editas MEDICINE

Scientific Sessions

EDIT-401: *IN VIVO* GENE EDITING TO ENHANCE LDLR FUNCTION FOR DURABLE LDL-C REDUCTION

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American Heart Association.

#ScientificSessions26

DISCLOSURE SLIDE



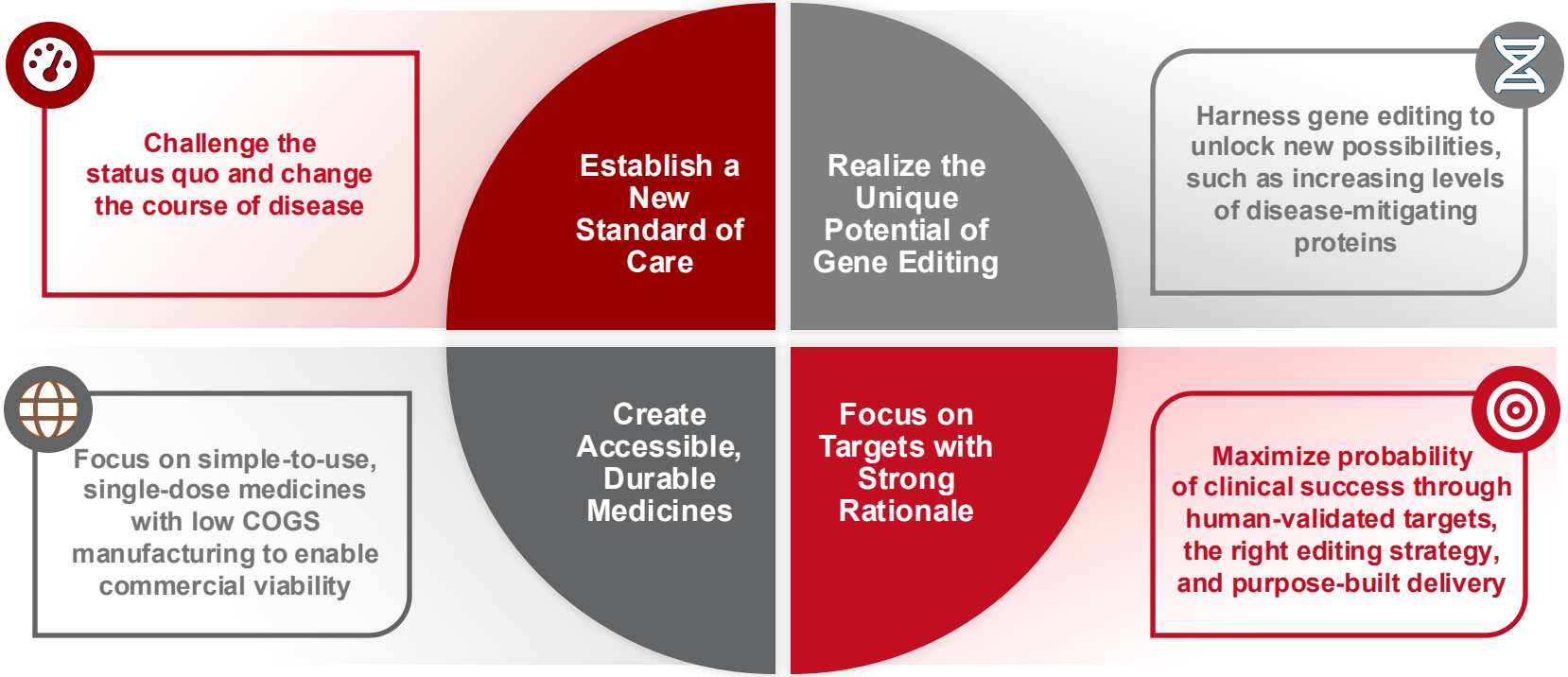
Daniel Ory, MD

is an employee of Editas Medicine

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EDITAS MEDICINE: A DIFFERENTIATED GENETIC MEDICINE ENGINE

Accessible, Durable Medicines: Single-dose, Lifelong Benefit



LOWER LDL-C IS BETTER IN PATIENTS WITH ASCVD

- **LDL-C** is the foundational marker of ASCVD risk,[1] and risk of CV events **continues to decrease** with lower LDL-C levels[2,3]
- Guidelines recommend **aggressive LDL-C reduction** with increasing ASCVD risk[1]; however, ~75% of patients with ASCVD **do not meet LDL-C goals**[4,5]

