CORRESPONDENCE

Durability of CRISPR-Cas9 Gene Editing Targeting ANGPTL3 with CTX310

TO THE EDITOR: The ability to edit an individual patient's genome is now possible with technological innovations including therapeutics that involve the use of CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats–Cas9 endonuclease).[1] Among patients with lipid disorders, the potential of a one-time treatment to produce a loss-of-function mutation in hepatocytes that mimics natural variants associated with a reduced risk of atherosclerotic cardiovascular disease represents a unique therapeutic opportunity.

We previously described the early safety and efficacy of CTX310, a lipid nanoparticle-encapsulated CRISPR-Cas9 messenger RNA and guide RNA targeting the gene encoding hepatic angiopoietin-like protein 3 (*ANGPTL3*) in a phase 1a, open-label, multicenter trial (Australia New Zealand Clinical Trials Registry number, ACTRN12623000809639).[2] From May 2024 through August 2025, a total of 15 adults who had received a diagnosis of uncontrolled hypercholesterolemia, moderate or severe hypertriglyceridemia, or mixed dyslipidemia were enrolled in the trial and received one of five doses (0.1, 0.3, 0.6, 0.7, or 0.8 mg per kilogram of body weight) of CTX310. Here, we provide a 1-year follow-up for all trial participants.

The primary end point was adverse events, including dose-limiting toxic effects. No such toxicity of CTX310 was reported. Adverse events throughout the trial are detailed in Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org. Two serious adverse events that had previously been reported were considered by the investigators to be unrelated to CTX310; one event was subsequently determined to be a preexisting condition. No new serious adverse events or adverse events of special interest occurred since the time of the initial publication. Beyond the transient elevation in aminotransferase values, which was previously reported in one participant shortly after treatment, no elevations in liver-function measures occurred throughout the remainder of the trial. The effect of CTX310 on ANGPTL3 levels and lipid biomarkers is shown in Table S2. The percent changes from baseline over time are shown in Figure 1 and Figure S1.

At 1 year after treatment, among the four participants who received the highest dose of CTX310 (0.8 mg per kilogram), the mean percent change was −78.6% (range, −89.0 to −63.1) in ANGPTL3, −52.5% (range, −84.2 to −24.4) in low-density lipoprotein cholesterol, and −47.8% (range, −77.6 to −14.7) in triglycerides. Changes in individual participants are shown in Figure S2. Changes in non–high-density lipoprotein (HDL) cholesterol and HDL cholesterol were −52.0% (range, −79.4 to −25.2) and −23.5% (range, −44.9 to 0.0), respectively. Other percent changes — including −37.2% (range, −61.2 to −12.9) in apolipoprotein B and −71.7% (range, −87.8 to −56.1) in triglyceride-rich lipoprotein cholesterol — may be relevant to the potential for cardiovascular benefit. Details regarding the representativeness of the trial population are provided in Table S3. Thus, CTX310 was associated with few adverse events and produced sustained changes in the levels of ANGPTL3 and atherogenic lipoproteins at 1 year, further supporting its potential as a one-time treatment.

Other approaches that have used in vivo base editing for patients with lipid disorders are targeting *PCSK9* (proprotein convertase subtilisin–kexin type 9).[3,4] Phase 1b of our trial is testing the administration of CTX310 targeting a fixed dose of 0.8 mg per kilogram of drug exposure in patients with refractory dyslipidemias (ClinicalTrials.gov number, NCT07491172). Biomarker changes after the receipt of CTX310 may vary according to lipid disorder. As such, efficacy in

