MP1123

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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#AHA25

SPEAKER DISCLOSURE

Anshul Gupta,
VP (Nonclinical Development) is an employee and equity holder of Editas Medicine, Inc.

FORWARD LOOKING STATEMENTS

This presentation contains forward-looking statements and information within the meaning of The Private Securities Litigation Reform Act of 1995, including statements regarding the potential market for EDIT-401, if approved. The words ‘‘anticipate,’’ ‘‘believe,’’ ‘‘continue,’’ ‘‘could,’’ ‘‘estimate,’’ ‘‘expect,’’ ‘‘intend,’’ ‘‘may,’’ ‘‘plan,’’ ‘‘potential,’’ ‘‘predict,’’ ‘‘project,’’ ‘‘target,’’ ‘‘should,’’ ‘‘would,’’ and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Forward-looking statements in this presentation include statements regarding the initiation, timing, progress and results of the Company’s preclinical studies and its research and development programs, including initiating a first-in-human study for EDIT-401 in 2026; the timing for the Company’s receipt and presentation of data from its preclinical studies; the potential of, and expectations for, EDIT-401; and the timing or likelihood of regulatory filings and approvals, including submitting an IND/CTA for EDIT-401 by mid-2026. The Company may not actually achieve the plans, intentions, or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various important factors, including: uncertainties inherent in the initiation and completion of preclinical studies; availability and timing of results from preclinical studies; expectations for regulatory approvals to conduct trials; and the availability of funding sufficient for the Company’s foreseeable and unforeseeable operating expenses and capital expenditure requirements. These and other risks are described in greater detail under the caption “Risk Factors” included in the Company’s most recent Annual Report on Form 10-K, which is on file with the Securities and Exchange Commission, as updated by the Company’s subsequent filings with the Securities and Exchange Commission, and in other filings that the Company may make with the Securities and Exchange Commission in the future. Any forward-looking statements contained in this presentation represent the Company’s views only as of the date hereof and should not be relied upon as representing its views as of any subsequent date. Except as required by law, the Company explicitly disclaims any obligation to update any forward-looking statements.

CTA, Clinical Trial Application; HSC, hematopoietic stem cell; IND, Investigational New Drug Application; LDLR, low-density lipoprotein receptor.

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]
- 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]

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

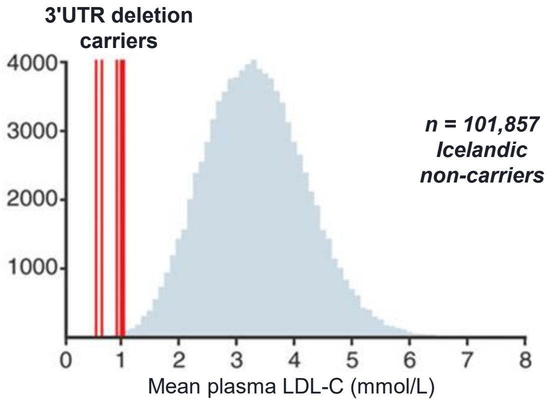
1. Arnett DK *et al. Circulation* 2019; 140 (11): e596–e646. **2**. Gu J *et al. Am J Prev Cardiol* 2022; 10: 100336. **3.** Klimchak AC *et al. Am J Prev Cardiol* 2020; 1: 100010. **4.** Cohen JC *et al. N Engl J Med* 2006; 354 (12): 1264–1272. **5.** Gaba P *et al. Circulation.* 2023; 147 (16): 1192–1203.