Continuous relationship between LDL-C lowering and reduced risk of CV events[2]

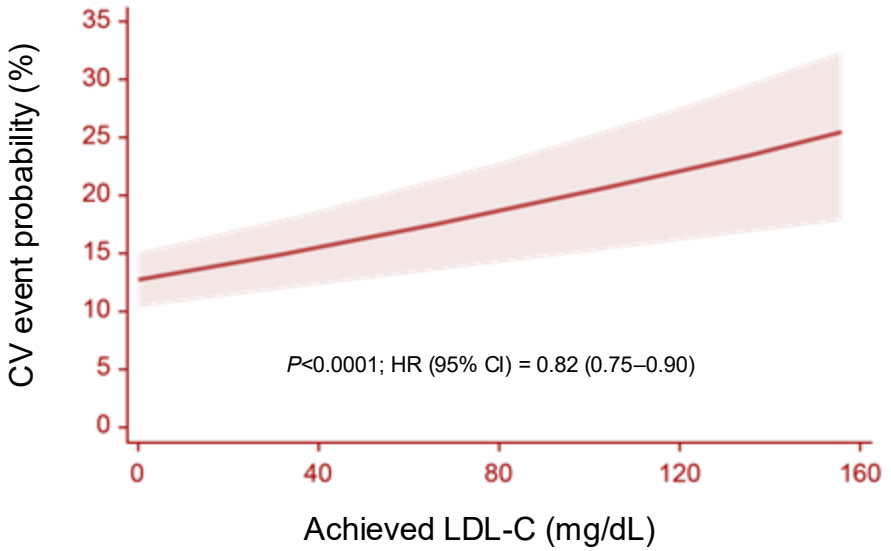


Figure adapted from Gaba *et al.* 2023.

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

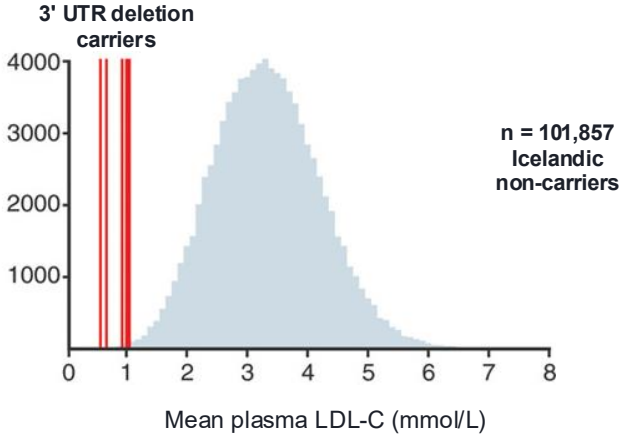
1. Blumenthal RS *et al. J Am Coll Cardiol* 2026; 87 (19): 2552–2554. 2. Gaba P *et al. Circulation* 2023; 147 (16) :1192–1203. 3. Lee Y-J *et al. N Eng J Med* 2026; 394: 1365–1375. 4. Gu J *et al. Am J Prev Cardiol* 2022; 10: 100336. 5. Klimchak AC *et al. Am J Prev Cardiol* 2020; 1: 100010.