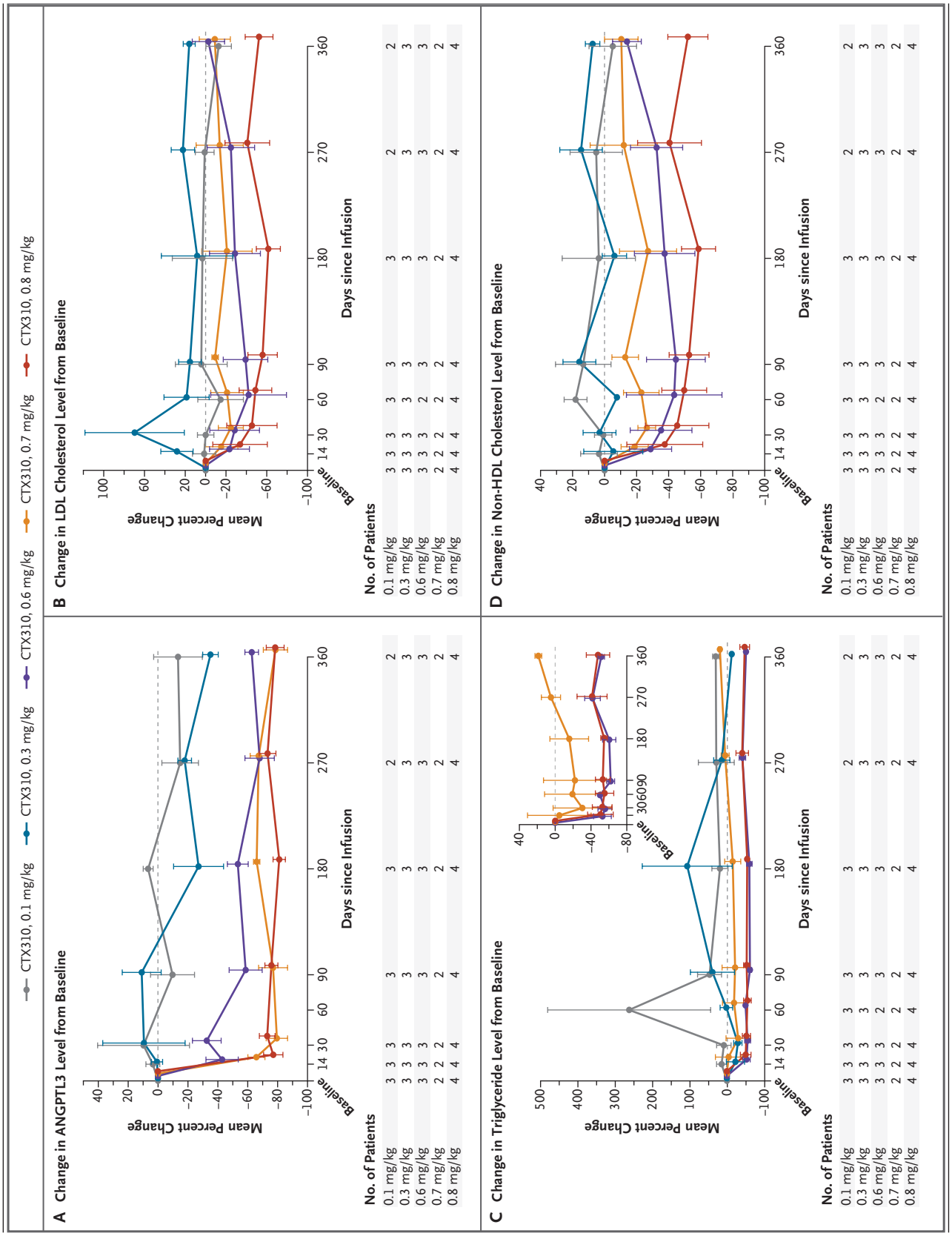

Figure 1 (facing page). Changes in ANGPTL3, LDL Cholesterol, Triglycerides, and Non-HDL Cholesterol after Receipt of CTX310.

Shown is the mean percent change from baseline for levels of angiopoietin-like protein 3 (ANGPTL3) (Panel A), low-density lipoprotein (LDL) cholesterol (Panel B), triglycerides (Panel C), and non–high-density lipoprotein (non-HDL) cholesterol (Panel D). The data are shown according to the patient's visit and at each dose level, with kilograms measured as the estimated lean body weight. The I bars indicate standard errors. In Panel C, the inset graph shows the same data on an expanded y axis for the highest three doses.

phase 1b is being assessed in separate cohorts of patients with specific lipid disorders.

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A complete list of investigators in the trial is provided in the Supplementary Appendix, available at NEJM.org.

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1. Ambardekar AV, Bhatt A, Hoekstra M, Kelly MA, Musunuru K, Natarajan P. Gene editing therapy in cardiovascular disease: 2026 ACC scientific statement: a report of the American College of Cardiology. J Am Coll Cardiol 2026 March 26 (Epub ahead of print).

2. Laffin LJ, Nicholls SJ, Scott RS, et al. Phase 1 trial of CRISPR-Cas9 gene editing targeting *ANGPTL3*. N Engl J Med 2025;393:2119-30.

3. Wan P, Tang S, Lin D, et al. In vivo base editing gene therapy for heterozygous familial hypercholesterolemia: a phase 1 trial. Nat Med 2026;32:1045-51.

4. Vafai SB, Täubel J, Ashdown T, et al. In vivo base editing of *PCSK9* with VERVE-102 for hypercholesterolemia. N Engl J Med 2026;395:648-59.

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