CRISPR/Cas9 Gene-editing to Upregulate LDLR for Treatment of Heterozygous Familial Hypercholesterolaemia

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BACKGROUND

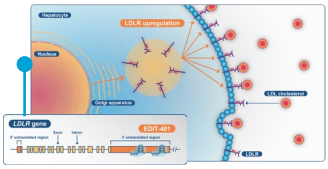
HeFH

- Heterozygous familial hypercholesterolaemia (HeFH) is a genetic disease characterised primarily by loss-of-function mutations in the low-density lipoprotein receptor gene (*LDLR*), leading to severely elevated serum low density lipoprotein cholesterol (LDL-C) levels.[1]
- Lifelong cumulative LDL-C exposure is the primary driver of atherosclerotic cardiovascular disease (ASCVD) risk in patients with familial hypercholesterolaemia.[2]
- Despite maximally tolerated therapies, many patients fail to achieve target LDL-C levels.[3]

Figure 2 caption:
D, day; LDL-C, low density lipoprotein cholesterol; LLoQ, lower limit of quantification; SD, standard deviation.
Values below lower limit of quantitation assigned as LLoQ/2.

EDIT-401

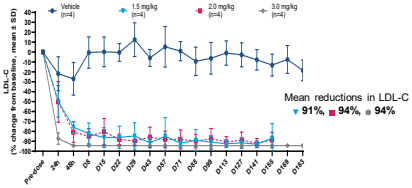
Figure 1. EDIT-401 therapeutic strategy for LDLR upregulation



LDLR upregulation strategy was informed by human genetics in 7 Icelandic individuals with partial *LDLR* 3' UTR deletion.[4]

3' UTR deletion disrupts negative regulatory elements of LDLR gene, increasing mRNA stability, enabling ≥6-fold increase in LDLR protein in NHP.

Figure 2. >90% mean reduction in LDL-C in non-human primates[5] after single doses of EDIT-401



STUDY DESIGN

This multicentre, multinational, Phase 1/2 study will assess the safety and efficacy of EDIT-401 as a potential best-in-class, one-time treatment for adults who require additional lowering of LDL-C (Figure 3).

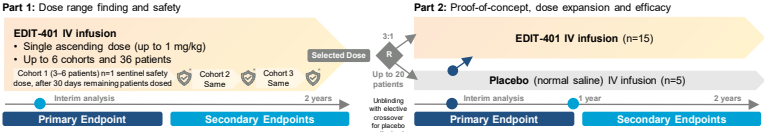
Key inclusion criteria

- Patients with HeFH ages 18–65 years with informed consent
- Documented clinical diagnosis of HeFH (probable or definitive)
- Weight >40 and ≤110 kg with body mass index ≤30 kg/m^2
- LDL-C ≥70 and ≤300 mg/dL
- Inadequate LDL-C lowering despite multiple therapies with ≥2 approved lipid-lowering therapies

Key exclusion criteria

- Homozygous familial hypercholesterolaemia
- Prior gene therapy or lipid apheresis; current or newly-prescribed GLP-1 agonist for weight loss (stable dose for ≥3 months for DM is permitted)
- History of diabetes, unstable or acute cardiovascular disease, deep vein thrombosis or pulmonary embolism, malignancy, renal impairment, metabolic dysfunction-associated steatohepatitis, active infection
- Pregnancy, breastfeeding

Figure 3. Study schematic



*The safety review committee will decide whether to advance to the next cohort or expand the current cohort with more patients (max 6).
After part 2, patients will proceed to a long-term extension study (up to 15 years of follow-up).
Exploratory endpoints include lipoproteins, other cardiometabolic parameters and immunogenicity.
IV, intravenous; LDL-C, low density lipoprotein cholesterol; R, randomisation; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- EDIT-401 has demonstrated dose-dependent mean decreases of ~90% in LDL-C, ApoB and Lp(a), and acceptable safety data in non-clinical studies to date
- This multi-centre, multinational, Phase 1/2 study will assess the safety and efficacy of EDIT-401, a potential best-in-class, one-time treatment for LDL-C reduction in patients with HeFH
- Part 1 is a single ascending dose designed to assess safety and tolerability
- Part 2 is a randomised, placebo-controlled design to assess LDL-C changes at 90 days
- Total follow-up is up to 15 years after receiving EDIT-401
- Trial is expected to start in early Q4 2026 in Australia and New Zealand

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Disclosures
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