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]

Similar deletions have been identified in families in France and the UK[2]

Plasma LDL-C levels[1]



Impact on carriers[1]

LDL-C:

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

LDLR:

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

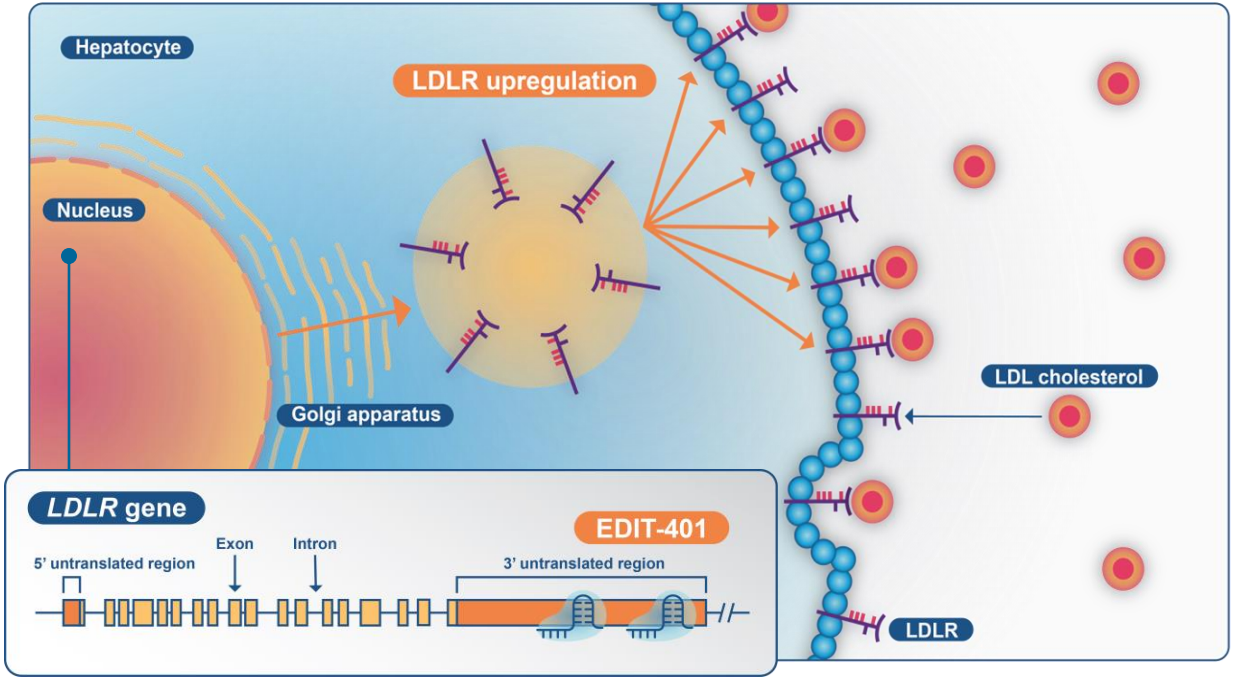
Health:

- **No apparent adverse consequences** of lifelong low LDL-C

*Noted value was for lymphocytes. Liver LDLR values are unknown.
LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; UTR, untranslated region.
1. Bjornsson E *et al. Circ Genom Precis Med* 2021; 14 (1): e003029. 2. Lainé A *et al. Arterioscler Thromb Vasc Biology* 2026; 46 (7): e324245.

EDIT-401 USES A DIFFERENTIATED MECHANISM OF ACTION TO REDUCE LDL-C

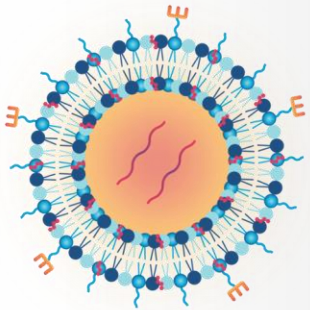
EDIT-401 therapeutic strategy for LDLR upregulation



- LDLR upregulation strategy targets functional alleles rather than correcting a deficient gene
- LDLR upregulation is achieved by disrupting negative regulatory elements of the *LDLR* gene
- Therapeutic strategy leads to mRNA stability, enabling **≥6-fold increase in LDLR protein in NHP**[1]

LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LDL, low-density lipoprotein; NHP, non-human primate.
1. Editas Medicine. Data on file.