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

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

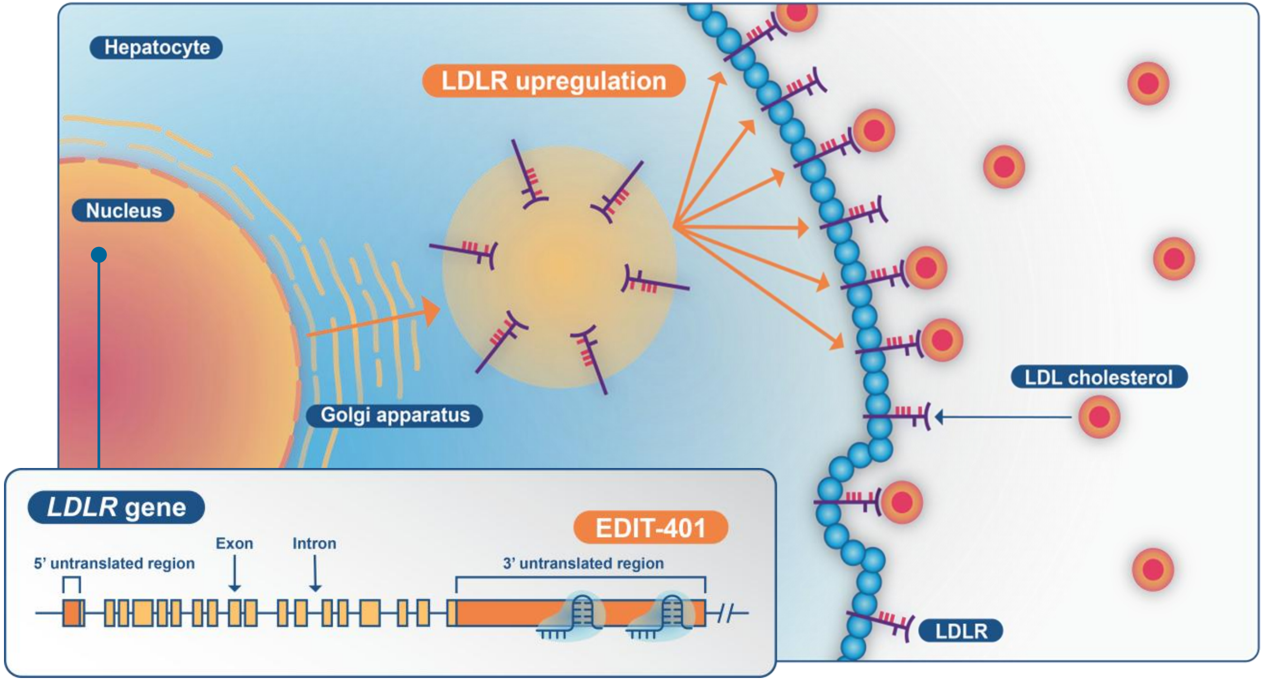
Safety:

- No adverse events

1. Bjornsson E *et al*. *Circ Genom Precis Med* 2021; 14 (1): e003029.
LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; UTR, untranslated region.

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**
- 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

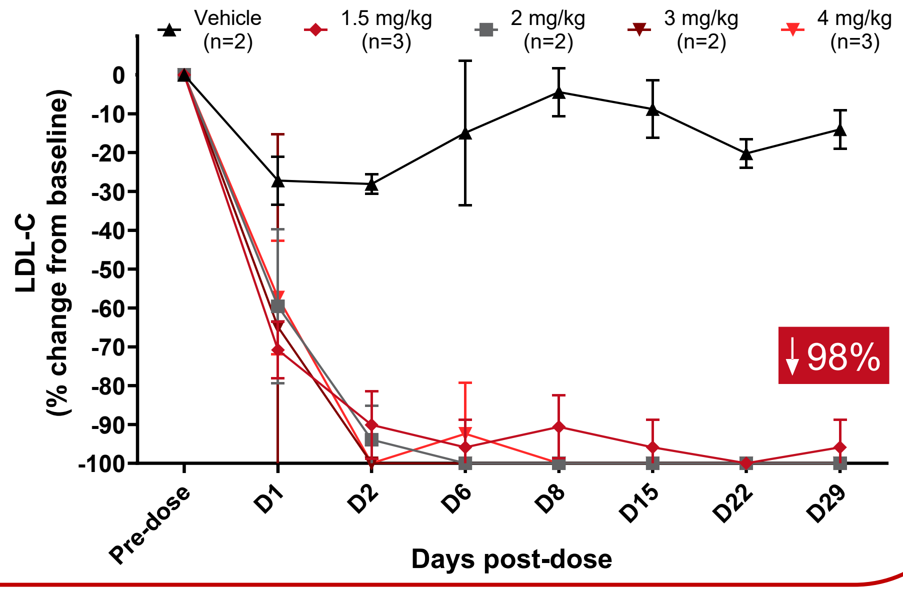
1. Editas Medicine. Data on file. **2.** B-hPCSK9 mice. Available at: https://biocytogen.com/gene-humanized-models/b-hpcsk9-mice. Accessed October 2025. **3.** Rashid S *et al*. *Proc Natl Acad Sci U S A* 2005; 102 (15): 5374–5379.
4. Thedrez A *et al*. *Arterioscler Throm Vasc Biol* 2018; 38 (3): 592–598.

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.

