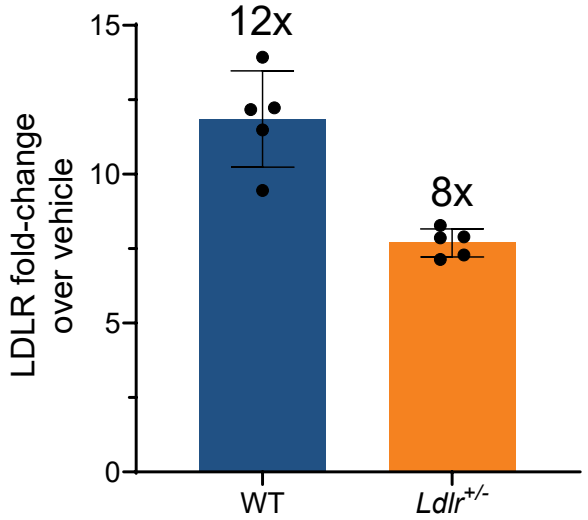
Absolute LDL-C refers to the concentration of LDL-C measured in mouse serum using a qualified bioanalytical APEX-HPLC method.
Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; ED_{50}, median effective dose; hr, hour; Ldlr, murine low-density lipoprotein receptor; LLOQ, lower limit of quantification; WT, wild-type; LDL-C, low-density lipoprotein cholesterol; EDIT-401(mu); murine surrogate of EDIT-401; LNPs licensed from Genevant Sciences Corporation.

EDIT-401 murine surrogate achieved durable ≥90% mean LDL-C reduction in WT and *Ldlr*$^{+/-}$ mice with high baseline LDL-C

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



LDLR protein fold-regulation in liver



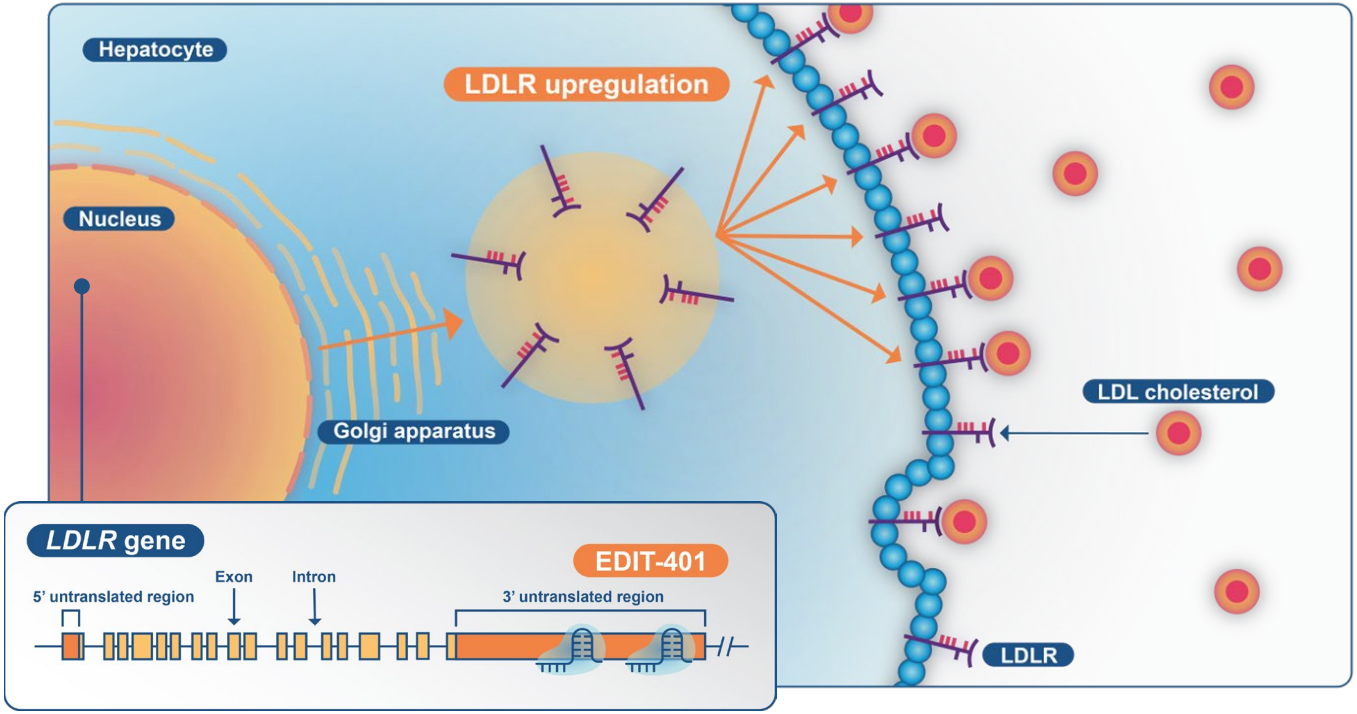
Mice on a high-fat diet had ≥3-fold elevated baseline LDL-C compared with mice on a regular-fat diet. N=5 for all WT and *Ldlr*$^{+/-}$ groups. *Ldlr*$^{+/-}$ edited, 100% mean LDL-C reduction from baseline at 12 weeks; WT edited, 99% mean LDL-C reduction from baseline at 11 weeks.

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; 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 in preclinical models
- 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

LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor.

Summary and conclusions

- EDIT-401 combines Editas' drug development expertise and Genevant 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 demonstrated a promising preclinical safety profile in NHPs that was well tolerated with high hepatocyte and undetectable oocyte delivery
- *Ldlr*$^{+/-}$ mouse model (containing single wild-type allele mimicking HeFH genotype) shows similar dose response as wild-type mouse model
- A single dose of EDIT-401 murine surrogate achieved ≥90% mean LDL-C reduction in *Ldlr*$^{+/-}$ mice with high baseline LDL-C, and demonstrated durability up to 12 weeks
- 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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Thank you!