SINGLE DOSE OF EDIT-401 EVALUATED ACROSS NHP STUDIES



EDIT-401 consists of LNPs containing a mRNA encoding Cas9 endonuclease and dual gRNAs

NHP Study Design

Single Dose

- **Vehicle Control**
- **EDIT-401**
  Dose Range:
  1 to 6 mg/kg

PD/Biomarker Endpoints

1. LDL-C levels
2. Lp(a) levels
3. ApoB levels

Safety Endpoints

1. Tolerability assessment
2. Liver function test
3. Histopathology

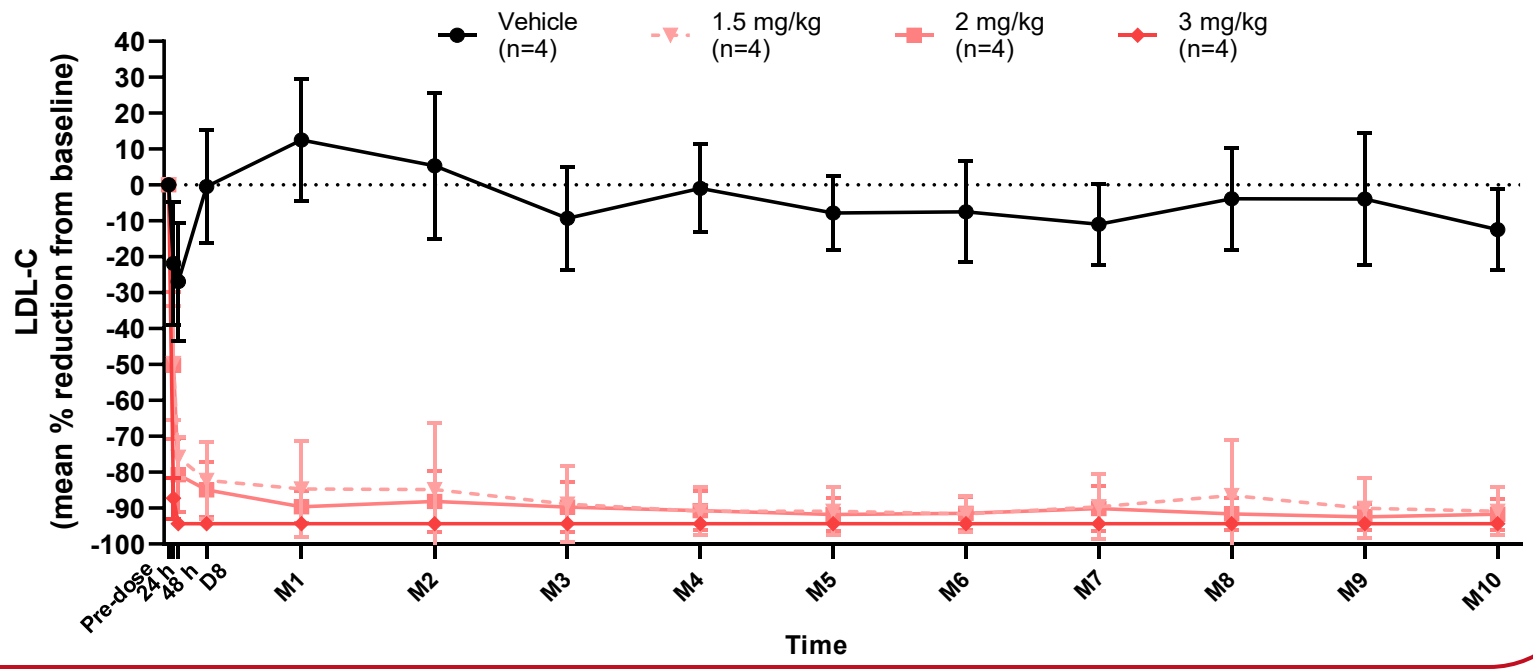
PK/Biodistribution Endpoints

1. LNP component exposure
2. Liver function test
3. Histopathology

ApoB, apolipoprotein B; Cas9, CRISPR-associated protein 9; CRISPR; clustered regularly interspaced short palindromic repeats; LDL-C, low-density lipoprotein cholesterol; LNP, lipid nanoparticle; Lp(a), lipoprotein(a); NHP, non-human primate; PD, pharmacodynamic; PK, pharmacokinetic.