EDIT-401 ACHIEVED 98% MEAN LDL-C REDUCTION BY INDUCING LDLR UPREGULATION IN NON-HUMAN PRIMATES

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

Single dose of EDIT-401



EDIT-401 in-life observations:

- Well tolerated across all doses administered
- No adverse clinical observations noted
- No significant changes in hematology or coagulation parameters
- Transient increases in AST and ALT that resolved within a week

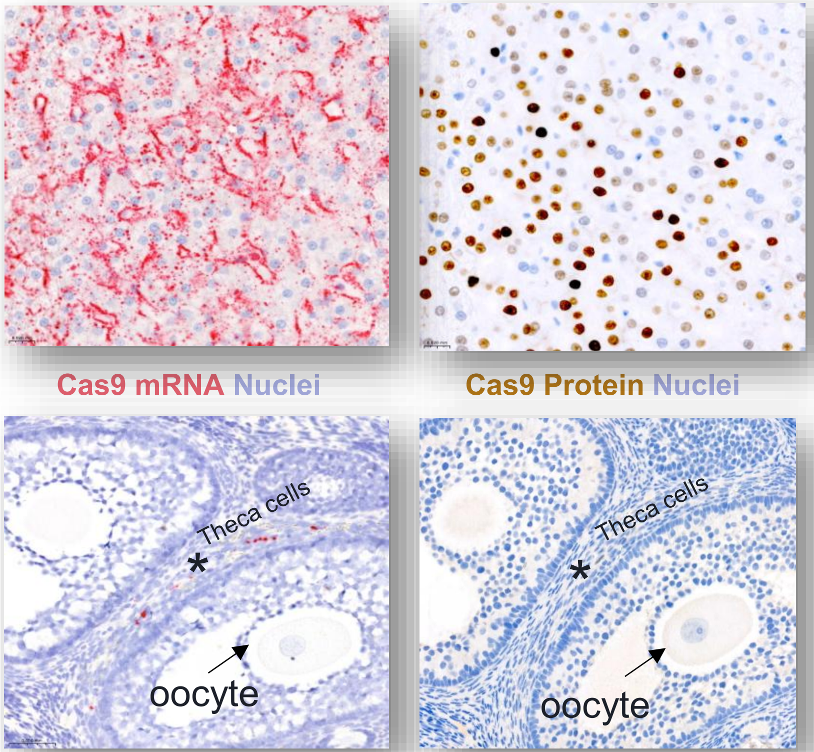
Pre-dose LDL-C was averaged across two timepoints to account for variability in measurements.
ALT, alanine transaminase; AST, aspartate transaminase; Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; D, day; GalNAc, N-acetylgalactosamine; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LNP, lipid nanoparticle; NHP, non-human primate.

EDIT-401 DEMONSTRATES HIGH DELIVERY IN HEPATOCYTES AND UNDETECTABLE CARGO IN OOCYTES

24hr ISH | 24hr IHC

Liver (20x)

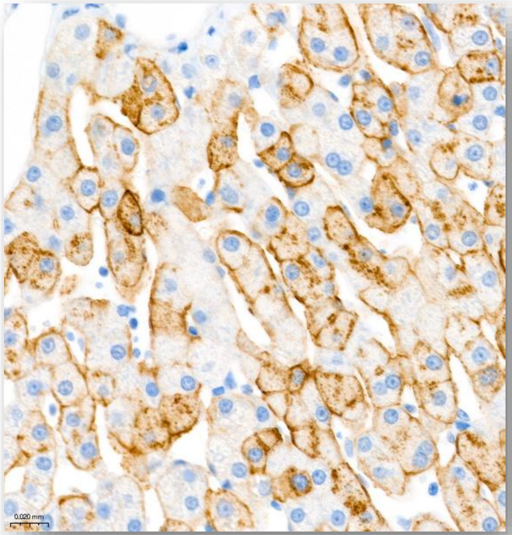
Ovary (30x)



Positivity restricted to Theca cells

Day 28 IHC

Liver (20x)



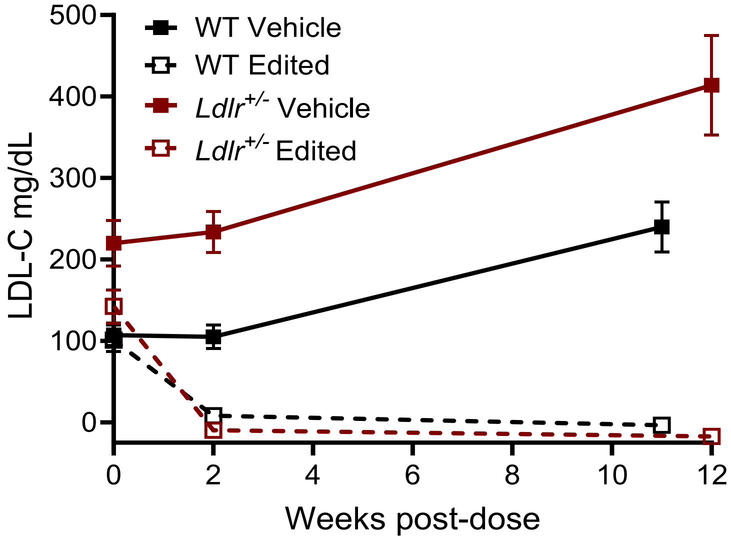
LDLR Protein Nuclei

Data generated at a pharmacologically relevant dose of 1.5 mg/kg (24 h post-dose)

