A potentially transformative investigational *in vivo* CRISPR gene editing medicine leads to upregulation of LDLR and robust reduction of two independent ASCVD risk factors, LDL-C and Lp(a), in non-human primates

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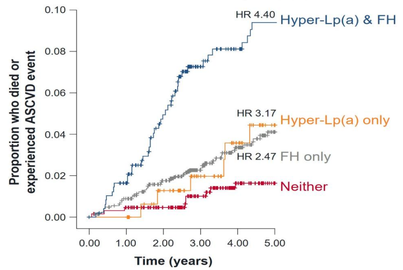
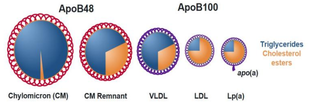
Background

- Atherosclerotic cardiovascular disease (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 low-density lipoprotein receptor (*LDLR*) gene.[2]
- LDL-C is the foundational marker of ASCVD risk.[3]
- Current guidelines recommend intensive LDL-C lowering, with targets <55 mg/dL (<1.4 mmol/L) for patients at very high ASCVD risk.[3]
- However, ~75% of patients with ASCVD do not meet LDL-C goals.[4,5]
- Apolipoprotein B (ApoB) captures all atherogenic particles – chylomicrons (CM), remnants, very low-density lipoprotein (VLDL), LDL, lipoprotein a [Lp(a)] – and lowering ApoB consistently reduces ASCVD risk.[6]
- Lp(a) adds independent risk beyond LDL-C or ApoB.[7,8]
- Newer dyslipidemia guidelines suggest measuring ApoB and Lp(a) in addition to LDL-C.[3]

ASCVD Risk with High Lp(a) & FH[8]



Hyper-Lp(a) is defined as Lp(a) >50 mg/dL.[8]



Robust, lifelong reduction of LDL-C and other atherogenic lipoproteins, such as Lp(a), are needed to provide maximal benefit.[9,10]

Figure 1: Editas' differentiated *in vivo* gene editing upregulation strategy

editas MEDICINE **Functional Upregulation**

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

Edit *non-coding, regulatory* regions

5' Region or 3' Region

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

Exon

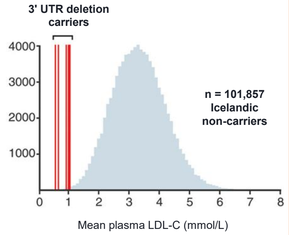
Gene correction of disease-causing protein

Exon

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' untranslated region (UTR) deletion.[11]

Plasma LDL-C levels[11]



Impact on carriers[11]

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

*Noted value was for lymphocytes. Liver values are unknown.

Figure 2: EDIT-401 achieved >90% mean LDL-C reduction by upregulating LDLR in NHPs

- >90% mean LDL-C reduction across all dosed non-human primates (NHPs).
- Response is dose-dependent and is consistent across 4 independent NHP studies.
- Doses were well-tolerated with no adverse clinical observations at the therapeutically relevant dose (1.5 mg/kg).
- Transient ALT elevations were observed with resolution in ~1 week at therapeutically relevant dose (1.5 mg/kg).

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 (LLoQ) assigned as LLoQ/2.

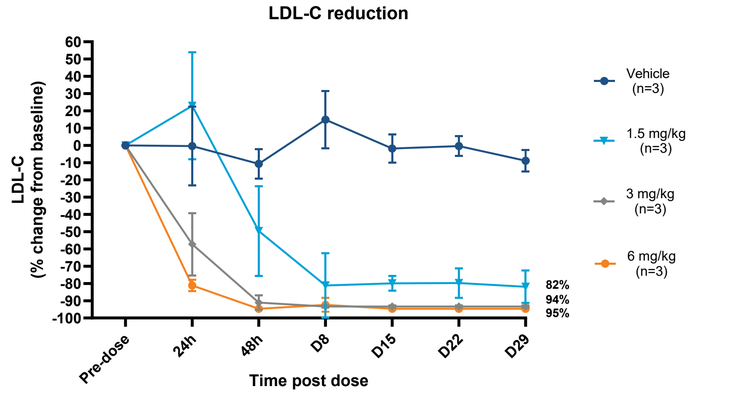
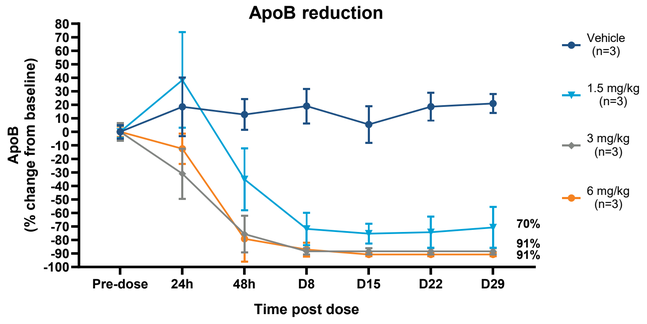
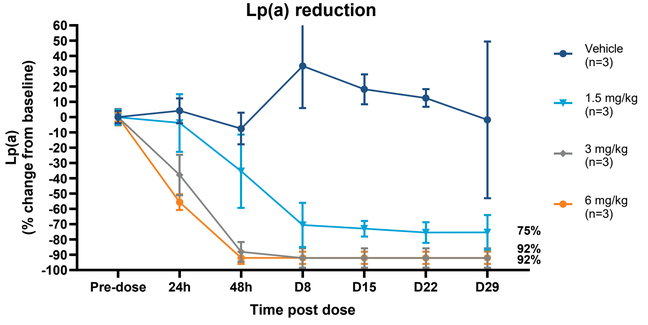


Figure 3: EDIT-401 achieved up to ~90% mean ApoB reduction and ~90% mean Lp(a) reduction in NHPs

- Dose-dependent, rapid ApoB and Lp(a) reductions correlate with LDL-C reduction after a single dose of EDIT-401.
- NHP baseline Lp(a) values approximate elevated CVD risk in humans.[12]

Pre-dose ApoB and Lp(a) were averaged across one or two timepoints to account for variability in measurements. Mean values are shown ± SD. Values below lower limit of quantitation (LLoQ) assigned as LLoQ/2. Animal baseline Lp(a) values with a range of ~22–159 mg/dL.





Conclusions

- EDIT-401 combines Editas' drug development expertise and Genevant's LNP to deliver a differentiated therapeutic strategy of functional LDLR upregulation.
- Low to moderate functional editing of LDLR alleles leads to ≥6-fold mean increase LDLR protein in liver of NHPs, resulting in ≥90% LDL-C reduction.
- A single dose of EDIT-401 achieved >90% mean LDL-C reduction and up to ~90% mean ApoB and Lp(a) reductions in NHPs.
- LDLR upregulation with EDIT-401 translates to a potentially transformative medicine to reduce LDL-C, ApoB, and Lp(a).
- Encouraging preclinical data supports advancing EDIT-401 towards a first-in-human clinical trial on track to be initiated in 2026.

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