LNPs licensed from Genevant Sciences GmbH.

ROBUST, DOSE-DEPENDENT, AND DURABLE LDL-C REDUCTION FOLLOWING A SINGLE DOSE OF EDIT-401

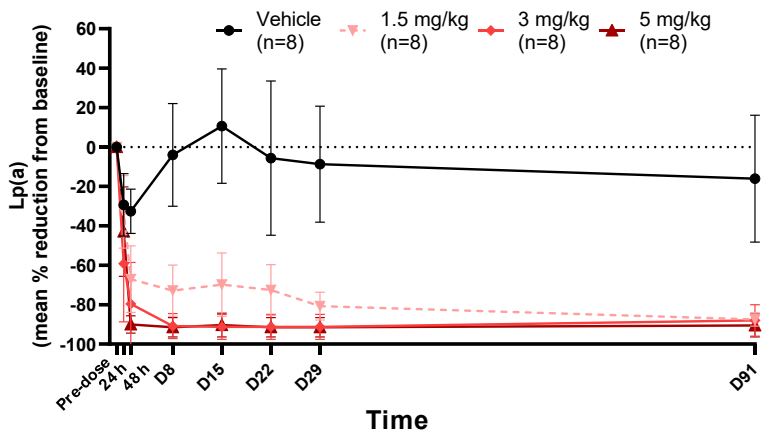
≥90% mean LDL-C reduction at 10 months



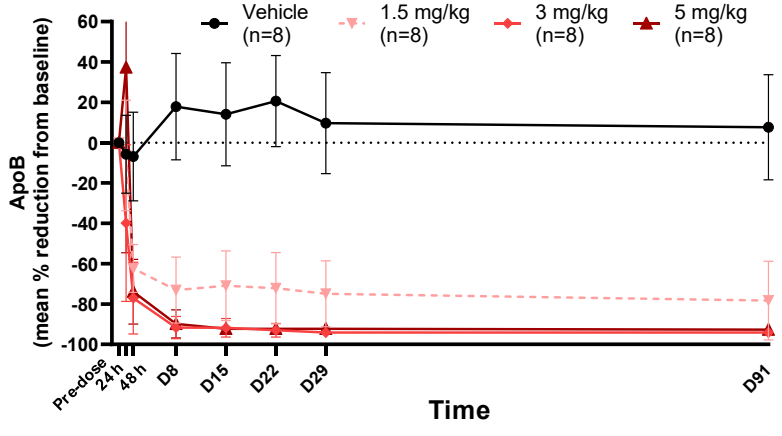
Mean values are shown ± SD. Values below lower limit of quantitation assigned as LLoQ/2.
D, day. h, hours; LDL-C, low-density lipoprotein cholesterol; LLoQ, lower limit of quantification; LNP, lipid nanoparticle; M, month; SD, standard deviation.
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SINGLE DOSE OF EDIT-401 LOWERS MULTIPLE ATHEROGENIC LIPOPROTEINS