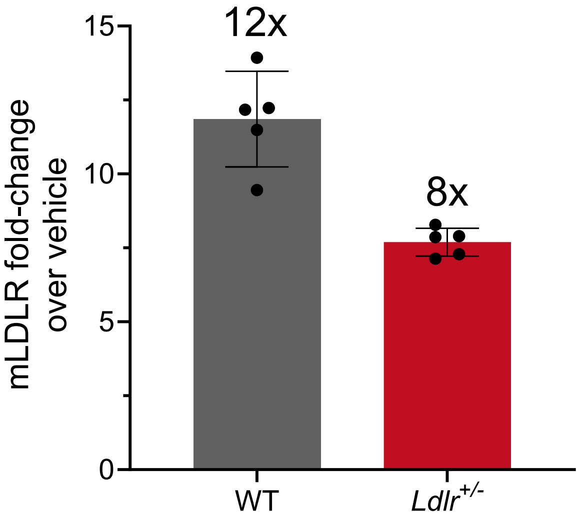
Cas mRNA detected by *in-situ* hybridization. Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; h, hour; IHC, immunohistochemistry; LDLR, low-density lipoprotein receptor.

LDLR UPREGULATION ACHIEVED DURABLE ≥90% MEAN LDL-C REDUCTION IN WT AND HETEROZYGOUS LOSS-OF-FUNCTION MICE (*Ldlr*$^{+/-}$) WITH HIGH BASELINE LDL-C

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



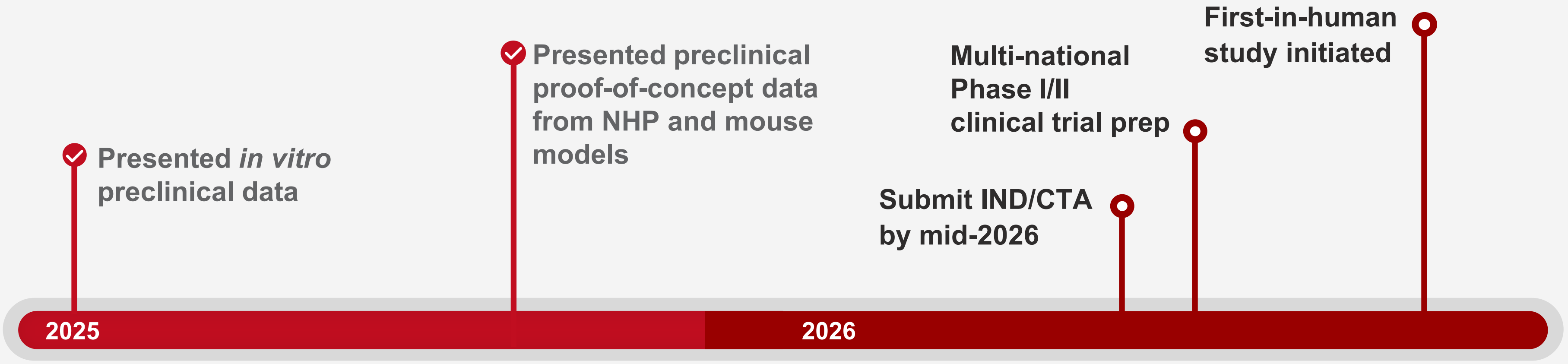
LDLR protein upregulation in liver



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; mLdlr, murine low-density lipoprotein receptor; mu, murine; WT, wild-type.

EDIT-401 RAPIDLY PROGRESSING TOWARDS PHASE 1 CLINICAL TRIALS



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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 and demonstrated a promising preclinical safety profile in NHPs that was well tolerated with high hepatocyte and undetectable oocyte delivery

A single dose of EDIT-401 murine surrogate achieved ≥90% mean LDL-C reduction in wild-type and *LDLR* heterozygous loss-of-function 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; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; Ldlr, murine low-density lipoprotein receptor; LNP, lipid nanoparticle; mu, murine; NHP, non-human primate.

THANK YOU!

Scientific Sessions

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