~90% mean Lp(a) reduction at 3 months



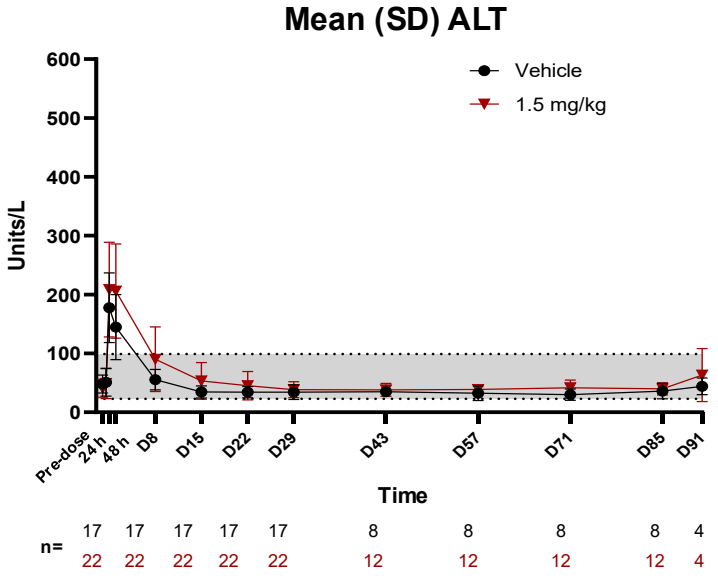
~90% mean ApoB reduction at 3 months

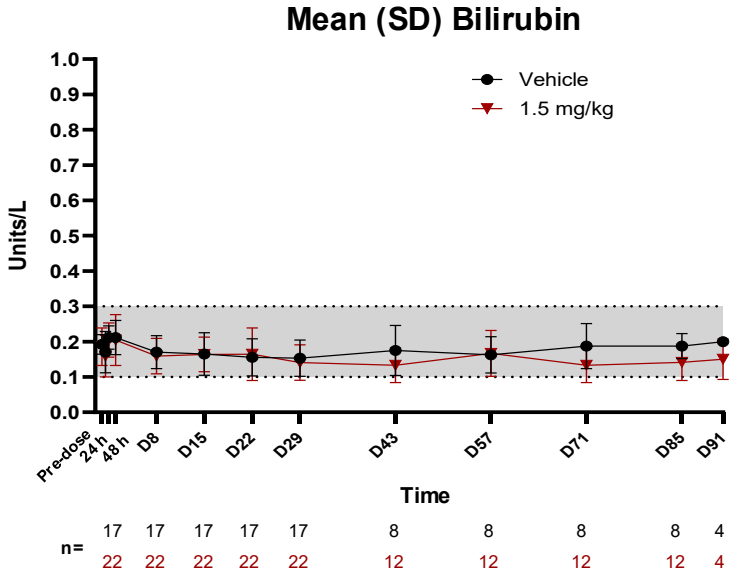


Mean values are shown ± SD. Values below lower limit of quantitation assigned as LLoQ/2.
ApoB, apolipoprotein B; D, day; h, hours; LLoQ, lower limit of quantification; LNP, lipid nanoparticle; Lp(a), lipoprotein(a); SD, standard deviation.
LNPs licensed from Genevant Sciences GmbH.

NO ADVERSE LIVER FINDINGS FOLLOWING SINGLE DOSE OF EDIT-401

- Transient ALT elevations
- No bilirubin elevations
- No histopathologic changes



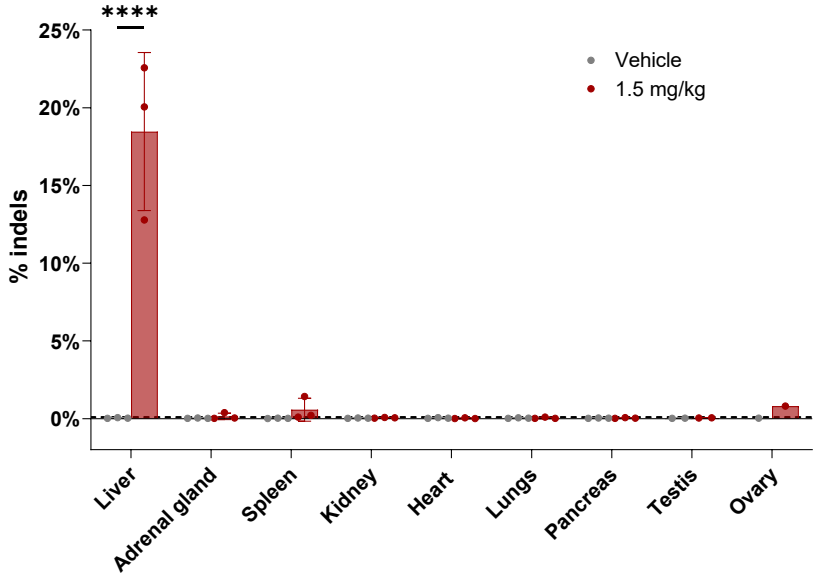


ALT and bilirubin data presented from 4 NHP studies. Shaded area represents normal range observed in NHPs. Vehicle dosed with saline following same pre-treatment regimen as EDIT-401.
ALT, alanine aminotransferase; D, day; h, hours; NHP, non-human primate; SD, standard deviation. LNPs licensed from Genevant Sciences GmbH.

EDIT-401 PROVIDES TARGETED DELIVERY TO THE LIVER WITH NO EVIDENCE OF GENOTOXICITY

- **High delivery to hepatocytes** with undetectable Cas9 mRNA in oocytes*
- **No off-target editing detected** in a panel of ~1500 candidate sites with frequencies of structural variants measured below LLoQ†

EDIT-401 delivers liver-targeted editing



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. ****P<0.0001

*In situ hybridization at 1.5 mg/kg. †Using an *in vitro* assessment in relevant human primary cell that represents clinical editing levels.
Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; LDLR, low-density lipoprotein receptor; LLoQ, lower limit of quantification; LNP, lipid nanoparticle; UTR, untranslated region. LNPs licensed from Genevant Sciences GmbH.

PHASE 1/2 STUDY DESIGN TO EVALUATE SAFETY AND EFFICACY OF EDIT-401 FOR LOWERING LDL-C

Adults with HeFH

LDL-C ≥70 and ≤300 mg/dL

Inadequate LDL-C lowering despite multiple therapies

PART 1 | 2-year follow-up

Dose ranging & safety study

Single ascending IV dose
Up to 6 cohorts (n=36)

C1 C2 C3 Selected doses

Primary endpoint

Severity and frequency of TEAEs and SAEs

Secondary endpoint

% change in LDL-C **at Day 90**

PART 2 | 2-year follow-up

Dose expansion & efficacy study

3:1 randomization (n=20)

EDIT-401 (n=15)

Placebo (n=5)

Elective crossover for placebo patients at Day 90 post-dose

Primary endpoint

% change in LDL-C **at Day 90**

Secondary endpoints

TEAEs and SAEs
LDL-C <70 or <55 mg/dL at Year 1

LONG-TERM EXTENSION

Up to 15 years of follow-up

Exploratory endpoints include Lp(a) & other lipoproteins, other cardiometabolic parameters, and immunogenicity

C, cohort; HeFH, heterozygous familial hypercholesterolemia; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); SAE, serious adverse event; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- EDIT-401 has demonstrated dose-dependent mean reductions of ~90% in LDL-C, ApoB, and Lp(a), and a consistent safety profile in non-clinical studies to date
- EDIT-401 presents a potential best-in-class, one-time treatment opportunity for patients with hypercholesterolemia to reduce LDL-C
- A multicenter, multinational, Phase 1/2 study to assess the safety and efficacy of EDIT-401 in patients with HeFH is approved for initiation in Australia with plans to expand globally

ApoB, apolipoprotein B; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); HeFH, heterozygous familial hypercholesterolemia.

THANK YOU

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